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Optimal management of atrial fibrillation: Recent advances

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Optimal management of atrial fibrillation: Recent advances

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Structural Remodeling and Rotational Activity in Persistent/Long-Lasting Atrial Fibrillation: Gender-Effect Differences and Impact on Post-ablation Outcome

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Background: Structural and post-ablation gender differences are reported in atrial fibrillation (AF). We analyzed the gender differences in structural remodeling and AF mechanisms in patients with persistent/long-lasting AF who underwent wide area circumferential pulmonary vein isolation (WACPVI).

Materials and Methods: Ultra-high-density mapping was used to study atrial remodeling and AF drivers in 85 consecutive patients. Focal and rotational activity (RAc) were identified with the CartoFinder system and activation sequence analysis. The impact of RAc location on post-ablation outcomes was analyzed.

Results: This study included 64 men and 21 women. RAc was detected in 73.4% of men and 38.1% of women ($p = 0.003$). RAc patients had higher left atrium (LA) voltage (0.64 ± 0.3 vs. 0.50 ± 0.2 mV; $p = 0.01$), RAc sites had higher voltage than non-RAc sites 0.77 ± 0.46 vs. 0.53 ± 0.37 mV ($p < 0.001$). Women had lower LA voltage than men (0.42 vs. 0.64 mV; $p < 0.001$), including pulmonary vein (PV) antra (0.16 vs. 0.30 mV; $p < 0.001$) and posterior wall (0.34 vs. 0.51 mV; $p < 0.001$). RAc in the posterior atrium was recorded in few women (23.8 vs. 54.7% in men; $p = 0.014$). AF recurrence rate was higher in patients with RAc outside WACPVI than those with all RAc inside WACPVI or no RAc (63.4 vs. 11.1 and 31.0%; $p = 0.008$ and $p = 0.01$). Comparison of selected patients using propensity score matching confirmed lower atrial voltage (0.4 ± 0.2 vs. 0.7 ± 0.3 mV; $p = 0.007$) and less RAc (38 vs. 75%; $p = 0.02$) in women.

Conclusion: Women have shown more advanced structural remodeling at ablation, which is associated with a lower incidence of RAc (usually located outside the WACPVI). These findings could explain post-ablation gender differences.

Keywords: atrial fibrillation, gender, rotational activity, ultra-high density mapping, AF ablation

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INTRODUCTION

Recent studies have reported the presence of multiple gender-related differences in patients with atrial fibrillation (AF) (1, 2). Women are older at the moment of the procedure and the probability of recurrences after catheter ablation (3) is significantly higher (4, 5). A recent study reported that after multiple procedures, women were more likely to have recurrences, despite that pulmonary veins (PVs) reconnection was less frequent (6). In long-standing AF, female sex was an independent factor for presenting a higher degree of fibrosis in the atria (7). The magnitude of this problem has been recently highlighted. At 30 days after ablation, readmissions were 48% higher in women than men, and the female sex was independently associated with readmission for AF/atrial tachycardia (AT) (8). These studies suggest that the structural remodeling and AF drivers could be different in women.

Multiple wandering wavelets and independent drivers have been proposed as the mechanisms maintaining AF (9–11), with studies ablating possible AF drivers outside PVs showing promising results (12, 13). Alleged AF drivers can be identified by wavefronts emanating from focal sources (foci or breakthrough sites) or by rotational activity (RAc) (11, 14–16).

Ultra-high-density mapping and new tools for the detection of AF drivers (17–19), may better define the structural remodeling and the mechanisms maintaining persistent AF. We evaluated the relationship between AF drivers and structural remodeling and the gender effect. Additionally, the present study evaluated the effect of the presence and anatomical distribution of alleged AF drivers on AF recurrences after wide area circumferential pulmonary vein isolation (WACPVI).

MATERIALS AND METHODS

Study Population

We studied a retrospective cohort of 90 (66 men and 23 women) consecutive patients with long-standing/persistent AF who underwent ultra-high-density mapping during stable AF and point-by-point WACPVI (16 redo procedures; 13 men, 3 women; $p = 0.542$). In 67 patients, AF was present at the arrival and at the electrophysiology laboratory, and in 18 patients it was induced by rapid pacing and remained stable thereafter. In 4 patients (2 men and 2 women) AF could not be induced and therefore they were excluded since RAc mapping could not be performed. The final sample size of the study was 85 patients (64 men and 21 women). AF terminated (sinus rhythm or AT) in 10 patients. The study was approved by the ethics committee of the center.

Electrophysiological Study and Electroanatomical Mapping

The electrophysiology study was performed under general anesthesia. Through the femoral vein, one decapolar catheter was placed in the coronary sinus and transseptal puncture was performed to advance the mapping and ablation catheters to the left atrium (LA). All patients underwent electroanatomical (EA) mapping during sustained AF (20). The EA mapping and signal acquisitions were performed using a 20-pole multi-electrode catheter (PentaRay, Biosense Webster, Diamond Bar, CA, USA) and tissue proximity index (TPI) active during all the procedures. For the ablation, an irrigated contact-force sensing catheter was used (SmartTouch, or SmartTouch SF, Biosense Webster, Diamond Bar, CA, USA). The ablation targeted a wide area around the PVs antra to achieve pulmonary vein isolation (PVI); additional lesions were delivered at the carinas. Ablation lesions were guided by the Ablation Index (CARTO3 V7, Biosense Webster, Diamond Bar, CA, USA), targeting values of 350 or 450 units at the posterior or anterior left atrial wall, respectively (21). Radiofrequency power was set at 35–50 W at the anterior aspect of the veins and 25–45 W at the posterior aspect, with an irrigation flow of 30 ml/min using power control mode.

Rotational and Focal Activity Mapping

The CartoFinder module in the CARTO3 V7 system detected rotational and focal activity (FAc) from unipolar electrogram (EGM) activation patterns (17–19). The module uses the PentaRay EGMs and acquires windows of 30 s for an activation sequence analysis (**Figure 1**). Acquisitions were accepted when the catheter splines were orderly deployed and in contact with the atrial wall. Briefly, the module detects the local activation times (LATs) as the time instant of the maximum negative slope of unipolar EGMs. The CartoFinder module detects an RAc event if the LATs of the four concentric rings span >50% of the dominant cycle length of the unipolar EGMs for two or more consecutive beats (rotations). The acquisition point and area covered by the catheter are highlighted on the CARTO3 3D mesh as a region of interest if a repetitive RAc is detected. Bipolar EGMs of all acquisitions in which the CartoFinder detected RAc were reviewed by expert electrophysiologists and the presence of RAc was only confirmed if there were more than 2 rotations with staircase activation sequence and simultaneous acceleration of discrete EGMs and appearance of continuous activity (22) (**Figure 1A**).

Moreover, CartoFinder provided FAc assessment. The algorithm identifies unipolar EGMs that exhibit a QS pattern. The module identifies the earliest QS morphology within a 10 mm radius and 50 ms window before its annotation. If the QS pattern occurs for two or more consecutive beats, it is considered repetitive (**Figure 1B**).

The continuous electrical activity that is a footprint of RAc (22) was quantified in each CartoFinder acquisition. The electrical burden of the bipolar EGMs was measured using an automatic activity detection algorithm based on the fully unsupervised Hidden Markov Models (HMMs) (23). The method automatically detects periods of electrical activity in AF bipolar EGMs and provides a score between 0 (no activity) and 1 (continuous activity), as shown in the **Supplementary Material**.

Mapping Data Analysis

The EA maps and CartoFinder files (3D coordinates and EGMs signals) were exported for offline processing and analysis. The maps were merged into a reference LA mesh for analysis with an in-house algorithm (**Supplementary Figure 1**). A 3D atrial shell with well-defined PVs and LAA was selected as the reference. The

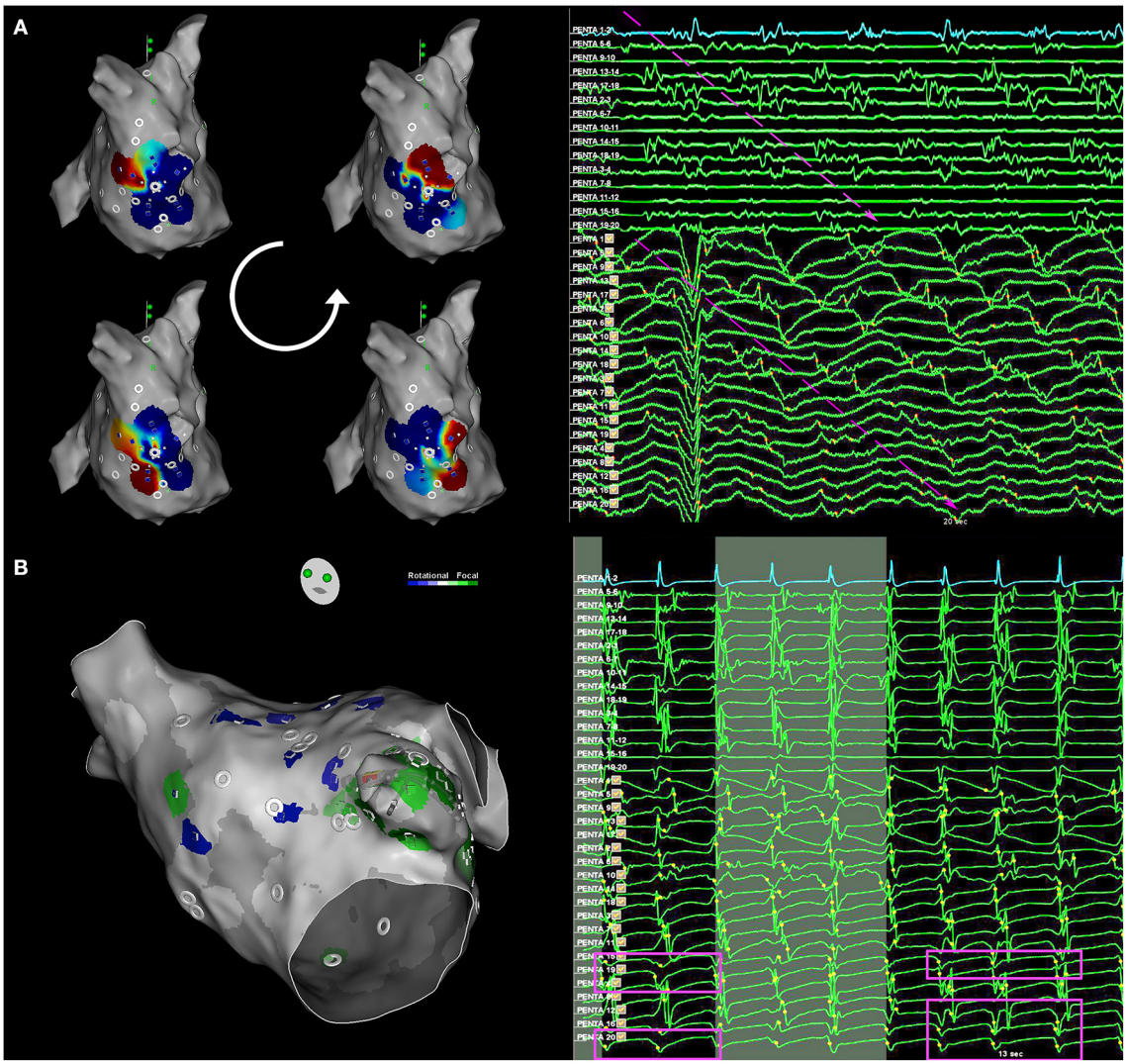

FIGURE 1 | Rotational and focal activity detection. **(A)** Rotational activity (RAc) detection with CartoFinder. Left, local activation map interactive view. One cycle of RAc is represented. Right, bipolar and unipolar EGMs from the multi-electrode catheter are shown. Electrograms (EGMs) are ordered by rings. Bipolar EGMs Penta 1–2 to Penta 17–18 form the external ring, Penta 2–3 to Penta 18–19 the middle ring, and Penta 3–4 to Penta 19-20 the internal ring. Unipolar EGMs Penta 1–17 form the external ring, Penta 2–18 form the external middle ring, Penta 3–19 form the internal middle ring, and Penta 4–20 form the internal ring. The staircase activation pattern expands the complete cycle. Long duration and low-amplitude EGMs are recorded by nearby electrodes: Penta 15–16, Penta 19–20, and Penta 18–19, where the center of rotation is located. The RAc has been highlighted by arrows. EGMs, electrograms. **(B)** Focal activity detection with CartoFinder. Left, the electroanatomical (EA) map view of the catheter was placed on the left atrial appendage. Focal activation is highlighted in green. Right, the darkest background window intervals show when repetitive focal activation events are detected with CartoFinder. The QS patterns are highlighted. Bipolar and unipolar EGMs are shown.

3D meshes were pre-aligned by centering them at point [0, 0, 0] in the 3D axes. Then, the algorithm applied a non-rigid Iterative Closest Point (ICP) method to merge all atrial meshes into the reference one (24). The algorithm automatically projected the voltage, cycle length, and driver locations onto the reference mesh. This merging method preserves the atrial structures and anatomical information and avoids manual quantification or visual transformations, e.g., representing the LA 3D mesh with a 2D projection.

The 3D left atrial shell was manually segmented into 9 areas: left atrial appendage (LAA), PVs, posterior wall, atrial roof, lateral wall, septum, anterior wall, atrial floor, and mitral ring. The PV antra limits were established at 1 cm of the PV ostia but at the anterior aspect of the left superior PV, in which the antrum limit was the ridge between the vein and the LAA (**Supplementary Figure 2**). The EA area and volume of the left atrium was obtained from the CARTO3 software excluding the PVs and mitral valve that were manually removed.

All the EA maps were reviewed to locate the RAc events with respect to the PV isolation lines by an author blinded to the recurrence status.

TABLE 1 | Baseline characteristics of the patients. Rotational activity (RAc) and gender differences.

		Overall	Men	Women	*P*-value*
N		85 (100.0)	64 (75.3)	21 (24.7)	-
Age (years)		60.9 ± 9.5	59.5 ± 9.3	65.2 ± 8.8	**0.014**
Procedure number		1.2 ± 0.5	1.2 ± 0.5	1.2 ± 0.5	0.823
Comorbidities					
Heart failure		13 (15.3)	13 (20.3)	4 (19.0)	0.897
Hypertension		41 (48.2)	26 (40.6)	15 (71.4)	**0.028**
Diabetes mellitus		17 (20.0)	11 (17.2)	6 (28.6)	0.345
Dyslipidemia		30 (35.3)	20 (31.2)	10 (47.6)	0.272
COPD		5 (5.9)	5 (7.8)	0 (0.0)	0.326
Obstructive sleep apnea		17 (20.0)	15 (23.4)	2 (9.5)	0.219
Stroke		7 (8.2)	5 (7.8)	2 (9.5)	0.803
SHD		28 (32.9)	23 (35.9)	5 (23.8)	0.448
BSA (m^2)		2.0 ± 0.2	2.1 ± 0.2	1.8 ± 0.1	**<0.001**
CHA2DS2-VASc		1.9 ± 1.5	1.5 ± 1.3	3.1 ± 1.3	**<0.001**
New York heart association functional classification		9 (10.6)	6 (9.4)	3 (14.3)	0.186
	I	28 (32.9)	25 (39.1)	3 (14.3)	
	II	30 (35.3)	22 (34.4)	8 (38.1)	
	III	17 (20.0)	10 (15.6)	7 (33.3)	
	IV	1 (1.2)	1 (1.6)		
Diagnosis of AF (years)		3.0 (3.6)	3.2 (3.8)	2.4 (2.9)	0.284
Echocardiographic parameters					
LVEF (%)		55.6 ± 10.8	55.5 ± 10.3	55.7 ± 12.5	0.953
LA area (cm^2)		29.3 ± 23.9	30.7 ± 27.1	24.9 ± 5.1	0.176
LA area/BSA (cm^2/m^2)		14.7 ± 11.6	14.9 ± 13.1	13.9 ± 2.9	0.477

*Values in the table are n (%) or mean ± SD. COPD, chronic obstructive pulmonary disease; SHD, structural heart disease; BSA, body surface area; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; and LA, left atrium. *Categorical data with the chi-square test for categorical data, continuous variables using Welch's two-sample t-test, and proportions based on normal z-test. Bold values indicates statistical significance.*

Discharge and Follow-Up

Antiarrhythmic drugs were maintained for 3 months and anticoagulation therapy for 8 weeks and thereafter it was based on the CHA2DS2-VASc score. Outpatient clinical follow-up was scheduled at 3, 6, and 12 months and included an ECG and a 24-h Holter recording. Any symptomatic or documented episodes of AF/AT longer than 30 s were considered as recurrence.

Statistical Analysis

We present categorical values as absolute and relative percentages (frequencies), and normally distributed variables are summarized by the mean and SD. We tested categorical data with the chi-square test, continuous variables using Welch's two-sample *t*-test, and proportions based on normal *z*-test. Contingency tables were analyzed using the chi-tests or Fisher's exact tests when appropriate. A logistic regression propensity score matching was applied to reduce the effect of baseline differences in the data population by gender, **Supplementary Table 4**. The propensity score analysis is detailed in the **Supplementary Material**. The analysis was performed in Python (PyCharm 2020.1.3) and JMP statistical software (14.3.0). All tests were 2-tailed, and a $p < 0.05$ was considered statistically significant.

RESULTS

Patient Demographic Characteristics

A total of 85 (64 men and 21 women) persistent/long-standing patients with AF were included in the study. Baseline characteristics are shown in **Table 1**. The AF duration was 3.2 ± 3.8 years for men and 2.4 ± 2.9 for women ($p = 0.284$). A left ventricular ejection fraction (LVEF) <50% was observed in 16 of the patients. Overall, women were older, had a higher CHA2DS2VASc score ($p < 0.001$), and a higher prevalence of hypertension ($p = 0.028$). These values and the BSA were used as covariates to perform the propensity score matching technique. **Supplementary Table 1** includes the paired baseline analysis by gender with no significant differences.

EA and AF Drivers Mapping

Differences Related to RAc and Gender

Differences between patients with and without RAc and between men and women are shown in **Table 2**. Propensity score matching analysis is shown in **Supplementary Table 2**. The left atrial structural remodeling was assessed by ultra-high-density mapping, 7.952.3 ± 3.325.8 points per map in men and 7.000.1 ± 2.924.2 points per map in women, *p*

TABLE 2 | Electroanatomical (EA) and AF drivers mapping. RAc and gender differences.

	Overall	No RAc	RAc	*P*-value*	Men	Women	*P*-value*
N	85 (100.0)	30 (35.3)	55 (64.7)	-	64 (75.3)	21 (24.7)	-
Electroanatomical mapping							
Num. EA points	7,717.0 ± 3,240.7	6,985.5 ± 2,961.6	8,116.0 ± 3,341.7	0.113	7,952.3 ± 3,325.8	7,000.1 ± 2,924.2	0.219
Num. cartofinder sites	36.4 ± 14.7	31.1 ± 15.6	39.3 ± 13.5	**0.018**	37.8 ± 15.0	32.3 ± 13.2	0.124
LA volume (cm^3)	148.3 ± 38.7	135.3 ± 34.2	155.4 ± 39.5	**0.017**	153.4 ± 38.5	132.9 ± 36.0	**0.033**
LA area (cm^2)	164.3 ± 31.7	150.8 ± 33.9	171.7 ± 28.0	**0.006**	167.9 ± 32.5	153.4 ± 26.9	**0.049**
LA volume/BSA (cm^3/m^2)	74.0 ± 19.3	69.9 ± 19.2	76.3 ± 19.2	0.146	74.5 ± 19.1	72.6 ± 20.3	0.710
LA area/BSA (cm^2/m^2)	82.0 ± 5.9	77.5 ± 18.0	84.5 ± 14.2	0.070	81.4 ± 16.0	83.3 ± 15.6	0.553
Total procedural time (min)	258 ± 36	241 ± 22	245 ± 41	0.560	260 ± 38	248 ± 33	0.172
Total mapping time (min)	61 ± 18	51 ± 17	66 ± 17	**<0.001**	63 ± 16	56 ± 25	0.239
Voltage mapping							
Mean bipolar voltage (mV)	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.3	**0.017**	0.6 ± 0.3	0.4 ± 0.2	**<0.001**
LA area <0.5 mV (%)	66.8 ± 20.4	73.5 ± 18.7	63.1 ± 20.6	**0.021**	62.4 ± 19.9	80.0 ± 16.1	**<0.001**
LA area <0.35 mV (%)	52.5 ± 21.3	60.3 ± 21.5	48.2 ± 20.2	**0.015**	47.1 ± 19.0	68.7 ± 19.4	**<0.001**
LA area <0.1 mV (%)	20.3 ± 8.5	21.7 ± 8.0	19.6 ± 8.8	0.270	19.1 ± 7.6	24.2 ± 10.1	**0.044**
EGM signal analysis							
EGMs cycle length (ms)	174.9 ± 33.7	188.4 ± 42.4	167.5 ± 25.4	**0.018**	167.4 ± 23.0	197.7 ± 48.7	**0.011**
EGM electrical burden	0.3 ± 0.2	0.2 ± 0.1	0.3 ± 0.2	**0.021**	0.3 ± 0.2	0.2 ± 0.2	**0.029**
Mechanistic mapping: rotational activity drivers							
Num. patients with RAc	55	0 (0.0)	55 (100.0)	1.000	47 (73.4)	8 (38.1)	**0.003**
RAc sites per patient with RAc	3.8 ± 3.2	-	3.8 ± 3.2	-	3.9 ± 3.4	3.1 ± 1.4	0.296
RAc events per patient with RAc	82.8 ± 129.4	-	82.8 ± 129.4	-	89.3 ± 138.1	44.5 ± 35.3	0.073
RAc events per acquisition per patient with RAc	2.5 ± 4.4	-	2.5 ± 4.4	-	2.6 ± 4.7	1.8 ± 2.0	0.431
RAc event duration (ms)	586.2 ± 531.9	-	586.2 ± 531.9	-	586.8 ± 550.1	582.0 ± 378.0	0.863
Total RAc event durations per RAc acquisition (ms)	4,361.5 ± 3,536.4	-	4,361.5 ± 3,536.4	-	4,314.8 ± 3,613.6	4,703.3 ± 2,886.8	0.552
Dominant cycle length for RAc acquisitions	161.3 ± 25.5	-	161.3 ± 25.5	-	159.0 ± 24.5	177.8 ± 26.3	**0.002**
Mechanistic mapping: focal activity drivers							
Num. patients with FAc	85 (100.0)	30 (100.0)	55 (100.0)	1.000	64 (100.0)	21 (100.0)	1.000
FAc sites per patient with FAc	13.4 ± 9.2	10.4 ± 7.0	15.0 ± 9.9	**0.017**	14.3 ± 9.7	10.6 ± 6.9	0.066
FAc events per patient with FAc	793.6 ± 947.3	486.9 ± 432.8	960.9 ± 1,098.0	**0.007**	886.3 ± 1,037.9	511.0 ± 493.2	**0.032**
FAc events per acquisition per patient with FAc	20.7 ± 19.6	16.1 ± 13.8	23.2 ± 21.7	0.072	22.3 ± 20.8	15.5 ± 14.0	0.102
FAc event duration per FAc acquisitions (ms)	274.6 ± 228.8	293.6 ± 248.7	269.2 ± 222.6	**<0.001**	268.0 ± 217.3	307.8 ± 277.2	**<0.001**
Total FAc event durations per FAc acquisition (ms)	5,743.1 ± 5,907.5	5,135.9 ± 5,436.0	5,961.2 ± 6,053.1	**0.030**	5,803.8 ± 5,978.9	5,497.5 ± 5,602.9	0.473
Dominant cycle length for FAc acquisitions	172.5 ± 29.2	181.4 ± 33.5	169.3 ± 26.7	**<0.001**	169.1 ± 27.0	186.2 ± 33.1	**<0.001**

*Values in the table are n (%) or mean ± SD. AF, atrial fibrillation; EA, Electroanatomical; LA, left atrium; RAc, rotational activity; FA, focal activity; EGM, electrogram. *Categorical data with the chi-square test for categorical data, continuous variables using Welch's two-sample t-test, and proportions based on normal z-test. Bold values indicates statistical significance.*

= 0.219. Structural remodeling in the light of lower voltage and larger low-voltage areas was more advanced in patients with no RAc and women (**Figure 2**). In women, only the LAA and the lateral wall had an average voltage above the threshold of 0.35 mV which better correlates with delayed enhancement MRI (25).

CartoFinder analyzed 46,425 bipolar EGMs from 3,095 acquisitions (37.8 ± 15.0 per man and 32.3 ± 13.2 per woman) in which the PentaRay splines were orderly deployed. RAc was found in 55 patients (64.7%), with a total of 4,555 RAc events in 208 different CartoFinder acquisitions. Areas with RAc showed a higher voltage than no-RAC areas (0.77 ± 0.46 vs. 0.53 ± 0.37 mV, $p < 0.001$). Revision of bipolar sequences by electrophysiologists confirmed the presence of RAc in all acquisitions in which CartoFinder detected RAc.

Rotational activity was more frequently recorded in men than women (73.4 vs. 38.1%, $p = 0.003$). The anatomical

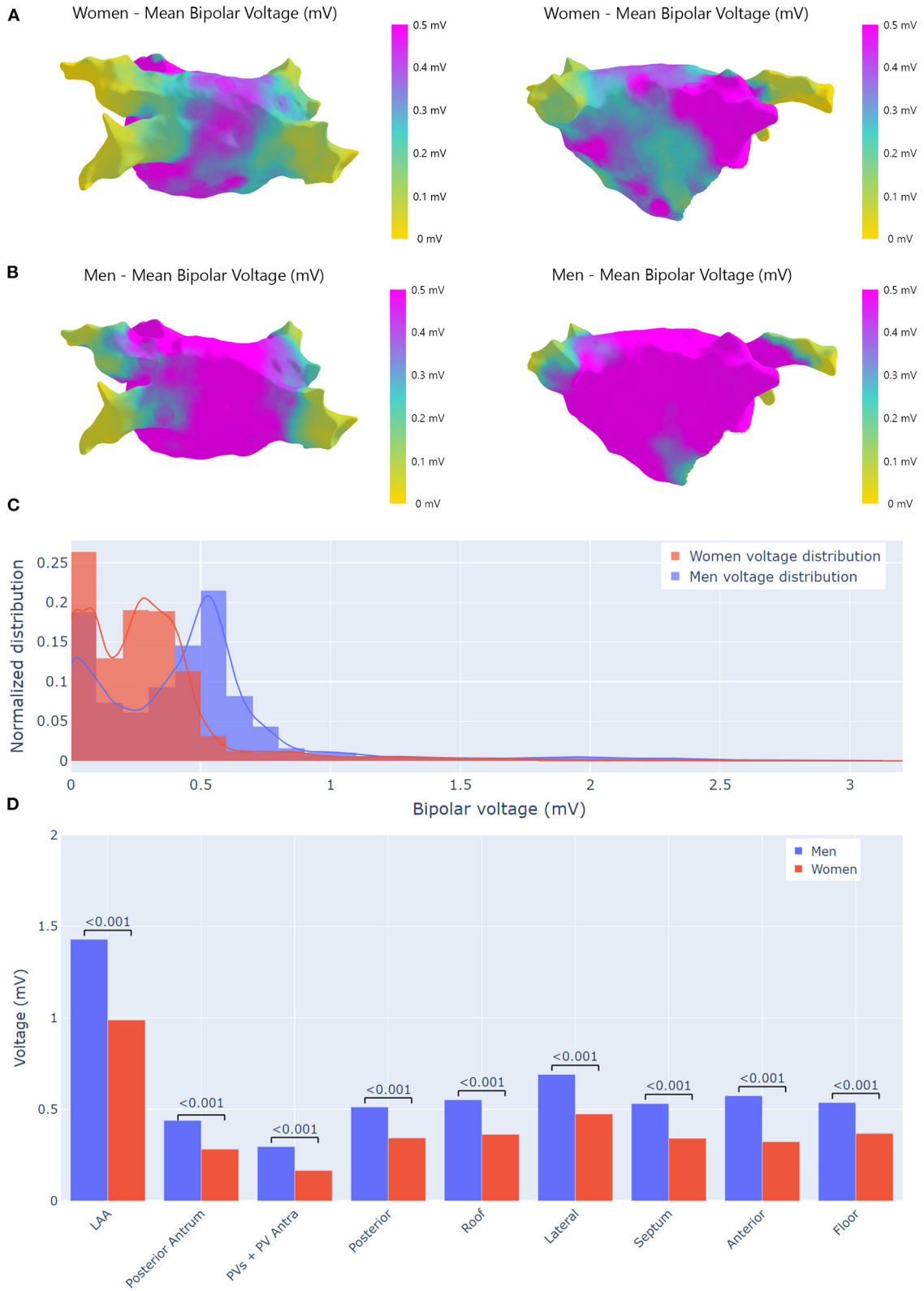

FIGURE 2 | Voltage analysis. **(A)** Bipolar voltage maps differences by gender. Bipolar voltage maps were obtained averaging all recorded points that were projected onto a reference left atrium (LA) mesh. **(A)** Averaged bipolar voltage map from 21 women in which the extension of low-voltage areas is appreciated, the LAA seems to avoid the extension of fibrosis. **(B)** Averaged bipolar voltage map from 64 men where the voltage is preserved in the whole atrium. **(C)** Bipolar voltage points distributions by gender. **(D)** Gender bipolar voltage differences by area. Bipolar voltage was significantly higher in men. In women only, the LAA had a voltage higher than 0.5 mV. LAA, left atrial appendage; PVs, pulmonary veins.

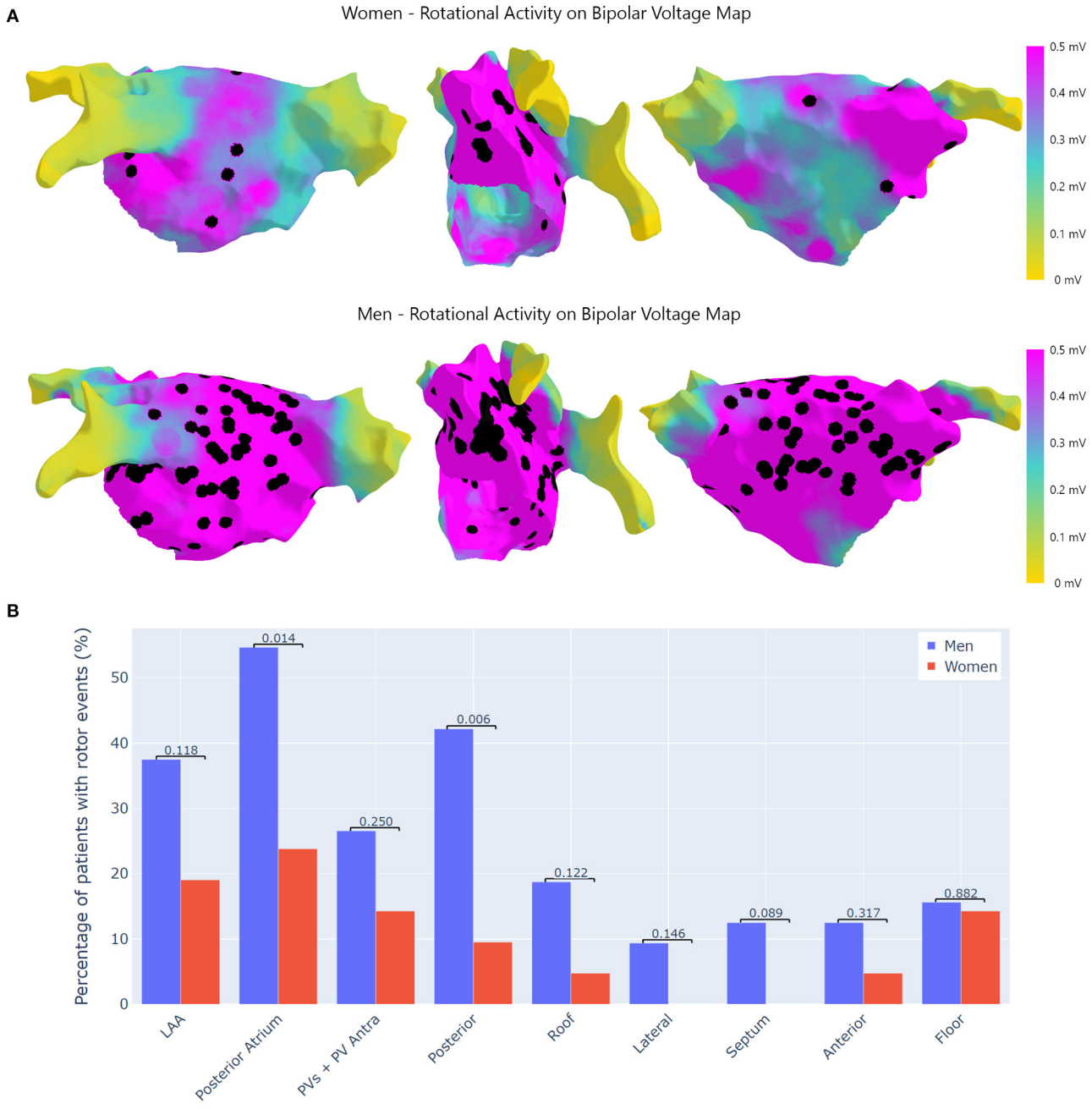

FIGURE 3 | Location of RAc. **(A)** Top: RAc in women. Bottom: RAc in men. RAc was located outside low-voltage areas. This explains why in women RAc converges in and around the LAA. In men as voltage around PV antra is well-preserved RAc is frequently observed. **(B)** Differences in RAc by regions. This figure shows the percentage (%) of patients with RAc at the pre-specified regions of the LA. RAc, rotational activity; LAA, left atrial appendage; PVs, pulmonary veins.

locations of all rotational events are displayed in **Figure 3A**. There were gender differences in the anatomical distribution of RAc (**Figure 3B**), such as the posterior wall (42.0% of men vs. 9.5% of women, $p = 0.006$) and the posterior atrium, such as PVs and posterior wall (54.7% of men vs. and 23.8% of women; $p = 0.01$). The LAA was the area that most frequently hosted RAc events in women.

Focal Activity

The number of focal events was 67.454 (56.723 in men and 10.731 in women), and were present in 1.136 different acquisitions (914 men and 222 women). All patients presented FAc and the number of focal events per patient was significantly higher in men ($p = 0.032$, **Table 2**). The anatomical distribution of FAc was similar between genders (**Figure 4**). The area

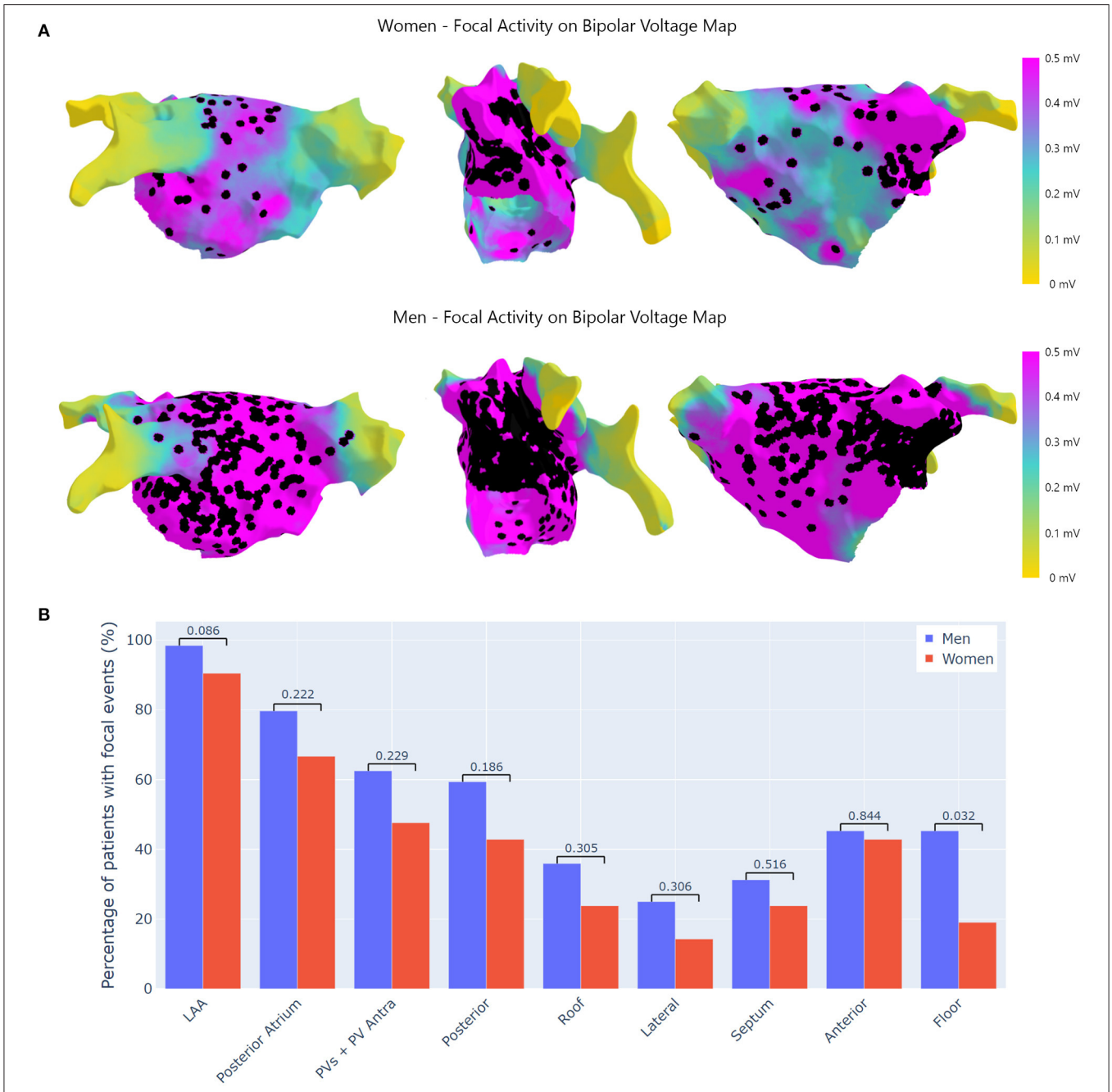

FIGURE 4 | Location of focal activity. **(A)** Top: focal activity in women. Bottom: focal activity in men. Focal activity located in all the LA, with high density predominance in the LAA where it is more frequently detected for all the patients. **(B)** Differences in focal activity by regions. This figure shows the percentage (%) of patients with focal activity at the pre-specified regions of the LA. LAA, left atrial appendage; PVs, pulmonary veins.

that exhibited more FAc was the LAA for both men and women (98.4 vs. 90.5%, $p = 0.086$).

Predictors of Post-ablation AF/AT Recurrences

Table 3 shows the differences between patients with and without recurrences. Propensity score matching analysis is shown in **Supplementary Table 3**. The association between AF/AT recurrences and AF drivers was analyzed in 79 patients with a follow-up longer than the 3 months post-ablation blanking period window. After a mean follow-up period of 357 days, AF/AT recurred in 36 patients, 25 men, and 11 women, with a median recurrence of 177.5 days. The LA volume and area were significantly larger in patients with recurrences than

TABLE 3 | Atrial fibrillation/Atrial tachycardia (AT) recurrence analysis.

	Overall Follow-up	AF/AT-Free	AF/AT Recurrence	*P*-value*
N	79	43 (54.4)	36 (45.6)	
Gender				
Men	58	33 (56.9)	25 (43.1)	0.634
Women	21	10 (47.6)	11 (52.3)	
Electroanatomical mapping				
Num. EA points	7,637.2 ± 3265.0	7,405.3 ± 3,047.5	7,914.1 ± 3,531.0	0.500
Num. CartoFinder sites	36.4 ± 15.0	32.1 ± 10.1	41.6 ± 18.1	**0.007**
LA volume (cm^3)	148.2 ± 39.5	134.0 ± 33.1	165.1 ± 40.4	**<0.001**
LA area (cm^2)	164.1 ± 32.5	155.8 ± 24.1	174.0 ± 38.5	**0.017**
Voltage mapping				
Mean bipolar voltage (mV)	0.6 ± 0.3	0.6 ± 0.3	0.5 ± 0.2	0.114
LA area <0.5 mV (%)	67.2 ± 20.1	63.3 ± 20.1	71.9 ± 19.1	**0.047**
LA area <0.35 mV (%)	53.1 ± 21.2	48.7 ± 20.1	58.3 ± 21.2	**0.046**
LA area <0.1 mV (%)	20.6 ± 8.5	19.2 ± 7.0	22.22 ± 9.8	0.130
EGM signal analysis				
EGMs cycle length (ms)	174.4 ± 80.6	176.2 ± 84.2	175.6 ± 82.0	0.851
EGM electrical burden	0.3 ± 0.3	0.3 ± 0.2	0.2 ± 0.2	**<0.001**
Mechanistic mapping: rotational activity drivers				
Num. patients with RAc	50 (63)	23 (53)	27 (75)	**0.048**
RAc sites per patient with RAc	3.7 ± 3.0	2.8 ± 1.8	4.5 ± 3.6	**0.040**
RAc events per patient with RAc	71.2 ± 110.1	57.9 ± 77.8	82.5 ± 130.5	0.424
RAc events per acquisition per patient with RAc	2.0 ± 3.0	1.9 ± 2.8	2.1 ± 3.1	0.799
RAc event duration (ms)	588.9 ± 459.7	591.2 ± 458.9	587.8 ± 460.1	0.887
Total RAc event durations per RAc acquisition (ms)	4,351.4 ± 3529.5	4,212.0 ± 3,363.6	4,425.2 ± 3,612.0	0.692
Dominant cycle length for RAc acquisitions	164.8 ± 24.4	167.0 ± 28.5	163.6 ± 21.8	0.397
Mechanistic mapping: focal activity drivers				
Num. patients with FA	79	43 (54.4)	36 (45.6)	
FA sites per patient with FA	13.4 ± 9.2	12.8 ± 8.8	14.2 ± 9.6	0.518
FA events per patient with FA	758.3 ± 901.4	640.8 ± 600.8	898.6 ± 1,147.1	0.236
FA events per acquisition per patient with FA	19.7 ± 18.1	19.4 ± 16.1	20.1 ± 20.3	0.870
FA event duration per FA acquisitions (ms)	276.8 ± 230.2	272.1 ± 222.2	281.1 ± 237.1	**<0.001**
Total FA event durations per FA acquisition (ms)	5,653.7 ± 5816.1	5,419.9 ± 5,544.3	5,898.5 ± 6,078.0	0.185
Dominant cycle length for FA acquisitions	173.5 ± 28.9	174.9 ± 30.3	172.1 ± 27.2	0.108
RAc presence location				
No RAc	29 (36.7)	20 (69.0)	9 (31.0)	**0.002**
RAc only inside WACPVI	9 (11.4)	8 (88.9)	1 (11.1)	
RAc outside WACPVI	41 (51.9)	15 (36.6)	26 (63.4)	

*Values in the table are n (%) or mean ± SD. AF, atrial fibrillation; AT, atrial tachycardia; RAc, rotational activity; WACPVI, wide area circumferential pulmonary vein isolation. *Categorical data with the chi-square test for categorical data, continuous variables using Welch's two-sample t-test, and proportions based on normal z-test. Bold values indicates statistical significance.*

those free of AF episodes. Patients with AF/AT recurrences had a higher incidence of RAc, more RAc sites, and higher electrical burden. The differences between patients with and without recurrences regarding the distribution of the RAc in relation to the ablation line during WACPVI are also shown in **Table 3**. When RAc was only recorded inside the ablation line, most patients were free of recurrences and there was a strong association between RAc outside the ablation and AF/AT recurrences which remained as the main predictor of recurrence after being adjusted for LA volume, surface, and ≤0.5 mV area (**Table 4** and **Figure 5A**).

DISCUSSION

Main Findings

This study describes the relationship between structural remodeling and AF drivers that could explain some gender differences in patients with persistent AF. First, RAc distribution in the LA seems related to the degree of structural remodeling which at the ablation time is more intense in women despite having a similar AF duration. Second, consequently with previous findings, women in comparison with men have much less RAc

which is commonly located outside the PV antra. Third, post-ablation AF recurrence was associated with RAc outside WACPVI.

TABLE 4 | Predictors of AF recurrence analysis after WACPVI ablation.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
RAc outside WACPVI	4.2 (1.6–11.2)	**0.002**	4.4 (1.5–13.8)	**0.007**
Scar (<0.5 mV)	5.4 (0.9–35.3)	**0.06**	10.2 (1.3–91)	0.1
LA area (cm^2)	83 (2.7–4,183)	**0.01**	13.0 (0.4–776)	0.8
LA volume (cm^3)	69.9 (6.3–1,036.7)	**0.001**	32.0 (0.8–6462)	0.08

RAc, rotational activity; WACPVI, wide area circumferential pulmonary vein isolation; LA, left atrium; OR, odds ratio; CI, confidence interval. Bold values indicates statistical significance.

Structural Remodeling

Voltage mapping was performed during AF based on previous data in which the correlation between low-voltage and contrast-enhanced MRI is significantly better when EGMs are acquired during AF than during sinus rhythm (25). Structural changes in LA in women are more extensive as suggested by the lower average voltage and larger scar areas. Since AF duration was similar, these changes could be due to the fact that women were older and had more hypertension. Nevertheless, the analysis based on propensity score matching suggests that differences in remodeling are not explained by differences in risk factors alone, but are also due to a gender effect. A previous study has revealed that women with longstanding persistent AF had a higher degree of fibrosis that could be due to the inherent differential expression of fibrosis-related genes (7). Voltage mapping suggests that in women fibrosis affects the posterior atrium more significantly than

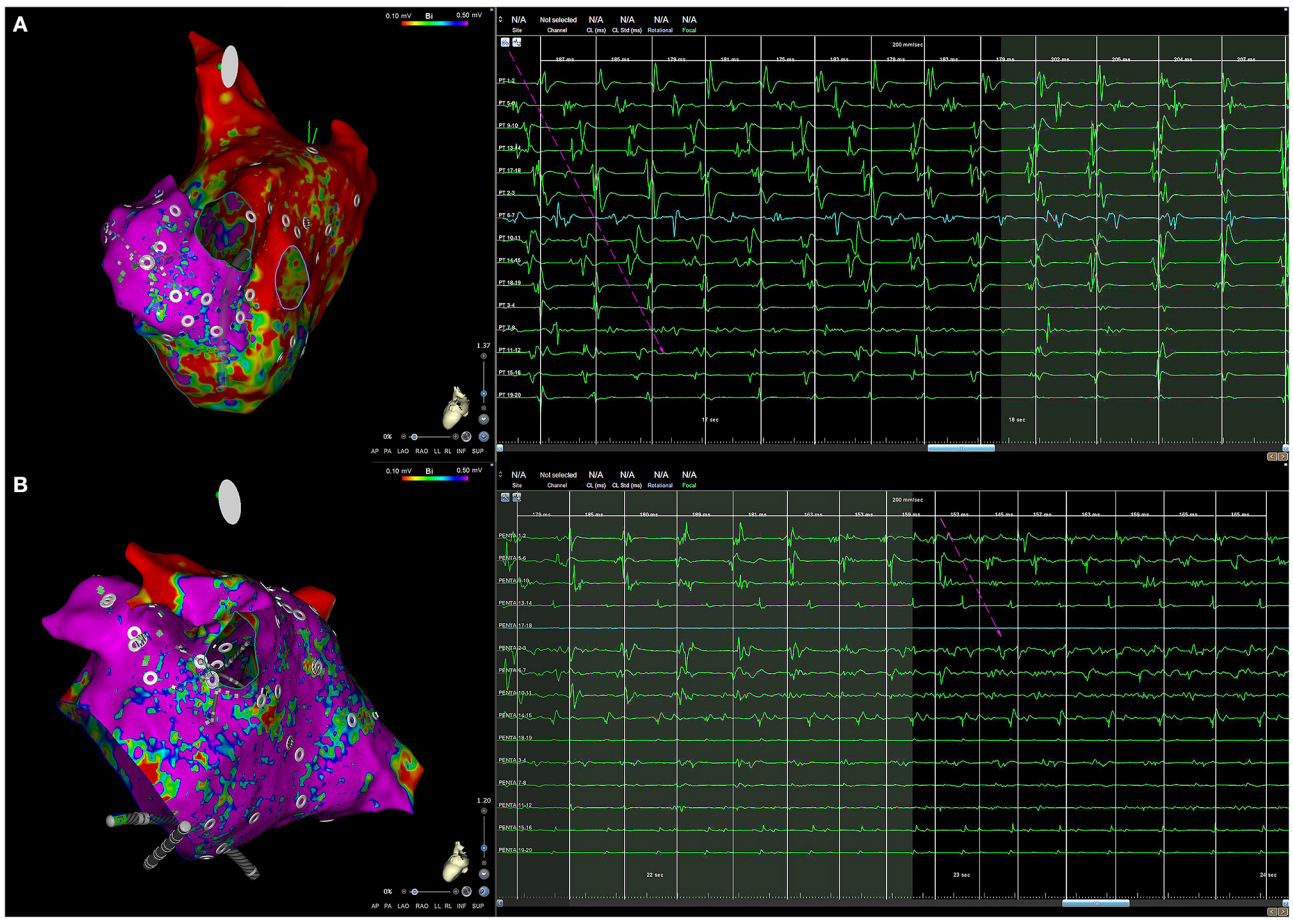

FIGURE 5 | (A) Example of a woman with AF recurrence after PVI. Left: RAc was detected only at the LAA, the remaining atrium had low voltage and RAc was not recorded inside the ablation line. Right: the rotational event expands the whole EGM cycle, highlighted with white arrows. The rotational event stops and the cycle length increases with almost simultaneous EGM activations. **(B)** Example of a man with no AF recurrence after PVI. The voltage is almost normal in the whole atrium (left), RAc was detected in the left inferior PV antra (right). The rotational event starts at the same time that acceleration of discrete EGMs appears (Penta 13–14 EGM) and fragmentation in middle ring electrodes (from Penta 3–4 to Penta 11–12 EGMs). AF, atrial fibrillation; PVI, pulmonary vein isolation; LAA, left atrial appendage; EGM, electrogram; PV, pulmonary vein.

the LAA, which seems to resist the advance of fibrosis (**Figure 2**).

Rotational Activity

With the use of new mapping techniques, several studies have suggested that rotors are a part of the electrophysiological AF substrate (26), but controversy remains over whether the RAc is critical for the maintenance of AF or if it is merely due to the collision of wandering atrial activation wave-fronts (27).

CartoFinder software has been reported to identify with high reproducibility RAc during both paroxysmal and persistent AF when applied to basket catheter recordings (17). In this study, we applied the CartoFinder software to endocardial recordings obtained with a high-resolution catheter that allows assessing the activation sequence with high-quality bipolar EGMs in which far-field activity is canceled. The presence of RAc was not only based on signal processing since all CartoFinder acquisitions were revised by electrophysiologists who confirmed the RAc when the sequential activation spanned the whole cycle length and it coincided with the appearance of high-frequency low amplitude at the inner rings and the acceleration of discrete EGMs (**Figure 5**). The fact that high-resolution catheters were used to detect RAc and assess structural remodeling reinforces the relationship between structural remodeling and the anatomical distribution of RAc.

The incidence of RAc was lower than in previous studies in which RAc was detected based on the signal processing of unipolar EGMs (15, 28, 29). It could be that high-resolution mapping was more specific to detect RAc. Inaccuracies during rotor identification may explain why the Randomized Evaluation of Atrial Fibrillation Treatment With Focal Impulse and Rotor Modulation Guided Procedures (REAFFIRM) trial found no difference between rotor ablation and conventional ablation (30).

We have not observed RAc in low voltage areas which is consistent with prior studies (26). Computational studies demonstrated that rotational drivers perpetuating AF were localized in boundary zones between fibrotic and non-fibrotic tissue (31) and that the moderate levels of fibrotic tissue, i.e., 40% of fibrotic elements, can anchor re-entry activity (32). Nevertheless, the higher levels of fibrosis can block the fast propagation of the electrical wavefronts since the interactions between myocytes are reduced (33). Low voltage areas probably (because of extensive fibrosis) may have more difficulties for housing a functional re-entry, this explains the lower incidence of RAc in the women group and suggests that RAc is not the main mechanism maintaining persistent AF in women and patients with extensive fibrosis.

RAc and WACPVI Efficacy

Although this study did not probe RAc as a mechanism that maintains persistent AF, the association between the presence and dispersion of RAc and the post-ablation AF recurrences highlights the role of RAc in AF. RAc outside the ablation area was the main predictor of AF recurrence and when RAc was included in the ablation line recurrences were very low, suggesting that AF drivers were eliminated. However, the absence of RAc outside WACPVI did not ensure freedom from recurrence, especially in women, suggesting that there are unidentified mechanisms other than RAc involved in AF recurrence after ablation.

Study Limitations

This was a retrospective single cohort and single-center study. The proportion of women and men in this study was not balanced possibly representing the real practice in which women are underrepresented in catheter ablation series (34). In the study, we included 69 first ablation and 16 redo procedures, equally distributed among men and women ($p = 0.542$). Patients in sinus rhythm in whom stable fibrillation was not induced to allow mapping of the RAc were not included. The right atrium was not explored and remapping was not done after ablation. Ablation was not guided by RAc. We did not quantify the inter-intraobserver correlation of RAc.

CONCLUSION

In women, structural remodeling at the ablation time is more severe and affects more intensively the posterior atrium. Structural remodeling could determine RAc distribution. RAc outside the ablation line is the main predictor of AF/AT recurrence suggesting RAc is mechanistically involved in AF maintenance.

DATA AVAILABILITY STATEMENT

The data of this study are available from the corresponding authors on request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee of the institution and following the European and Spanish regulations on the subject (Code: GÉNERO-FA, Approval date: 8th March 2021). The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

PÁ, AC, FA, TD, EG-T, and FF-A collected data and gave final approval of the manuscript. ÁA, NS, and GR-M conceived and designed the study, analyzed the data, drafted the manuscript, and gave final approval of the manuscript. All authors substantially contributed to conducting the underlying research and drafting the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.819429/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Undertreatment of Anticoagulant Therapy in Hospitalized Acute Ischemic Stroke Patients With Atrial Fibrillation

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Background: This study aimed to investigate the prevalence and factors associated with the initiation of oral anticoagulation among patients with acute ischemic stroke (AIS) and concurrent atrial fibrillation (AF) at discharge in China.

Methods: We continuously included hospitalized patients with AIS with an AF diagnosis registered in the computer-based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation (CASE II) from January 2016 to December 2020 and divided them into a and non-anticoagulant groups according to the medications at discharge. Binary logistic regression was used to determine the factors associated with the prescription of anticoagulants in patients with AF.

Results: A total of 16,162 patients were enrolled. The mean age was 77 ± 9 years, 8,596 (53.2%) were males, and the median baseline National Institute of Health Stroke Scale score was 5 (2–12). Of the 14,838 patients without contraindications of antithrombotic therapy, 6,335 (42.7%) patients were initiated with anticoagulation treatment at discharge. Prior history of hemorrhagic stroke (OR 0.647, p <0.001) and gastrointestinal bleeding (OR 0.607, $p = 0.003$) were associated with a lower rate of anticoagulation at discharge. Patients with any intracranial hemorrhage (OR 0.268, $p < 0.001$), gastrointestinal bleeding (OR 0.353, p <0.001), or pneumonia during hospitalization (OR 0.601, $p < 0.001$) were less likely to receive anticoagulants at discharge. Among 7,807 patients with previously diagnosed AF and high risk of stroke (CHA_2DS_2-VASc ≥2), only 1,585 (20.3%) had been receiving anticoagulation treatment prior to the onset of stroke. However, the mean international normalized ratio (INR) was 1.5 on the first test during hospitalization in patients receiving warfarin. Patients complicated with a previous history of ischemic stroke/transient ischemic attack (TIA; OR 2.303, $p < 0.001$) and peripheral artery disease (OR 1.456, $p = 0.003$) were more common to start anticoagulants.

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Conclusions: Less than half of patients with AIS and concurrent AF initiated guideline-recommended oral anticoagulation at discharge, while only 20% of patients with previously diagnosed AF with a high risk of stroke had been using anticoagulants prior to the onset of stroke, which highlights a large care gap in hospitalized stroke patients and the importance of AF management.

Keywords: acute ischemic stroke, atrial fibrillation, anticoagulant therapy, cerebral infarction, undertreatment

INTRODUCTION

Atrial fibrillation (AF) increases the risk of ischemic stroke from thromboembolism, and oral anticoagulation (OAC) is recommended for preventing ischemic strokes (1, 2). Patients who receive OAC according to guideline recommendations have a better prognosis compared with those whose treatment deviated from guideline recommendations. Meanwhile, a lower rate of OAC was found to be associated with increased incidence of ischemic stroke and all-cause mortality (3). However, AF undertreatment is still a long-established healthcare concern. Multiple studies investigating the prevalence of AF undertreatment among patients with stroke have reported that the proportion of patients who did not receive OAC treatment varied worldwide, ranging from approximately 20 to 60%, which highlighted a large care gap and an opportunity to improve AF management (3–7). In Asia, the proportion of insufficient treatment is generally higher (6, 8, 9), but there is still a lack of large data about the undertreatment of anticoagulant therapy in hospitalized patients with acute ischemic stroke (AIS) with AF. Moreover, it remains unclear what factors affect an individual's risk of undertreatment. Thus, this study aimed to investigate the point prevalence and factors associated with the initiation of anticoagulation among hospitalized patients with AIS and concurrent AF in China.

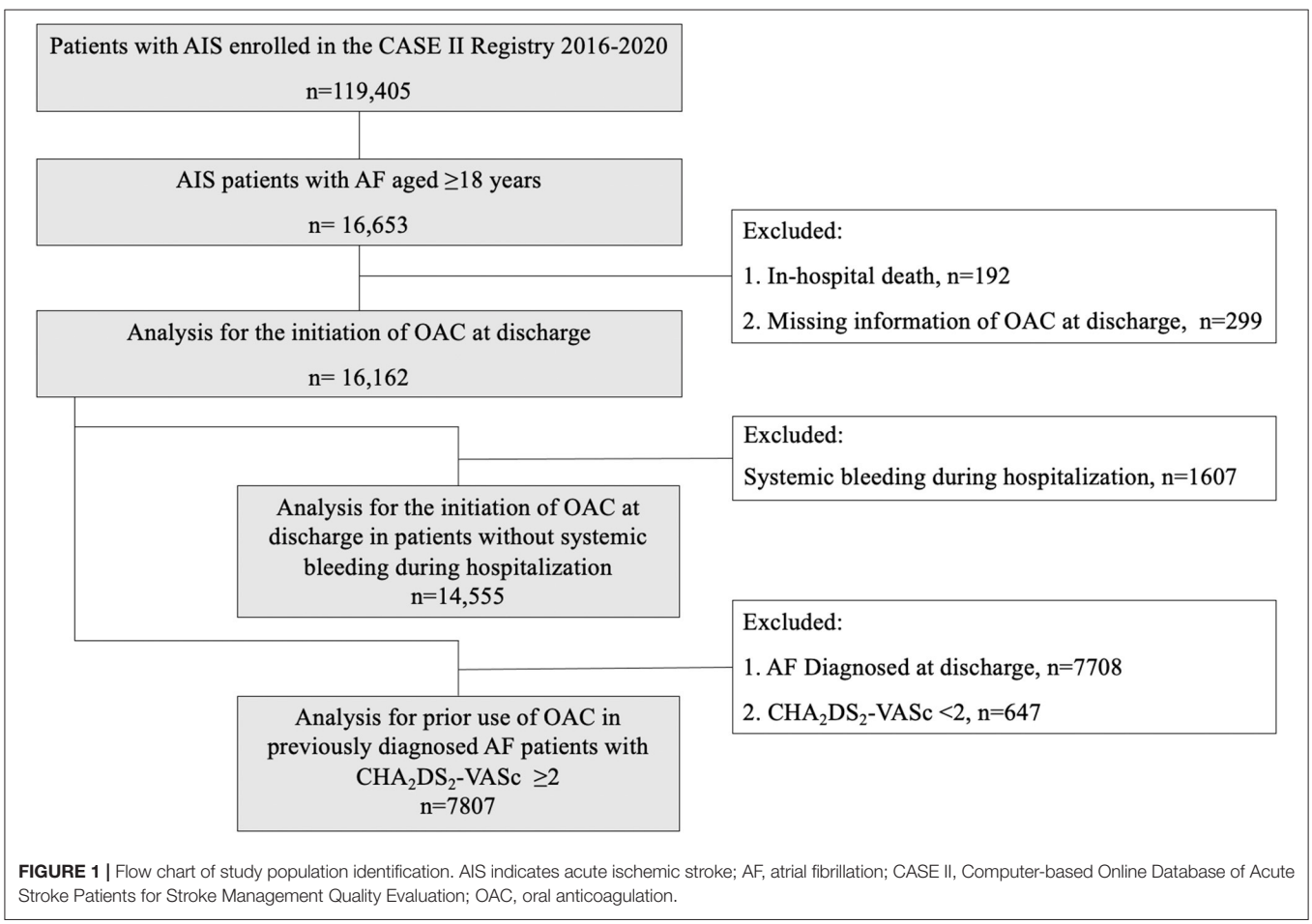

FIGURE 1 | Flow chart of study population identification. AIS indicates acute ischemic stroke; AF, atrial fibrillation; CASE II, Computer-based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation; OAC, oral anticoagulation.

METHODS

Data Collection and Monitoring

This study came from the Computer-based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation (CASE-II, NCT04487340), a multicenter prospective registry. Initiated in 2016, CASE-II was designed to examine the current status of stroke care in China to help develop strategies to improve stroke care. The medical documents during hospitalization of consecutive patients with stroke were collected through a special electronic data capture system. Briefly, original hospital records of patients were saved as images or portable document formats. Specific software pre-processed the above materials and sent them to multiple Optical Character Recognition (10) engines to build documents with recognized text, which were subsequently re-segmented and synthesized. Required data was extracted from the post-processed text, and the cross-check of each case was carried out by a quality control team. Only the de-identified documents were preserved in a safe information database and monitored by an independent contract research organization throughout the study period.

Patients

The CASE-II has consecutively recruited patients with stroke who were diagnosed with AIS, transient ischemic attack (TIA), hemorrhagic stroke, or subarachnoid hemorrhage and admitted within 7 days of symptom onset in China. Because patient information in the CASE-II was de-identified and anonymized before being released to the researchers, the informed consent requirement was waived by Institutional Review Board. For the present analysis, patients with AIS with concurrent AF aged $\geq$18 years were enrolled in the CASE-II between January 2016 and December 2020. AIS was diagnosed according to the World Health Organization criteria (11) and confirmed by computed tomography or magnetic resonance imaging. AF was defined as atrial arrhythmia with irregular R-R intervals and no clear repetitive P waves, and diagnosed with an electrocardiograph, 24- or 48-h Holter, or telemonitoring with recording and automated rhythm detection. Patients with incomplete information on anticoagulation at discharge or who died during hospitalization were excluded.

Variables

We collected the following patient information during hospitalization: demographics (age, sex); blood pressure at admission, baseline National Institutes of Health Stroke Scale (NIHSS) score, and baseline CHA_2DS_2-VASc score; medical history and medication history; reperfusion therapy (intravenous thrombosis with recombinant tissue-type plasminogen activator, mechanical thrombectomy with stent retrievers, and/or thromboaspiration, balloon angioplasty, stenting, or intra-arterial thrombolysis); laboratory tests at admission; medications usage at discharge; and reasons for non-treatment were documented in patient records, which include medical contraindications, refusal against medical advice, or transfer to another hospital.

Statistical Analysis

Clinical characteristics were summarized by computing the mean [standard deviation (SD)] or median [interquartile range (IQR)]. Differences between the two groups were estimated by the *t*-test or Mann-Whitney U test if they were continuous variables. Categorical variables were summarized by proportion (n), and differences between the two groups were estimated by the Pearson χ^2 test. To avoid overfitting, we ran logistic regression with a lasso regularization to select variables associated with the use of anticoagulation. Lambda parameters, which minimize the 10-fold cross-validation prediction error rate, were determined automatically using the function cv. glmnet (12). Function fixed Lasso Inf was used to compute *p*-values and confidence intervals for the lasso estimate. When analyzing the factors associated with prior use of anticoagulation in previously diagnosed patients with AF with a high risk of stroke, clinical information prior to the index stroke was included in the multivariate analysis. All comparisons were two-sided, with statistical significance defined as $p < 0.05$. All statistical analysis was performed using SPSS, Version 24.0 (IBM, Armonk,

TABLE 1 | Characteristics of acute ischemic stroke patients with atrial fibrillation.

Variable	
Number of patients	16,162
Age, years, Mean ± SD	77 ± 9
Male, n (%)	8,596 (53.2)
Baseline NIHSS score, (median [IQR])*	5 (2–12)
CHA_2DS_2-VASc score, (median [IQR])	4 (3–5)
Prior medical history	
Ischemic stroke/TIA, n (%)	4,544 (28.1)
Hypertension, n (%)	13,320 (82.4)
Diabetes, n (%)	3,118 (19.3)
Dyslipidemia, n (%)	5,796 (35.9)
Coronary heart disease, n (%)	3,190 (19.7)
Smoking, n (%)	3,965 (24.5)
Reperfusion therapy, n (%)	2,919 (18.1)
Number of eligible patients for antithrombotic agents at discharge	14,838
Antiplatelets only, n (%)	5,895 (39.7)
Anticoagulants only, n (%)	6,061 (40.8)
Antiplatelets and Anticoagulants, n (%)	274 (1.8)
No-antithrombotic agent due to clear documentation of refusal or transfer to another hospital, n (%)	904 (6.1)
No-antithrombotic agent due to unknown reasons, n (%)	1,704 (11.5)
Types of anticoagulants	6,335
Warfarin, n (%)	2,916 (46.0)
Direct oral anticoagulants, n (%)	3,419 (54.0)

IQR indicates interquartile range; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; TIA, Transient ischemic attack.
**NIHSS was available for 13,766 patients.*

New York), and R software, Version 4.1.0 (R Foundation, Vienna, Austria).

RESULTS

Patient Characteristics of the Study Population

A total of 16,162 patients with AIS and concurrent AF were included for analysis in this study (**Figure 1**). Mean age was 77 ± 9 years, 8,596 (53.2%) were males, and median baseline NIHSS score was 5 (2–12). There were 14,838 patients having no clear documentation of antithrombotic contraindications at discharge. Among them, 5,895 patients (39.7%) received antiplatelets, 6,061 (40.8%) were on OAC, 274 (1.8%) were on both antiplatelet and OAC, while 2,608 patients (17.6%) did not receive any antithrombotic agents (**Table 1**). Initiation of anticoagulation at discharge was increased from 30.1% (52 of 173) in 2016 to 49.6% (2,266 of 4,573) in 2020. From **Figure 2**, we could observe an increased use of direct oral anticoagulants (DOACs) [from 8.7% (15 of 173) to 30.5% (1,397 of 4,573)] and a slight decline of warfarin usage [from 21.4% (37 of 173) to 19.0% (869 of 4573)].

Factors Associated With the Initiation of Anticoagulation in AIS Patients With AF at Discharge

As shown in **Table 2**, patients with the initiation of anticoagulants at discharge were younger (OR 0.973, 95% CI 0.970–0.977), had lower systolic blood pressure (OR 0.998, 95% CI 0.996–0.999), and baseline NIHSS score (OR 0.943, 95% CI 0.937–0.947) than patients who were not on OAC treatment. The prior anticoagulants usage (OR 3.408, 95% CI 3.065–3.789), complication with deep vein thrombosis (OR 1.711, 95% CI 1.446–2.020), and longer hospital stay (OR 1.044, 95% CI 1.039–1.050) were all associated with increased odds of receiving anticoagulation. The previous medical history associated with lower frequency of anticoagulation at discharge includes ischemic stroke/TIA (OR 0.890, 95% CI 0.826–0.965), hemorrhagic stroke (OR 0.647, 95% CI 0.527–0.795), and gastrointestinal bleeding (OR 0.607, 95% CI 0.463–0.804). In addition, patients with any intracranial hemorrhage (OR 0.268, 95% CI 0.232–0.309), gastrointestinal bleeding (OR 0.353, 95% CI 0.263–0.475), pneumonia during hospitalization (OR 0.601, 95% CI 0.553–0.652), or combined with renal insufficiency (OR 0.841, 95% CI 0.752–0.952) were less likely to receive anticoagulants at discharge.

Additional sensitivity analyses were performed to determine the factors associated with anticoagulant therapy at discharge in patients without systemic bleeding during hospitalization, and the findings were generally comparable with that in the primary analysis (**Table 3**).

Factors Associated With Prior Use of Anticoagulation in Previously Diagnosed Patients With AF With a High Risk of Stroke

Among 7,807 patients with previously diagnosed AF and high risk of stroke (CHA_2DS_2-VASc ≥2), 1,585 patients (20.3%)

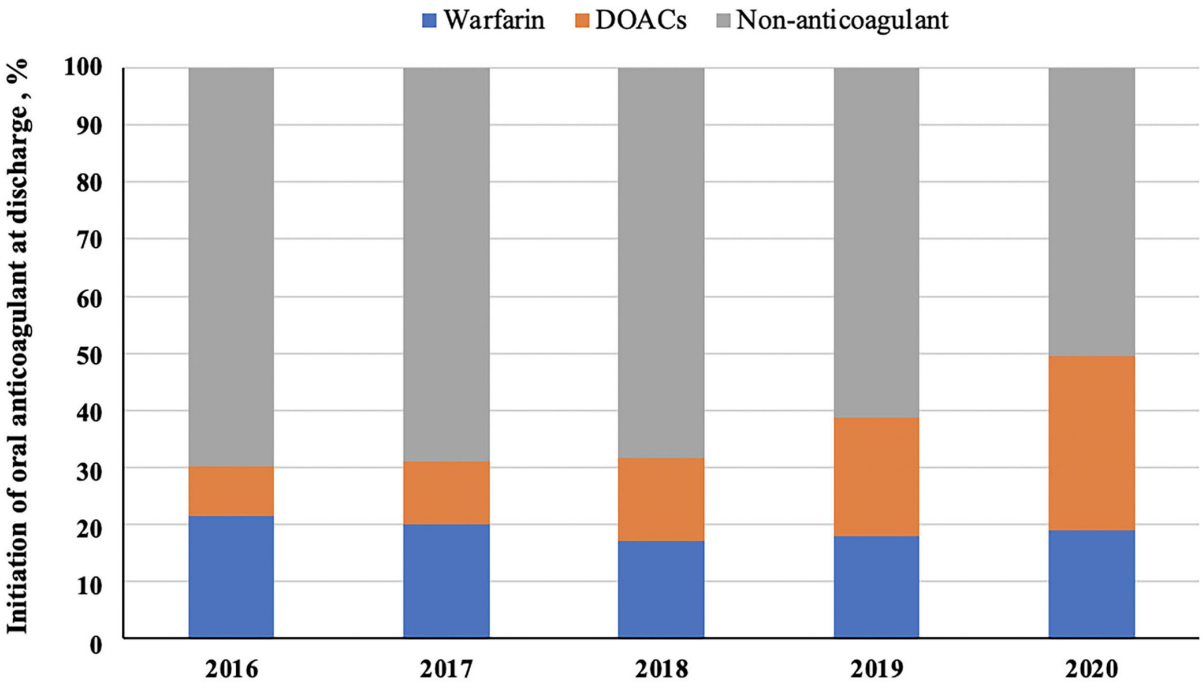

FIGURE 2 | The trends of oral anticoagulant use at discharge. DOACs indicate direct oral anticoagulants.

TABLE 2 | Univariate and multivariate analysis for the initiation of anticoagulation at discharge.

Variable	Univariate analysis			Multivariate analysis		
	Non-anticoagulant group (*n* =9,827)	Anticoagulant group (*n* = 6,335)	*P* value	OR	(95% CI)	*P* value
Age, years, Mean ± SD	78 ± 9	75 ± 10	<0.001	0.973	(0.970–0.977)	<0.001
Male, n (%)	5,061 (51.5)	3,535 (55.8)	<0.001	1.014	(0.526–1.120)	0.786
Prior medical history						
Ischemic stroke/TIA, n (%)	2,825 (28.7)	1,719 (27.1)	0.026	0.890	(0.826–0.965)	0.011
Hemorrhagic stroke, n (%)	327 (3.3)	125 (2.0)	<0.001	0.647	(0.527–0.795)	<0.001
Gastrointestinal bleeding, n (%)	187 (1.9)	73 (1.2)	<0.001	0.607	(0.463–0.804)	0.003
Urinary tract bleeding, n (%)	3 (0)	2 (0)	0.971	-		
Smoking, n (%)	2,271 (23.1)	1,694 (26.7)	<0.001	1.029	(0.760–1.471)	0.400
Anticoagulants, n (%)	585 (6.0)	1,173 (18.5)	<0.001	3.408	(3.065–3.789)	<0.001
New comorbidity during hospitalization						
Any intracranial bleeding, n (%)	1,112 (11.3)	222 (3.5)	<0.001	0.268	(0.232–0.309)	<0.001
Gastrointestinal bleeding, n (%)	427 (4.3)	122 (1.9)	<0.001	0.353	(0.263–0.475)	<0.001
Urinary tract bleeding, n (%)	14 (0.1)	11 (0.2)	0.622	-		
Pneumonia, n (%)	3,345 (34.0)	1,113 (17.6)	<0.001	0.601	(0.553–0.652)	<0.001
Hypertension, n (%)	8,098 (82.4)	5,222 (82.4)	0.967	-		
Diabetes, n (%)	1,885 (19.2)	1,233 (19.5)	0.658	-		
Dyslipidemia, n (%)	3,401 (34.6)	2,395 (37.8)	<0.001	1.044	(0.910–1.112)	0.324
Coronary heart disease, n (%)	2,030 (20.7)	1,160 (18.3)	<0.001	0.942	(0.869–1.095)	0.258
Heart failure, n (%)	402 (4.1)	180 (2.8)	<0.001	0.884	(0.745–1.241)	0.282
Renal insufficiency, n (%)	961 (9.8)	498 (7.9)	<0.001	0.841	(0.752–0.952)	0.013
Peripheral artery disease, n (%)	404 (4.1)	297 (4.7)	0.079	-		
Anemia, n (%)	444 (4.5)	203 (3.2)	<0.001	0.823	(0.696–1.018)	0.062
Deep vein thrombosis, n (%)	308 (3.1)	252 (4.0)	0.004	1.711	(1.446–2.020)	<0.001
SBP, mmHg, Mean ± SD	151 ± 24	148±23	<0.001	0.998	(0.996–0.999)	0.003
DBP, mmHg, Mean ± SD	85 ± 15	85±15	0.98	-		
Baseline NIHSS score, Median (IQR)*	6 (2,14)	3 (1,7)	<0.001	0.943	(0.937–0.947)	<0.001
Reperfusion therapy, n (%)	1,786 (18.2)	1,133 (17.9)	0.64	-		
Length of stay, days, Median (IQR)	11 (8–15)	11 (9–15)	<0.001	1.044	(1.039–1.050)	<0.001

CI indicates confidence interval; DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, national institutes of health stroke scale; OR, odds ratio; SD, standard deviation; SBP, systolic blood pressure; TIA, transient ischemic attack.

**NIHSS was available for 13,766 patients (5,570 in anticoagulant group and 8,196 in non-anticoagulant group).*

had been receiving anticoagulation prior to the onset of stroke (17.9% anticoagulants only, and 2.4% were on both antiplatelets and anticoagulants). As seen in **Table 4**, patients who had been receiving anticoagulation had lower baseline NIHSS scores than those who are not. However, the mean international normalized ratio (INR) was 1.5 on the first test during hospitalization in patients receiving warfarin. Previously diagnosed patients with AF with a high risk of stroke who used anticoagulation were younger (OR 0.962, 95% CI 0.955–0.968), had a higher rate of ischemic stroke/TIA (OR 2.303, 95% CI 2.069–2.563), and peripheral artery disease (OR 1.456, 95% CI 1.176–1.795), and a lower rate of hemorrhagic stroke (OR 0.353, 95% CI 0.264–0.474) and hypertension (OR 0.634, 95% CI 0.562–0.717) compared with patients who do not use anticoagulants. Interestingly, patients who underwent anticoagulation before onset also had a higher rate of medication with antihypertensive, hypoglycemic agents, and statins.

DISCUSSION

In this large prospective multicenter registry of stroke patients in China, <50% of patients with AIS with concurrent AF received guideline-recommended anticoagulation at discharge, which highlights a large care gap between guideline and practice. Prior hemorrhagic diseases and the presence of pneumonia during hospitalization were related to a lower rate of anticoagulant therapy. Furthermore, among our patients who were having a pre-index diagnosis of AF with a high risk of stroke and final ischemic event, only 20% received guideline-recommended OAC treatment, indicating the importance of AF management.

Guidelines from the European Society of Cardiology, European Heart Rhythm Association, and Heart and Stroke Foundation Canadian Stroke Best Practice Committees all highlight that weighing the risk of recurrence and bleeding is the core strategy to initiate anticoagulation after ischemic

TABLE 3 | Univariate and multivariate analysis for the initiation of anticoagulation at discharge in patients without systemic bleeding during hospitalization.

Variable	Univariate analysis			Multivariate analysis		
	Non-anticoagulant group (n = 8,498)	Anticoagulant group (n = 6,057)	P value	OR	(95% CI)	P value
Age, years, Mean ± SD	78 ± 9	75 ± 9	<0.001	0.980	(0.970–0.978)	<0.001
Male, n (%)	4,389 (51.6)	3,375 (55.7)	<0.001	1.011	(0.385–1.119)	0.832
Prior medical history						
Ischemic stroke/TIA, n (%)	2,488 (29.3)	1,638 (27.0)	0.003	0.875	(0.811–0.949)	0.005
Hemorrhagic stroke, n (%)	297 (3.5)	116 (1.9)	<0.001	0.582	(0.468–0.723)	<0.001
Gastrointestinal bleeding, n (%)	173 (2.0)	67 (1.1)	<0.001	0.546	(0.411–0.725)	<0.001
Urinary tract bleeding, n (%)	3 (0)	2 (0)	0.942	-		
Smoking, n (%)	1,949 (22.9)	1,608 (26.5)	<0.001	1.027	(0.723–1.733)	0.369
Anticoagulants, n (%)	482 (5.7)	1,123 (18.5)	<0.001	3.525	(3.152–3.939)	<0.001
New comorbidity during hospitalization						
Hypertension, n (%)	6,983 (82.2)	5,000 (82.5)	0.557	-		
Diabetes, n (%)	1,597 (18.8)	1,162 (19.2)	0.552	-		
Dyslipidemia, n (%)	2,982 (35.1)	2,284 (37.7)	0.001	1.026	(0.782–1.088)	0.611
Pneumonia, n (%)	2,685 (31.6)	1,007 (16.6)	<0.001	0.583	(0.535–0.635)	<0.001
Coronary heart disease, n (%)	1,797 (21.1)	1,105 (18.2)	<0.001	0.919	(0.845–1.034)	0.109
Heart failure, n (%)	347 (4.1)	174 (2.9)	<0.001	0.931	(0.799–1.881)	0.601
Renal Insufficiency, n (%)	839 (9.9)	477 (7.9)	<0.001	0.847	(0.754–0.966)	0.021
Peripheral artery disease, n (%)	347 (4.1)	286 (4.7)	0.063	-		
Anemia, n (%)	369 (4.3)	189 (3.1)	<0.001	0.836	(0.702–1.066)	0.104
Tumor, n (%)	603 (7.1)	386 (6.4)	0.088	-		
Deep vein thrombosis, n (%)	238 (2.8)	223 (3.7)	0.003	1.631	(1.365–1.950)	<0.001
SBP, mmHg, Mean ± SD	151 ± 24	148 ± 23	<0.001	0.998	(0.996–0.999)	0.006
DBP, mmHg, Mean ± SD	85 ± 15	85 ± 14	0.855	-		
Baseline NIHSS score, Median (IQR)*	6 (2–14)	3 (1–7)	<0.001	0.941	(0.934–0.946)	<0.001
Reperfusion therapy, n (%)	1,442 (17.0)	1,058 (17.5)	0.432	-		
Length of stay, days, Median (IQR)	10 (8–14)	11 (9–15)	<0.001	1.047	(1.042–1.053)	<0.001

CI indicates confidence interval; DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, national institutes of health stroke scale; OR, odds ratio; SD, standard deviation; SBP, systolic blood pressure; TIA, transient ischemic attack.

**NIHSS was available for 12,342 patients (5,324 in anticoagulant group and 7,018 in non-anticoagulant group).*

stroke (13–15). Several factors need to be considered in support of early or delayed anticoagulation. For example, early initiation of anticoagulation can be considered for young patients with lower NIHSS scores and well-controlled blood pressure, while delayed anticoagulation could be considered for ongoing intracerebral hemorrhage and gastrointestinal bleeding or combined renal insufficiency. Our study has similar findings.

Notably, we found several factors that are not recommended in the guidelines, which may explain the low proportion of anticoagulation in the real world. Prior hemorrhagic diseases, including intracerebral and gastrointestinal hemorrhage, were related to the absence of anticoagulants in this study. Increased undertreatment among patients with past bleeding events has been shown in previous studies (16, 17), indicating an excessive concern about the bleeding risk of patients. Waldo et al. found that perceived or actual bleeding risk was a significant predictor for warfarin undertreatment (18). Patient and family education on the benefits and risks associated with using anticoagulants should be made available and widely adopted by health care professionals. In the FibStroke study done in Finland, Palomäki et al. also found that patients with high HAS-BLED scores (HAS-BLED ≥3) were at an increased risk of OAC undertreatment than those with HAS-BLED <3 (17). Especially in the Asian population, a high rate of non-adherence to guidelines was found (6, 8, 9), which may be due to the higher rate of major bleeding, including intracranial hemorrhage in Asians than Caucasians (19–21). However, despite the fear of OAC-related bleeding complications in Asian patients, individualized assessment of bleeding risk is still needed (22, 23). Moreover, a high bleeding risk itself should not inevitably result in the decision not to use anticoagulants. Stroke and bleeding risk factors overlap, and patients at high risk of bleeding often have a high risk of ischemic stroke (24). To prevent bleeding while on treatment with anticoagulants, dynamic risk assessment to minimize the modifiable risk factors is of great importance (25).

The recommended general approach on the target timing of initiation of anticoagulation after stroke is as follows: 1 day or the same day after a TIA, 3 days after a mild stroke, 6 days after a moderate stroke, and 12–14 days after a severe stroke (26).

TABLE 4 | Univariate and multivariate analysis for prior use of anticoagulation in patients with previously diagnosed atrial fibrillation (AF) with high risk of stroke.

Variable	Univariate analysis			Multivariate analysis		
	Non-anticoagulant group (n =6222)	Anticoagulant group (n =1585)	*P* value	OR	(95% CI)	*P* value
Age, years, Mean ± SD	79 ± 8	76 ± 9	<0.001	0.962	(0.955–0.968)	<0.001
Male, n (%)	3,088 (49.6)	803 (50.7)	0.463	-		
Prior medical history						
Ischemic stroke/TIA, n (%)	2,213 (35.6)	847 (53.4)	<0.001	2.303	(2.069–2.563)	<0.001
Hemorrhagic stroke, n (%)	238 (3.8)	44 (2.8)	0.046	0.353	(0.264–0.474)	<0.001
Gastrointestinal bleeding, n (%)	134 (2.2)	36 (2.3)	0.775	-		
Urinary tract bleeding, n (%)	16 (0.3)	4 (0.3)	0.779	-		
Hypertension, n (%)	4,548 (73.1)	1,087 (68.6)	<0.001	0.634	(0.562–0.717)	<0.001
Diabetes, n (%)	998 (16.0)	288 (18.2)	0.041	1.020	(0.980–1.261)	0.336
Dyslipidemia, n (%)	68 (1.1)	25 (1.6)	0.113	-		
Coronary heart disease, n (%)	1,308 (21.0)	328 (20.7)	0.774	-		
Tumor, n (%)	408 (6.6)	89 (5.6)	0.170	-		
Renal Insufficiency, n (%)	248 (4.0)	73 (4.6)	0.267	-		
Peripheral artery disease, n (%)	315 (5.1)	114 (7.2)	0.001	1.456	(1.176–1.795)	0.003
Smoking, n (%)	1,331 (21.4)	345 (21.8)	0.746	-		
Prior medication history						
Antiplatelets, n (%)	2,072 (33.3)	188 (11.9)	<0.001	0.103	(0.087–0.122)	<0.001
Antihypertensive agents, n (%)	3,121 (50.2)	955 (60.3)	<0.001	1.927	(1.714–2.164)	<0.001
Hypoglycemic agents, n (%)	678 (10.9)	227 (14.3)	<0.001	1.582	(1.177–2.071)	0.008
Statins, n (%)	1,113 (17.9)	459 (29.0)	<0.001	3.800	(3.271–4.406)	<0.001
Clinical characteristics at stroke onset						
SBP, mmHg, Mean ± SD	150 ± 23	145 ± 22	<0.001	-		
DBP, mmHg, Mean ± SD	85 ± 15	84 ± 14	0.004	-		
Baseline NIHSS score, median (IQR)*	5 (2–12)	4 (2–10)	<0.001	-		
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	4 (3–5)	<0.001	-		
Reperfusion therapy, n (%)	1,144 (18.4)	142 (9.0)	<0.001	-		
INR (on warfarin), Mean ± SD	1.1 ± 0.2	1.5 ± 0.6	<0.001	-		

CI indicates confidence interval; DBP, diastolic blood pressure; IQR, interquartile range; INR, international standardized ratio; NIHSS, national institutes of health stroke scale; OR, odds ratio; SD, standard deviation; SBP, systolic blood pressure; TIA, transient ischemic attack.

**NIHSS was available for 6,654 patients (1,316 in anticoagulant group and 5,338 in non-anticoagulant group).*

In our study, the length of hospital stay was about 10 days in the non-anticoagulant therapy group without systemic bleeding during hospitalization, with their baseline NIHSS score only at 6 (indicating a mild-to-moderate stroke). It was also found that longer hospital stay was associated with increased odds of receiving anticoagulation. Therefore, these results revealed that there was a significant delay in the initiation of anticoagulation in the current clinical practice, which needs to be improved, potentially, by the education of clinicians.

Indeed, an increasing number of studies are focusing on the early prevention of hospitalized patients with AIS with concurrent AF. Data from observational studies and randomized controlled trials suggest that early recurrence of AIS in patients with concurrent AF ranges from 0.5 to 1.3% per day during the first two weeks (27, 28). In addition, early initiation of anticoagulation is particularly important for those who have a high risk of recurrences (29–31), such as those with high NIHSS scores and those with symptoms of atrial enlargement and atrial thrombus. Nowadays, small randomized trials (32) have reported that early initiation (1–5 days) of OAC treatment in patients with mild-to-moderate stroke or small-to-medium sized infarcts (less than a third of the affected arterial territory) could lead to both low frequency of symptomatic and asymptomatic intracranial hemorrhage and low rate of recurrent ischemic stroke. Furthermore, four randomized controlled trials [ELAN (NCT03148457; Switzerland), OPTIMAS (EudraCT, 2018-003859-38; UK), TIMING (NCT02961348; Sweden), and START (NCT03021928; USA)] which plan to recruit ∼9,000 participants are underway, with methods that either use safer DOACs to initiate anticoagulation earlier or selecting the initiation time of OAC based on the risk judgment from the severity or imaging features of stroke (33). The results of these trials will help to persuade the clinicians to initiate early anticoagulation, improving the secondary prevention of stroke.

Guidelines recommend OAC for all patients with a high risk of stroke (CHA_2DS_2-VASc $\geq$ 2) unless contraindicated (34, 35). However, in this study, we found that only 20.3% of patients with AF with a high risk of stroke used anticoagulants

prior to the onset of stroke, far lower than the current global anticoagulation rate of 42–60% (4, 36–38). The characteristics of patients receiving OAC before the index stroke include young age, fewer history of hypertension, and intracerebral hemorrhage. This phenomenon still reflects the excessive fear of anticoagulation-related bleeding in old patients and prior hemorrhage. It is worth noting that patients with higher compliance of medication for risk factors were more likely to accept anticoagulants, highlighting the importance of patient education for primary prevention.

For patients with AF taking warfarin, careful dosing and consistent INR monitoring are important. This is due to how warfarin efficacy depends on therapeutic INR control (INR range 2.0–3.0; if the presence of mechanical valve range is 2.5–3.5) and declines when the INR falls lower than 2.0 (14). It is also important to note that the mean INR in patients with prior warfarin use was only 1.5, which does not meet the targets, which could be a direct cause of the current stroke. Moreover, INR also influences the decision of acute treatment, as the rate of reperfusion therapy was significantly decreased in patients using anticoagulants prior to the stroke. In view of this, DOACs may be a better choice as treatment compared to warfarin. Overall, optimizing the anticoagulant strategy could be another direction to improve AF management in the future.

Notably, the presence of pneumonia during hospitalization was associated with reduced use of anticoagulants at discharge. This result is hard to explain as no research has shown that pneumonia increases the risk of anticoagulation. Stroke-associated pneumonia (SAP) was reported to be associated with poor prognosis (39), preventing clinicians from initiating anticoagulation in patients. It is unclear whether prevention and improved management of SAP for patients with AIS could increase the use of anticoagulants during hospitalization. Strengthening the prevention and management of complications during the acute phase may lead to improving the anticoagulation rate.

Strength and Limitations

As large cohort research that used patient data from a prospectively constructed database with predefined variables, this study is prone to bias despite how the comprehensive data collection allowed us to take a closer look at specific comorbidities, such as systemic hemorrhage, anemia, and tumor. Another limitation was the lack of information on stroke etiology, size of stroke lesions, and outcomes of patients as data were not available in the complete database. Also, we included data from regional stroke units and both tertiary and secondary hospitals, indicating that our findings could be generalizable. Since patient records were documented by the treating physician, contraindications were sought out as thoroughly as possible in patients who did not receive anticoagulants. However, 11.5% of patients in this study were unclear for the deferring reason, which may underestimate the proportion of anticoagulation contraindications. Finally, the present study was a cross-sectional study. Hence, there is a need for further longitudinal studies to determine the differences made in survival/mortality or stroke recurrence due to undertreatment of AF. Despite these limitations, our study presents a realistic view of the situation where a clinician is placed when deciding whether to use anticoagulant therapy in a given patient. In addition, provides new directions for research and quality improvement targeting anticoagulation.

CONCLUSIONS

Less than half of patients with AIS and AF received guideline-recommended anticoagulation at discharge, while only one in five patients with AF with a high risk of stroke had been using anticoagulants prior to the onset of stroke, which highlights a large care gap in hospitalized patients with stroke. To improve AF management in China, greater efforts must be made to educate both clinicians and patients to increase the rate of anticoagulation and optimize the anticoagulant strategy, including strengthening the health education of patients, improving the comprehensive acute stroke care quality, and enhancing the anticoagulant treatment experience of clinicians.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XG and HC performed the drafting and critical revision of the article and tables. ML had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, performed conceptualization, drafting, and critical revision of the article. The remaining authors were involved in the critical revision of the article. All authors contributed to the article and approved the submitted version.

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Long-Term Efficacy and Anticoagulation Strategy of Left Atrial Appendage Occlusion During Total Thoracoscopic Ablation of Atrial Fibrillation to Prevent Ischemic Stroke

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Objectives: Atrial fibrillation (AF) is associated with an increased ischemic stroke, and the left atrial appendage (LAA) represents the main source of thrombus formation. We evaluated the long-term efficacy of surgical thoracoscopic LAA occlusion during total thoracoscopic ablation of AF to prevent the stroke and anticoagulation strategy after surgery.

Methods: Patients who underwent total thoracoscopic ablation for AF, from February 2012 to May 2020, were included; Patients who did not receive LAA occlusion were excluded. We evaluated the development of thromboembolism in these patients.

Results: The total number of 460 patients [mean age, 57.1 ± 9.2 years; 400 (87.0%) males] were included in the study. The mean follow-up duration was 44.8 months. The mean CHA_2DS_2-VASc score was 1.9 ± 1.6. Median OAC duration was 109.5 days after the surgery, and the final number of patients who discontinued OAC were 411 (89.3%) in total. Anticoagulation discontinuation rate according to CHA_2DS_2-VASc score are as follows; (i) 0 = 99.0%; (ii) 1 = 98.2%; and (iii) ≥2 = 81.3%. The annualized incidence rate of ischemic stroke was 0.78%/year, showing a 73% risk reduction compared with the CHA_2DS_2-VASc predicted rate without anticoagulation. The hazard ratio for ischemic stroke according to previous stroke history was 1.5 [95% confidential interval (CI) 0.3–7.3, $p = 0.62$], and that of remnant LAA was 5.1 (1.2–20.9, $p = 0.02$).

Conclusions: Thoracoscopic LAA occlusion during total thoracoscopic ablation of AF was effective to prevent ischemic stroke. Most patients could discontinue OAC therapy after the procedure. Patients who had a residual trabeculated LAA, or peri-occluder pouch in follow-up CT need to maintain OAC therapy even after LAA occlusion.

Keywords: atrial fibrillation, appendage, thoracoscope surgery, anticoagulation, ischemic stroke

INTRODUCTION

Atrial fibrillation (AF) is associated with an increased risk of ischemic stroke (1). The etiology of ischemic stroke secondary to AF is cardio-embolism, and the most common site of thrombus formation is the left atrial appendage (LAA). Oral anticoagulants are effective on the prevention of thromboembolism. However, some patients experienced an ischemic stroke during the treatment of anticoagulation. Furthermore, anticoagulation increases the risk of bleeding and can cause life-threatening events. LAA closure with devices or surgical LAA occlusion is a potential alternative for this population (2–5). LAA occlusion using a closure device combined with catheter ablation for AF can be performed safely in a single procedure at a reduced stroke rate (6). However, device-related thrombus after LAA closure can develop and is associated with a higher rate of stroke (7). LAA occlusion during other cardiac surgery procedures also reduced stroke risk compared with the no-occlusion group (4). Thoracoscopic ablation is a less invasive approach without opening the cardiac chamber for stand-alone surgery for treatment of AF. Concomitant occlusion of the LAA through a thoracoscopic approach could be performed. The surgical occlusion device is placed epicardially to exclude the trabeculated LAA (8). Little is known about the long-term outcomes and feasibility of these procedures.

In this study, we evaluated the long-term efficacy of surgical thoracoscopic LAA occlusion during total thoracoscopic ablation of AF to prevent ischemic stroke and the anticoagulation strategy after surgery.

METHODS

Study Population

This study was a single-center, retrospective, observational study. Consecutive patients who underwent total thoracoscopic ablation for AF, from February 2012 to May 2020, were included. Patients who converted to open Cox–Maze surgery exhibited underlying moderate to severe mitral stenosis or were subjected to short-term follow-up loss after <1 year were excluded. In addition, patients who did not receive LAA occlusion were excluded. Patients who underwent unilateral pulmonary vein isolation (PVI) or thoracoscopic LAA occlusion only without AF ablation were included (**Figure 1**). We evaluated the development of thromboembolism during follow-ups. This study was approved by the Institutional Review Board of Samsung Medical Center, South Korea (IRB No. 2020-06-159).

Surgical Techniques

Before surgery, all patients underwent transesophageal echocardiography (TEE) to exclude LAA thrombus. Total thoracoscopic ablation procedures were performed under general anesthesia. All procedures were performed using standard techniques as described previously (9). The bilateral thoracoscopic approach was used with a video-assisted thoracoscopic surgical technique. Beginning on the right side, a 5-mm port was introduced into the fourth intercostal space at the mid-axillary line. After carbon dioxide insufflation to expand the operative field and depress the diaphragm, the remaining two ports were placed into the third intercostal space

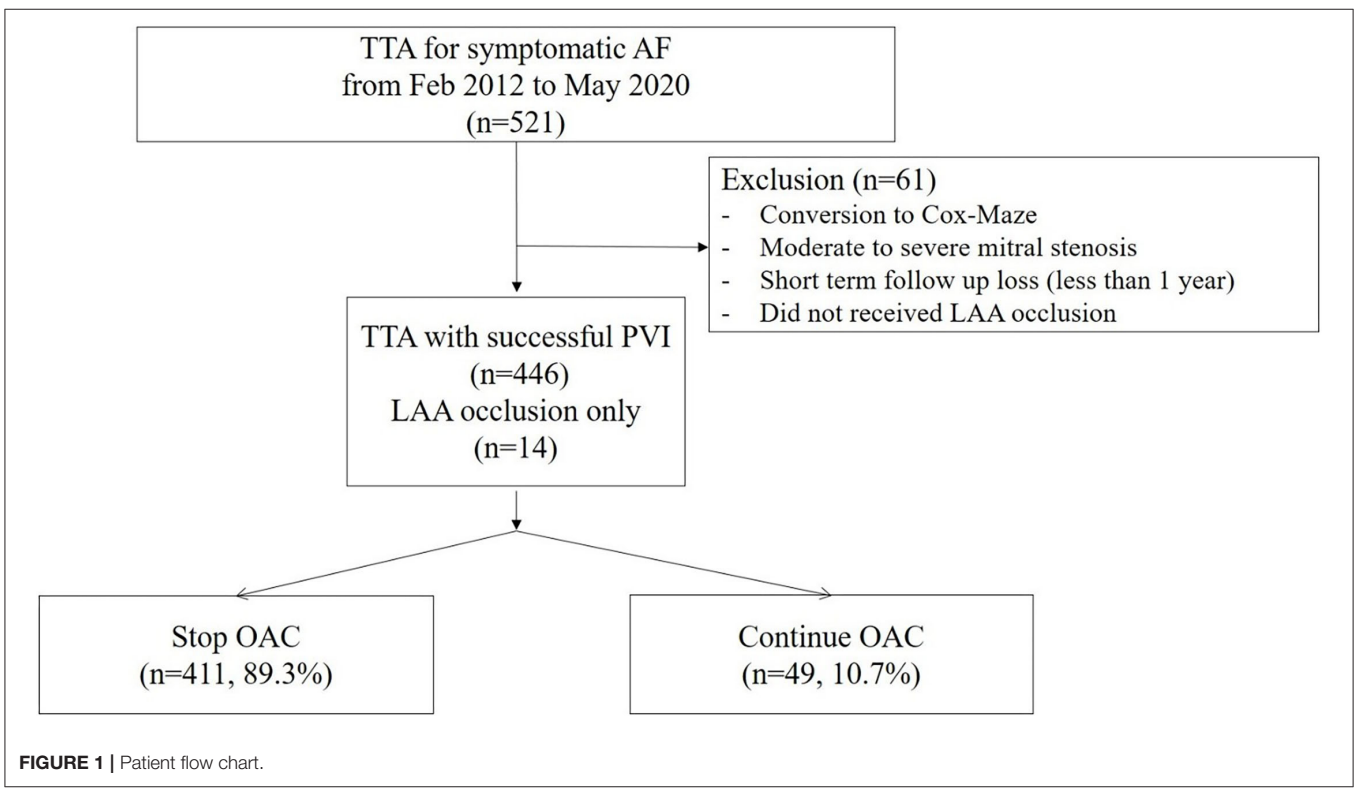

FIGURE 1 | Patient flow chart.

at the anterior axillary line and the sixth intercostal space at the mid-axillary line. After pericardial tenting, a lighted dissector (AtriCure Lumitip Dissector, Atricure, Inc., Cincinnati, OH, USA) was used to pass a rubber band under the PV antrum through the oblique sinus. An AtriCure Isolator Transpolar Clamp (Atricure, Inc.) was connected to the rubber band and positioned around the PV antrum. PV antrum isolation was performed by applying bipolar radiofrequency energy 6 times to the clamps around the PV antrum. Additional superior and inferior ablation lines connecting both PV isolation lines were created epicardially using a linear pen device (MLP, Atricure, Inc.). Ganglionated plexi subsequently were ablated with bipolar radiofrequency energy with the aid of high-frequency stimulation. Confirmation of ablation lines was obtained by pacing testing using the AtriCure Cooltip pen (MAX5, Atricure). The procedure was repeated on the left side. Before PV and ganglionated plexus ablation, the ligament of Marshall was dissected and ablated. When all ablations were complete and the conduction block was confirmed, the left atrial appendage was removed using an Echelon Flex 60 articulating endoscopic linear stapler (Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) (**Figure 2**).

Outcome

The primary outcome was the occurrence of ischemic stroke and thromboembolism after surgery. The etiology of ischemic stroke was evaluated and determined to be procedure-related, cardio-embolic, or resulted from small artery occlusion.

Follow-Up

All patients were followed up by 2 weeks, 3 months, 6 months, and every 6 months thereafter.

Electrocardiography (ECG) was performed at each visit, and 24-h Holter monitoring was performed at three, six, and 12 months and annually thereafter. Additional monitoring was performed when patients experienced tachyarrhythmia symptoms. Follow-up computed tomography (CT) – angiography was performed to identify residual LAA or LA thrombus formation at least 6 months afterwards. Successful LAA occlusion was defined as the absence of a residual trabeculated LAA stump. Other findings such as LA thrombus, accessory appendage, and remnant peri-occluder pouch were evaluated. Oral anticoagulant (OAC) was resumed 1 or 2 days after the procedure with complete hemostasis and continued for at least 3 months.

Statistical Analysis

Statistical analysis was performed using SPSS ver. 27.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using the unpaired *t*-test or Wilcoxon rank-sum test, and categorical variables were compared using either the Chi-squared test or Fisher's exact test as determined appropriate. The incidence rates of clinical events are presented as person-years and events rate curves were obtained by Kaplan–Meier analysis. The risk of thromboembolism was assessed using a Cox proportional hazards model, and is presented as the hazard ratio (HR). A p-value < 0.05 was considered significant.

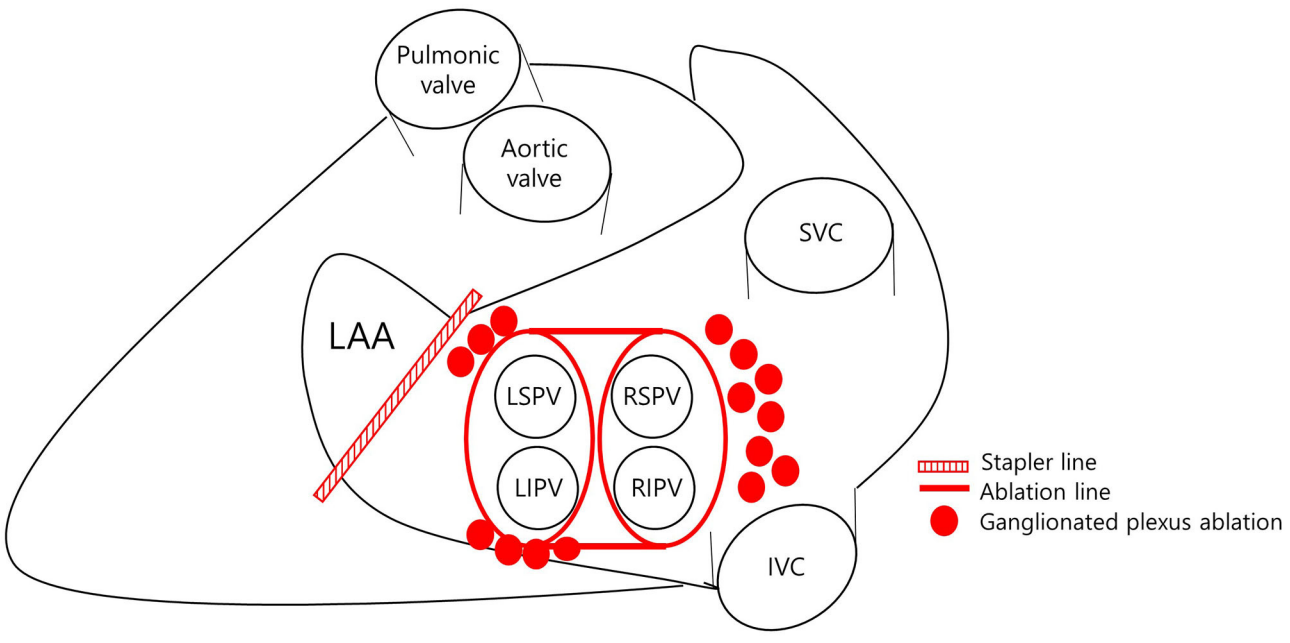

FIGURE 2 | Ablation strategy. LAA, left atrial appendage; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; SVC, superior vena cava; IVC, inferior vena cava.

RESULTS

Baseline Characteristics

The total number of 521 patients underwent the total thoracoscopic ablation procedure, and 61 were excluded from the study. Fifteen patients were converted to open Cox–Maze surgery, three patients were mitral stenosis, 16 patients were lost to follow-up after <1 year, and 27 patients did not receive LAA occlusion due to advanced heart failure or small LAA. 460 patients [mean age, 57.1 ± 9.2 years; 400 (87.0%) males] were included for analysis. Among these patients, 14 received only thoracoscopic LAA occlusion without AF ablation. The mean follow-up duration was 44.8 months. 385 (83.7%) patients exhibited persistent AF and 94 (20.4%) had a previous history of ischemic stroke. The median OAC duration was 109.5 days after the surgery, and the total of 411 (89.3%) patients discontinued OAC. Anticoagulation discontinuation rate according to CHA_2DS_2-VASc score are as follows; (i) 0 = 99.0%; (ii) 1 = 98.2%; and (iii) ≥2 = 81.3%. The mean CHA_2DS_2-VASc score was 1.9 ± 1.6, and 104 (22.6%) patients exhibited score 0 (**Figure 3**). The mean CHA_2DS_2-VASc score excluding the score 0 was 2.4 ± 1.3. Follow-up CT was performed in 337 (73.3%) patients, and 26 (7.7%) patients exhibited remnant LAA. Total 277 (60.2%) patients have maintained sinus rhythm during overall follow-up. The one- and two-year atrial tachyarrhythmia–free survival rates were 84.5 and 70.9%, respectively. The annualized recurrence rate of atrial tachyarrhythmia was 14.2%/year. The other baseline characteristics are summarized in **Tables 1**, **2**.

Outcomes

The annualized incidence rate of ischemic stroke was 0.78%/year, comprising 13 patients, which demonstrated a 73% risk reduction compared with the CHA_2DS_2-VASc-predicted rate without anticoagulation (10). Four patients exhibited procedure

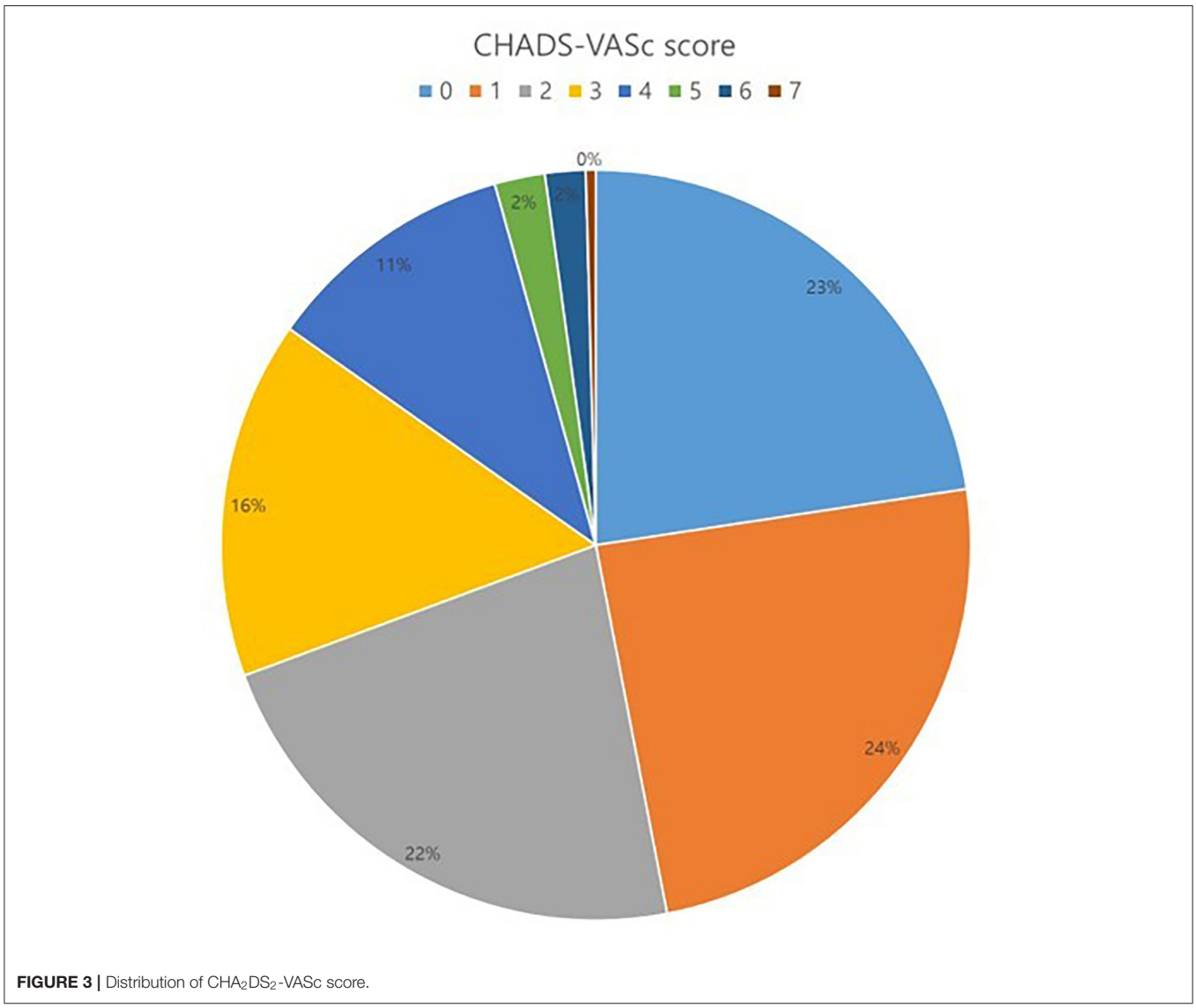

FIGURE 3 | Distribution of CHA_2DS_2-VASc score.

TABLE 1 | Baseline characteristics of overall population.

Variables	All patients (*N* = 460)
Age (years)	57.1 ± 9.2
Sex (male) (*n*, %)	400 (87.0%)
Hypertension (*n*, %)	230 (50.0%)
Diabetes mellitus (*n*, %)	60 (13.0%)
Previous stroke (*n*, %)	94 (20.4%)
Congestive heart failure (*n*,%)	73 (15.9%)
CHA_2DS_2-VASc	1.9 ± 1.6
AF type (*n*, %)	
Paroxysmal	75 (16.3%)
Persistent	100 (21.7%)
LS persistent	285 (62.0%)
EF (%)	59.7 ± 7.2
LA diameter (mm)	46.3 ± 7.2
LA volume index (ml/m^2)	49.7 ± 17.3
E/e'	8.91 ± 3.54

AF, atrial fibrillation; EF, ejection fraction; LA, left atrium; LS, long standing.

TABLE 2 | Baseline characteristics between patients with or without stroke.

Variables	Stroke patients (*N* = 13)	Non-stroke patients (*N* = 447)	*P*-value
Age (years)	62.8 ± 9.4	57.0 ± 9.1	0.05
Sex (male) (*n*, %)	9 (69.2%)	391 (87.5%)	0.08
Hypertension (*n*, %)	6 (46.2%)	224 (50.1%)	1.00
Diabetes mellitus (*n*, %)	3 (23.1%)	57 (12.8%)	0.39
Previous stroke (*n*, %)	4 (30.8%)	90 (20.1%)	0.48
Congestive heart failure (*n*, %)	4 (30.8%)	69 (15.4%)	0.24
CHA_2DS_2-VASc	4.5 ± 1.7	1.8 ± 1.5	<0.001
AF type (*n*, %)			0.56
Paroxysmal	1 (7.7%)	74 (16.6%)	
Persistent	2 (15.4%)	98 (21.9%)	
LS persistent	10 (76.9%)	275 (61.5%)	
EF (%)	58.7 ± 6.2	59.7 ± 7.3	0.62
LA diameter (mm)	45.8 ± 10.2	46.3 ± 7.1	0.78
LA volume index (ml/m^2)	56.1 ± 31.7	49.5 ± 16.7	0.19
E/e'	11.5 ± 5.6	7.5 ±3.7	0.25
OAC treatment	4 (30.8%)	45 (10.1%)	0.04
Incomplete LAA occlusion	3 (33.3%)	23 (7.0%)	0.03
AF recurrence	7 (53.8%)	176 (39.4%)	0.39

AF, atrial fibrillation; EF, ejection fraction; LA, left atrium; LS, long standing; OAC, oral anticoagulation.

related ischemic stroke – three occurred <4 days after the surgery and one was stroke related with an atrial-esophageal fistula after 1 month of the surgery. Four patients had a history of previous embolic stroke. Only one patient experienced an ischemic stroke during OAC therapy. That patient had a history of three previous embolic strokes, and follow-up CT revealed remnant LAA (**Figure 4**). Patient characteristics are summarized in **Table 3**. The annualized incidence rate of ischemic stroke excluding the CHA_2DS_2-VASc score 0 was 0.84%/year, showing a 77% risk reduction (**Figure 5**). Hospitalization due to heart failure aggravation was observed in two patients during follow-up. The procedure related complications are summarized in **Table 4**.

The hazard ratio for ischemic stroke according to previous stroke history was 1.5 [95% confidential interval (CI) 0.3–7.3, $p = 0.62$], those of remnant LAA was 5.1 (1.2–20.9, $p = 0.02$), and CHA_2DS_2-VASc was 2.9 (1.6−−5.2, $p < 0.001$). The recurrence of AF or the use of OAC was not associated with ischemic stroke. The hazard ratio of the recurrence of AF was 0.7 (0.2–2.7, $p = 0.57$), that of OAC use was 2.6 (0.4–15.5, $p = 0.30$) and age was 0.9 (0.8–1.0, $p = 0.21$) (**Figure 6**).

DISCUSSION

This is the largest and longest follow-up study evaluating the efficacy of thoracoscopic LAA occlusion during lone AF surgery for ischemic stroke prevention. Thoracoscopic LAA occlusion can prevent ischemic stroke with a 73% risk reduction. Patients who had previous stroke history or residual LAA in CT findings should maintain OAC therapy even after LAA occlusion.

The Effect of LAA Occlusion

LAA represents the sources of thrombus formation in patients with AF associated with blood stasis. Decreased LAA peak flow velocity is associated with increased thromboembolic risk (11). In addition, LAA morphology correlates with the risk of stroke, especially with an increased number of lobes independent of blood stasis (12). In this regard, several methods were used to perform occlusion of LAA including surgical resection or LAA device occlusion. LAA occlusion with a device can be considered in patients with higher stroke or bleeding risk. The ischemic stroke rate was reduced by 67% with device closure. However, device-related thrombosis was seen in 1.6% of patients (13). Recently, LAA occlusion during cardiac surgery among patients accompanied with AF exhibited a benefit for ischemic stroke prevention compared with the non-occlusion group (4). Several methods including amputation and closure, stapler closure, double-layer linear closure, or closure with a surgical occlusion device were performed without complications or increase in the risk of heart failure or major bleeding. The study included patients scheduled to undergo cardiac surgery with cardiopulmonary bypass and excluded those who underwent off-pump surgery. Cardiopulmonary bypass surgery itself has the risk of thrombus formation compared with off-pump surgery (14). Therefore, early events during the first 30 days after the surgery showed no difference between the two groups associated with peri-procedural stroke. In addition, concomitant surgical ablation of AF was performed in about 30% of patients in both groups in the study. Another small study demonstrated that thoracoscopic

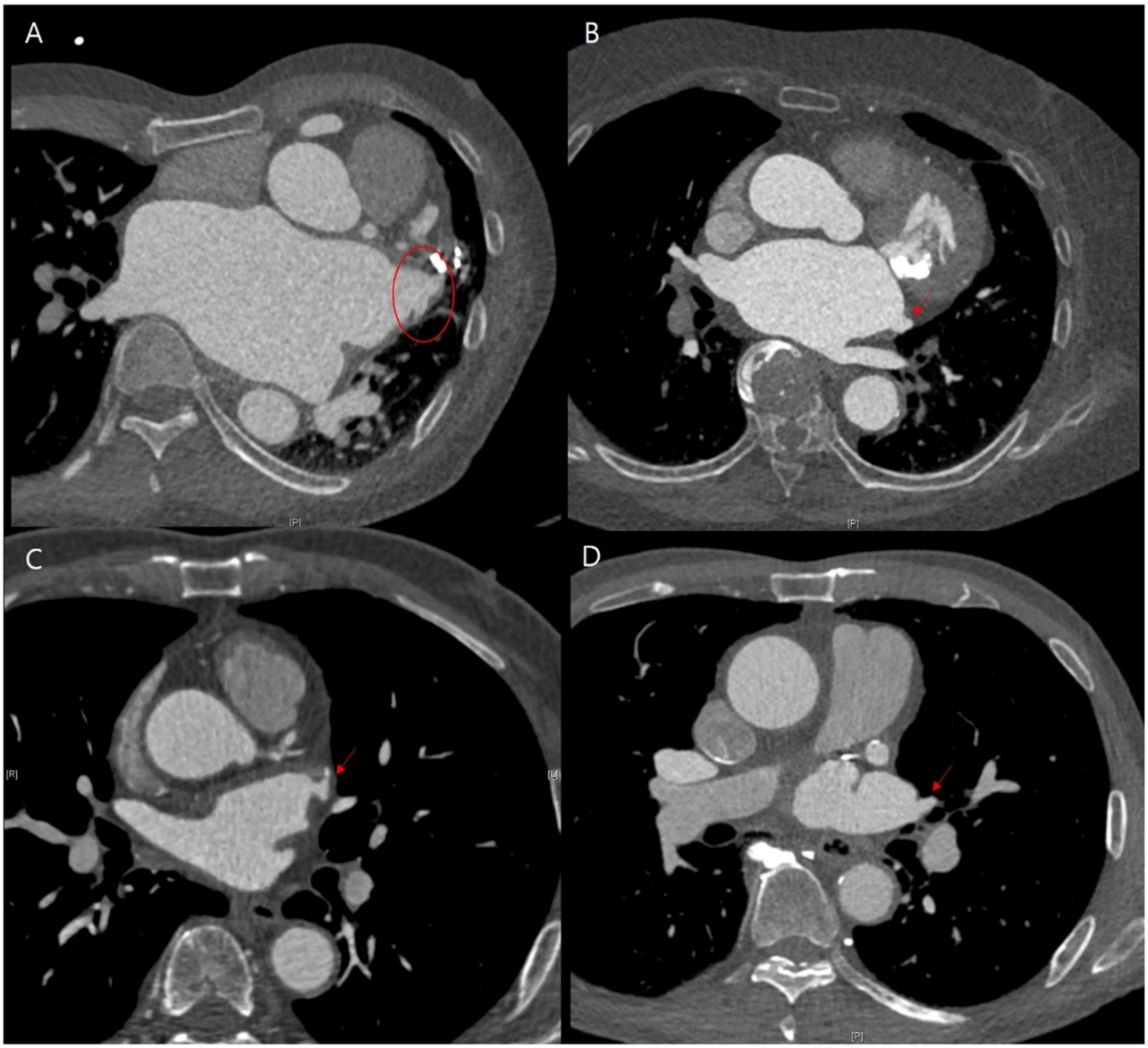

FIGURE 4 | Representative cases of follow-up computed tomography (CT) findings that showed residual left atrial appendage (LAA). **(A,B)** Patients exhibited the occurrence of ischemic stroke, while **(C,D)** did not. **(A)** Residual trabeculated LAA. **(B)** Left atrial accessory appendage and mitral annular calcification without functional mitral stenosis. **(C,D)** Remnant LAA pouch.

ablation with appendage ligation could prevent recurrent stroke in patients with AF with a previous stroke compared to medical therapy (15). In our study, we conducted minimally invasive surgery using video-assisted thoracoscopy concomitant with AF rhythm control surgery without cardiopulmonary bypass. 94 (20.4%) patients had a previous history of ischemic stroke. Although, peri-procedural stroke was observed only in 0.8% of patients. Furthermore, 97% of patients underwent surgical ablation of AF. Maintaining sinus rhythms can have an influence on the risk reduction of thrombus formation after surgery.

The function of the LAA is not well-known. In animal studies, removal of the LAA resulted in decreased compliance of the LA, which was associated with decreased reservoir function (16). In our study, only two exhibited aggravation of heart failure during follow-up. We conducted LAA occlusion using an articulating endoscopic linear stapler targeting the removal of the trabeculated portion and preservation of the basal portion of the LAA, which was confirmed with CT angiography after surgery. This might have affected LA function maintenance with lowered risk of thrombus formation.

TABLE 3 | Detailed characteristics of patients who developed ischemic stroke.

Cases	CHA_2DS_2-VASc score	Previous stroke history	Major stroke (1) TIA (2)	Procedure related stroke	OAC treatment	Residual LAA in CT	AF recurrence
1	3	0	1	1	0		1
2	3	0	1	0	0		1
3	0	0	1	1	0	0	1
4	4	1	1	1	0		1
5	4	0	2	0	0	0	0
6	4	0	1	0	0	0	0
7	1	0	1	0	0	1	0
8	4	1	2	0	0	0	0
9	0	0	2	0	0		1
10	1	0	1	0	0	0	0
11	4	0	1	0	0	1	0
12	4	1	1	1	0	0	1
13	4	1	1	0	1	1	1

TIA, transient ischemic attack; OAC, oral anticoagulant; LAA, left atrial appendage; CT, computed tomography; AF, atrial fibrillation.

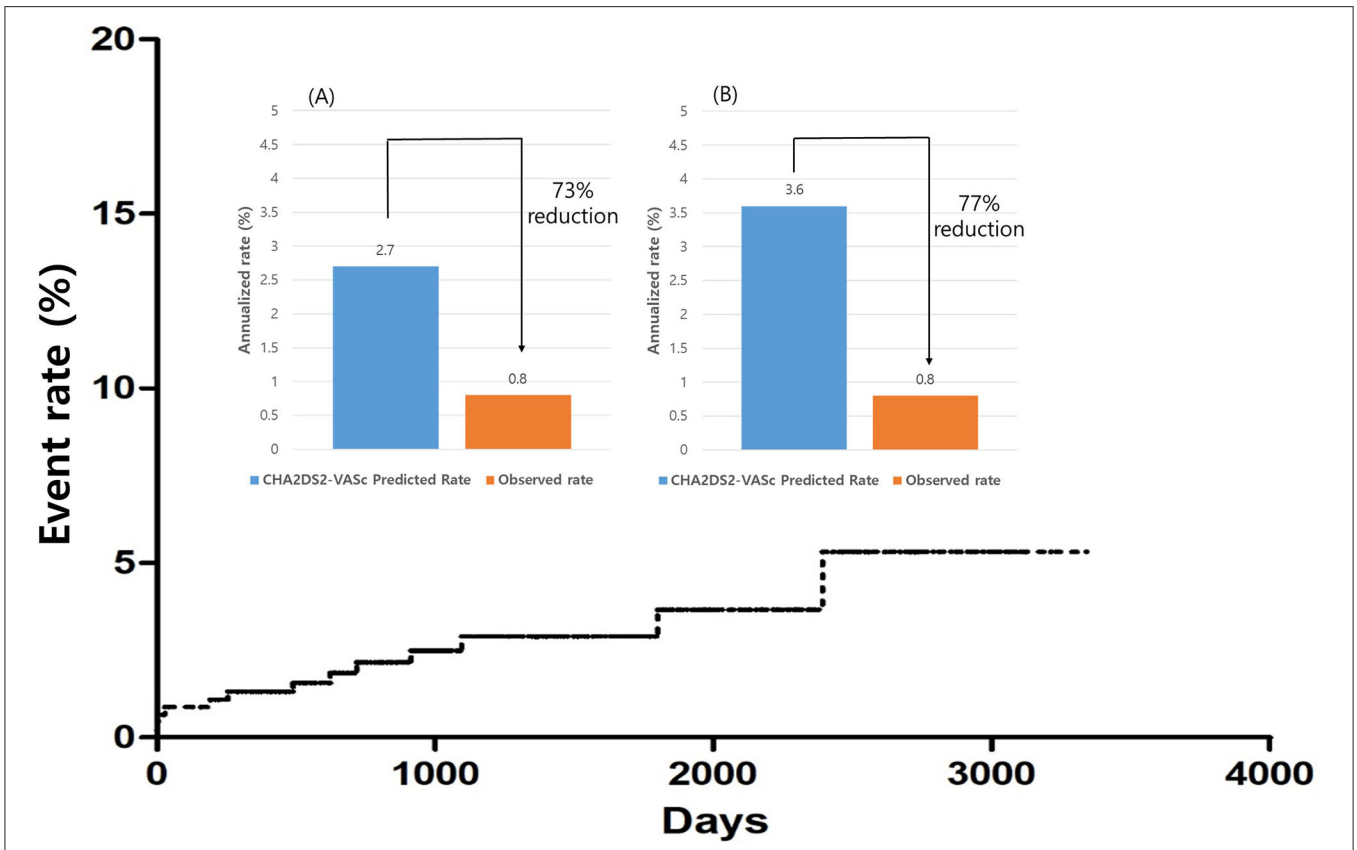

FIGURE 5 | Overall ischemic stroke event rates. Relative ischemic stroke reduction compared with the predicted rate. **(A)** Overall patients. **(B)** Patients other than that with CHA_2DS_2-VASc score 0.

Anticoagulation Strategy

Most of the patients discontinued OAC during the follow-up, and the median OAC use-duration was 109.5 days in our study. Nearly 90% of patients discontinued OAC but showed 73% risk reduction compared with the CHA_2DS_2-VASc predicted rate without anticoagulation. Very few patients developed ischemic stroke after OAC discontinuation.

Lee et al. reported that LAA ligation or stapled excision may increase the embolic risk compared to surgical excision technique due to incompletely elimination of LAA (17). Our study showed that the remnant trabeculated LAA or peri-occluder pouch confirmed with CT was associated with increased ischemic stroke risk. The previous history of stroke exhibited a tendency to increase the risk of ischemic stroke. Therefore, CT findings after surgery were important in determining whether to continue anticoagulation therapy. In addition, patients who had a history of recurrent ischemic stroke should consider continuing OAC therapy.

LIMITATIONS

This is a single-center, single-arm, retrospective registry cohort study. However, most of our patients received a standardized strategy and the same follow-up protocol. Although there was no control group of non-occlusion, the effectiveness of ischemic stroke prevention has been demonstrated through comparisons with CHA_2DS_2-VASc predicted rates. The major limitation of this study is that the mean CHA_2DS_2-VASc score included in the study was 1.9. Patients with CHA_2DS_2-VASc 0 scores have low ischemic stroke rates, and current guidelines recommend no stroke prevention treatment in this group (18). Also, 22% of patients had a CHA_2DS_2-VASc score of 0, hindering discussion of the efficacy of LAA occlusion for these patients. Therefore, we analyzed patients who had CHA_2DS_2-VASc scores of, at least, 1 point and showed greater risk reduction in preventing stroke in this group. In our study, most of the patients had lone AF and our cohort consisted of relatively younger patients. Age is an important risk factor in ischemic stroke, so older patients need to be studied further. Lastly, we included patients who underwent unilateral pulmonary vein isolation or thoracoscopic LAA occlusion only. Rhythm status may affect the occurrence of ischemic stroke, however, the main purpose of this study was to identify whether LAA occlusion is effective in preventing ischemic stroke. Our study results suggested that residual LAA was a risk factor for ischemic stroke.

TABLE 4 | Procedure-related complications.

	All patients (n = 460)
Total	25 (5.4%)
Pacemaker insertion due to bradycardia	5 (1.1%)
Atrioesophageal fistula	1 (0.2%)
Pericarditis	16 (3.5%)
Pleuritis	3 (0.7%)

CONCLUSION

Thoracoscopic LAA occlusion during total thoracoscopic ablation of AF was effective in preventing ischemic stroke without any increase of the additional complications or development of heart failure. Most patients could discontinue OAC therapy after the procedure. Patients who had a residual trabeculated LAA or peri-occluder pouch in follow-up CT need to maintain OAC therapy even after LAA occlusion.

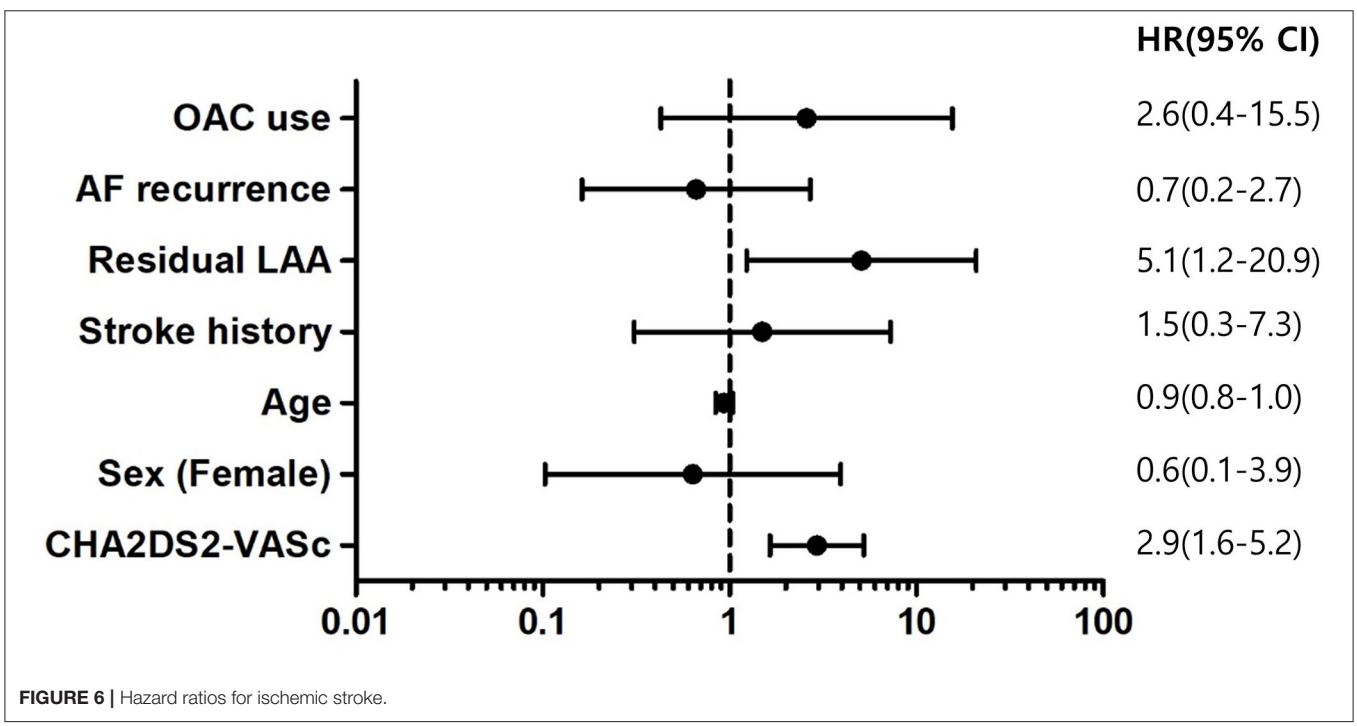

FIGURE 6 | Hazard ratios for ischemic stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Samsung Medical Center, South Korea (IRB No. 2020-06-159). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JYK contributed to study design, data analysis, data interpretation, and writing of the report. DJ contributed to data acquisition, writing, and critical revision of the report. S-JP, K-MP, and JSK contributed to critical revision of the report. YO contributed to study conception and design, data interpretation, and critical revision of the report. All authors contributed to the article and approved the submitted version.

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Optimal Lesion Size Index for Pulmonary Vein Isolation in High-Power Radiofrequency Catheter Ablation of Atrial Fibrillation

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Background: Although both high-power (HP) ablation and lesion size index (LSI) are novel approaches to make effective lesions during pulmonary vein isolation (PVI) for atrial fibrillation (AF), the optimal LSI in HP ablation for PVI is still unclear. Our study sought to explore the association between LSI and acute conduction gap formation and investigate the optimal LSI in HP ablation for PVI.

Methods: A total of 105 consecutive patients with AF who underwent HP ablation guided by LSI (LSI-guided HP) for PVI in our institute between June 2019 and July 2020 were retrospectively enrolled. Each ipsilateral PV circle was subdivided into four segments, and ablation power was set to 50 W with target LSI values at 5.0 and 4.0 for anterior and posterior walls, respectively. We compared the LSI values with and without acute conduction gaps after the initial first-pass PVI.

Results: PVI was achieved in all patients, and the incidence of first-pass PVI was 78.1% (82/105). A total of 6,842 lesion sites were analyzed, and the acute conduction gaps were observed in 23 patients (21.9%) with 45 (0.7%) lesion points. The gap formation was significantly associated with lower LSI (3.9 ± 0.4 vs. 4.6 ± 0.4, $p < 0.001$), lower force-time integral (82.6 ± 24.6 vs. 120.9 ± 40.4 gs, $p < 0.001$), lower mean contact force (5.7 ± 2.4 vs. 8.5 ± 2.8 g, $p < 0.001$), shorter ablation duration (10.5 ± 3.6 vs. 15.4 ± 6.4 s, $p < 0.001$), lower mean temperature (34.4 ± 1.4 vs. 35.6 ± 2.6°C, $p < 0.001$), and longer interlesion distance (4.4 ± 0.3 vs. 4.3 ± 0.4 mm, p = 0.031). As per the receiver operating characteristic analysis, the LSI had the highest predictive value for gap formation in all PVs segments, with a cutoff of 4.35 for effective ablation (sensitivity 80.0%; specificity 75.4%, areas under the curve: 0.87). The LSI of 4.55 and 3.95 had the highest predictive value for gap formation for the anterior and posterior segments of PVs, respectively.

Conclusion: Using LSI-guided HP ablation for PVI, more than 4.35 of LSI for all PVs segments showed the best predictive value to avoid gap formation for achieving effective first-pass PVI. The LSI of 4.55 for the anterior wall and 3.95 for the posterior wall were the best cutoff values for predicting gap formation, respectively.

Keywords: atrial fibrillation, radiofrequency, catheter ablation, pulmonary vein isolation, high-power, lesion size index, conduction gap

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INTRODUCTION

Radiofrequency (RF) ablation for pulmonary vein isolation (PVI) has become the standard treatment for patients with atrial fibrillation (AF) (1). Recent studies have shown that high-power (HP) ablation has been shown to be feasible and effective in achieving a high rate of PVI and reducing procedure complications (2–6). Previous *in vivo* and *ex vivo* studies have demonstrated that, in contrast to conventional low-power (LP) ablation, HP ablation generates a broader zone of direct resistive heating of tissue with a shorter temperature decay time, creating a larger diameter and lesser depth with similar lesion volumes compared with conventional LP ablation (7, 8), which can reduce the risk of steam pops and collateral damage to adjacent structures like the esophagus.

To control and minimize time-dependent deep tissue heat transfer, the ablation duration should be short (2–5 s or no more than 15 s at each location) in the HP setting (9–12). Nevertheless, the subjective determination of each site ablation duration preselected by the operators might lead to incomplete ablation lesions and subsequent increased likelihood of reconnection and gap formation of left atrium-pulmonary vein (LA-PV), which may cause recurrence of AF and atrial tachyarrhythmia/flutter (AT/AFL) (2, 11, 13). The lesion size index (LSI) is a multiparameter index incorporating power, contact force (CF), impedance, and time, and is found to be highly predictive of RF lesion width and depth in *ex vivo* studies, which is a better predictor of RF lesion dimensions than each of its components and is expected to be used as a surrogate end point to determine the duration of ablation (14–16). Recently, it was reported that the HP ablation guided by LSI (LSI-guided HP) could help manage the ablation duration and was shown to be feasible and effective for AF (17, 18). Nevertheless, although several studies have evaluated the optimal LSI cutoff value for predicting acute LA-PV conduction gaps in LP ablation (16, 19), the optimal LSI in HP ablation approach for PVI has yet to be determined. The aim of this study was to explore the efficacy of LSI-guided HP (50 W) ablation technique for PVI and further investigate the association between LSI values and acute conduction gap formation, and further evaluate the optimal LSI in HP ablation for PVI in patients with AF.

METHODS

Study Population

A total of 105 patients with AF who received LSI-guided HP (50 W) ablation for PVI at Fuwai hospital between June 2019 to July 2020 were consecutively enrolled in this study. Prior to the procedure, the patients were required to take anticoagulant agents for at least 4 weeks. The absence of thrombus in the LA was confirmed using cardiac CT angiogram or transesophageal echocardiogram before the procedure. The key exclusion criteria were 1) prior catheter or surgical ablation for AF; 2) valvular-related AF; 3) LA diameter >55 mm, or left ventricular ejection fraction (LVEF) <35%; 4) stroke, or transient ischemic attack within 6 months; and 5) pregnancy. All demographic and clinical data were extracted in the institutional medical record system. All patients signed informed consent forms, and the study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Fuwai Hospital.

LSI-Guided HP Ablation for PVI Procedure

The procedure was performed under conscious sedation anesthesia with fentanyl citrate. Local right cervical and groin anesthesia was performed with lidocaine 1%, 5–10 ml. Under fluoroscopy, the decapolar catheter was placed in the coronary sinus by the right internal jugular vein route. After a double transseptal puncture was performed from right femoral vein access, anticoagulation with heparin was initiated to maintain a target-activated clotting time of 250–350 s. Through transseptal access, a nonsteerable sheath (SL1, 8.5F; Abbott) and a steerable sheath (Agilis, 11.5F; Abbott) were placed into the LA. Then, the 10-pole circular mapping catheter (AFocus II, Abbott) and a CF-sensing catheter with a 3.5-mm tip electrode with six small irrigation holes (TactiCath Quartz; Abbott) were advanced into the LA via the above both sheaths. A three-dimensional electroanatomic mapping system (Ensite V5 system, Abbott) was used to perform an electro-anatomical map of the LA and PVs using the circular mapping catheter.

Contiguous point-by-point ipsilateral PVI for left PVs and right PVs was achieved guided by a three-dimensional mapping system. The decision to perform additional linear ablation depended on the LA substrate and the operator. All ablation lesions were performed using a power-controlled mode with the power limited to 50 W in both the anterior and posterior segments, temperature limit 43°C at 25 ml/min flow rate. The target CF was between 5 and 15 g with target LSI values at 5.0 and 4.0 for anterior and posterior walls, respectively (16). Once the target LSI was reached, the RF application was stopped, and the catheter was moved to an adjacent spot. The ablation duration should not be over 30 s for each ablation point, otherwise reablation was performed after adjusting CF. Surface 12-lead ECG and intracardiac electrograms were recorded continuously at a speed of 100 mm/s on LabSystem Pro (Bard Electrophysiology, Lowell, MA).

AutoMark Settings

In this study, PVI was conducted with the AutoMark system (Abbott), which automatically detects the ablation duration and calculates force–time integral (FTI) and LSI for each lesion only when the ablation catheter stays within the confined area. FTI was defined as the total CF integrated over the time of RF application. LSI is calculated and displayed in real time that aggregates CF and RF current data across time and is calculated as follows (15):

$$LSI = b_0\left(1 - \frac{-F}{b_1} + b_2\right)\left(1 - e^{\frac{-I^2}{b_3^2}}\right)\left(1 - b_4 + \frac{b_4\left(1 - \frac{-T}{b_5}\right)}{1 - \frac{-60}{b_5}}\right)$$

where LSI is the lesion index (arbitrary units); b_{0-5} are scaling constants; F is a 6-s sliding window average of CF; I is a 6-s sliding window average of RF current; and T is time.

For catheter position stability, AutoMark settings for filter thresholds were the minimum marker time was 3 s, the marker

spacing was 6 mm, and the away time was 5 s. The lesion tag size was 4 mm, and the target interlesion distance (ILD) between the two neighboring lesions was 5 mm or less according to the recommendation of a previous study (20, 21).

Pulmonary Vein Segments and Ablation Parameters

For each ipsilateral pair of PVs, we divided the PV antrum into four regions, including two segments at the anterior wall and two segments at the posterior wall, respectively (as shown in **Figure 1A**). A total of 210 PV circles (840 PV segments) were analyzed and ablation points were assigned to each segment of the PV antrum. Allowing for a detailed ablation lesion analysis, the following parameters of each ablation site, including FTI, LSI, RF power, CF, RF duration, impedance drop (Δ-Imp), RF temperature, and ILD, were analyzed offline and quantitative measurements for the respective eight circumferential PVs segments were performed in each patient.

The Definition of Conduction Gaps

PVI was verified as the absence of any PV or LA potential in the PV antral ablation area using a circular catheter and/or the ablation catheter, and bidirectional conduction block between the PV and the LA were also assessed. First-pass PVI was defined if PVI was achieved following complete circumferential PV antral ablation surrounded by a line of contiguous ablation lesions. PVs were further assessed for acute conduction gap formation after a minimum 30-min waiting period of the first-pass completion of ipsilateral circumferential PVs ablation. The location of conduction gap was detected by using the circular catheter and ablation catheter, which was located just adjacent to the ablation line as close as possible, and was defined as a change of clear activation sequence or elimination of PV potential from the LA to PV caused by additional RF application. When one gap site included multiple ablation points with the target tag size, all of these ablation points were counted as gaps. For each subject, the ablation map was carefully reviewed and analyzed offline

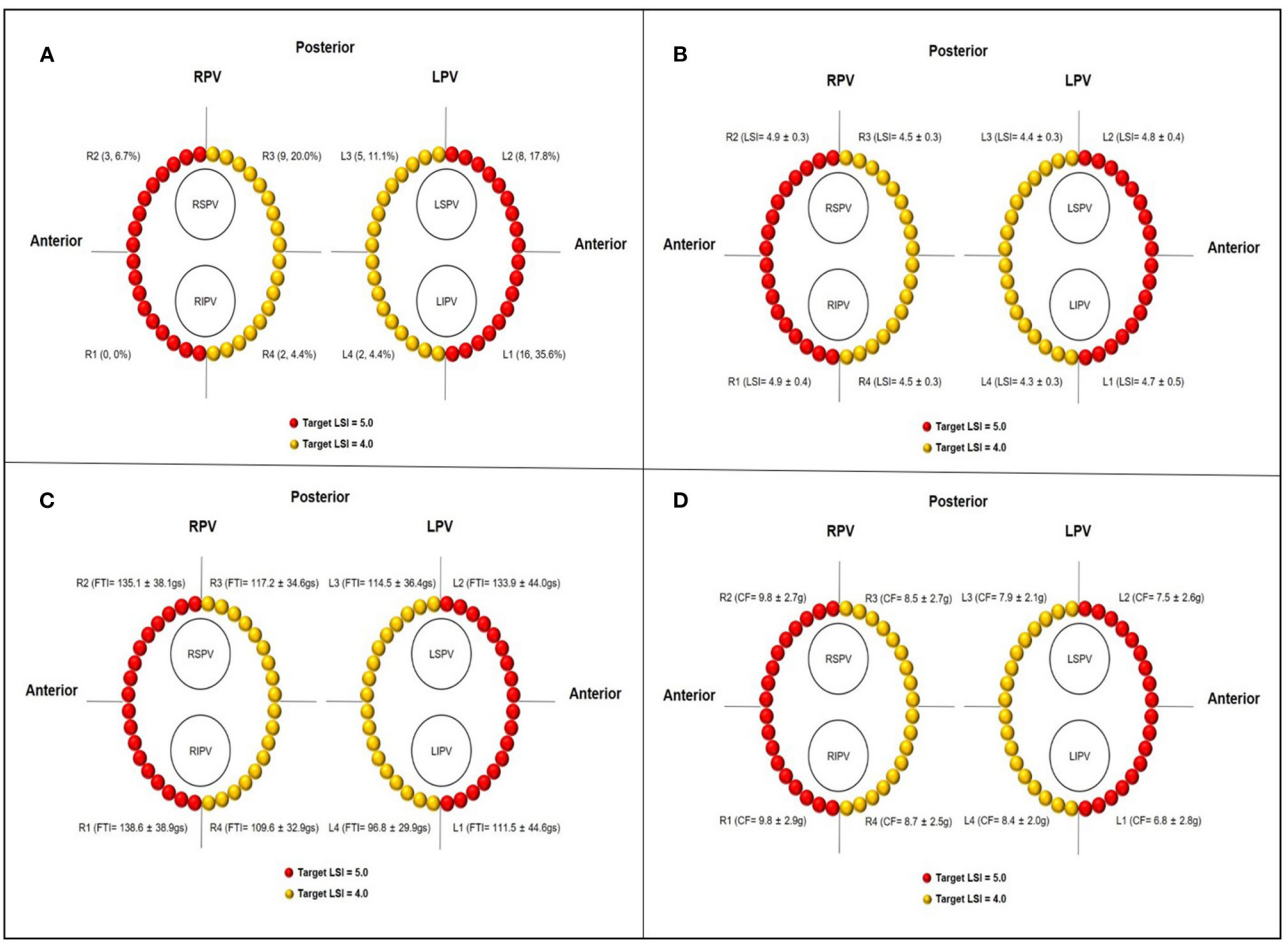

FIGURE 1 | (A) Schematic diagrams of target LSI at different PVs segments and distribution of conduction gaps after first-past PVI attempt. **(B–D)** The actual regional LSI, FTI, and CF at different PVs segments, respectively. LPV, left pulmonary vein; RPV, right pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; L1 and R1, anterior inferior segments of LPV and RPV, respectively; L2 and R2, anterior superior segments of LPV and RPV, respectively; L3 and R3, posterior superior segments of LPV and RPV, respectively; L4 and R4, posterior inferior segments of LPV and RPV, respectively.

to identify the conduction gap localization for the respective 8 circumferential PVs segments.

Statistical Analysis

Continuous data are presented as mean ± SD, and dichotomous data are expressed as numbers and percentages. A comparison of continuous variables between different PVs segments was performed with a one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* testing. A comparison of ablation characteristics with and without conduction gaps was performed using the unpaired samples *t*-test. The univariable and multivariable binary logistic regression analysis used parameters that have already been reported to have a relationship with conduction gaps, and the *p*-values were <0.05 to predict conduction gaps. The predictive value of different threshold levels of ablation parameters for conduction gaps was assessed using sensitivity, specificity, and receiver operating characteristic (ROC) curve analysis. A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed with SPSS for Windows, version 22.0 (SPSS, Chicago, USA).

RESULTS

Patient and Procedure Characteristics

The clinical and procedure characteristics at baseline are summarized in **Table 1**. Of those, 76 (72.4%) were men. The mean age was 57.8 ± 9.8 years, and the mean body mass index was 26.0 ± 3.1 kg/m^2. The whole study cohort included 59 patients with paroxysmal AF and 46 patients with persistent AF with a mean LA diameter of 39.5 ± 5.5 mm and mean LVEF of 62.0 ± 5.9 %. All patients with targeted PVs (210 ipsilateral veins) were successfully isolated following RF ablation procedure. The first-pass PVI was achieved in 82 (78.1%) patients. The total RF duration for PVI per procedure was 30.4 ± 6.8 min, and the mean fluoroscopy time was 38.0 ± 27.7 s with mean ablation points of 65.6 ± 10.6.

Steam pops without pericardial effusion were found in 3 (0.04%) out of 6,842 lesions and in 3 (2.9%) out of 105 patients, including 2 in the anterior superior segments of right pulmonary vein (RPV) and 1 in the anterior ridge segment of left pulmonary vein (LPV). The mean CF, time and LSI at the site of the steam pops in three patients were 21 g, 6 s, 5.1; 25 g, 5 s, 5.6; 27 g, 6 s, 5.9, respectively. An arteriovenous fistula was found at the puncture site of the right femoral vein in three patients (2.9%) and one patient (1.0%) had a pseudoaneurysm. No esophageal injury, phrenic nerve injury, cardiac tamponade, or stroke occurred.

Ablation Lesion Analysis

As shown in **Figures 1B–D** and **Table 2**, the total number of RF application was 6,842 with 3,269 for the LPV circles and 3,573 for the RPV circles. Overall, the mean LSI value and FTI per lesion were 4.6 ± 0.4 and 120.6 ± 40.4 gs based on ablation duration of 15.4 ± 6.4 s and mean CF of 8.4 ± 2.8 g. The mean Δ-Imp (%) per lesion was 17.3 ± 6.9 Ω (13.8 ± 4.4%), and the mean temperature per lesion was 35.5 ± 2.6°C. The mean ILD between two neighboring lesions was 4.3 ± 0.4 mm. Compared with the ablation lesion parameters of respective left and right posterior segments, left and right anterior segments have significantly higher mean CF and mean temperature, longer ILD and higher LSI (all $p < 0.05$), and tended to have higher FTI, longer ablation duration, and larger mean Δ-Imp.

TABLE 1 | Baseline clinical and procedure characteristics.

	Study patients ($n = 105$)
Age, yrs	57.8 ± 9.8
Male, %	76 (72.4)
BMI, kg/m^2	26.0 ± 3.1
History of AF, mths	33.8 ± 30.6
CHA_2DS_2-VASc score	1.3 ± 1.2
Paroxysmal AF	59 (56.2)
Persistent AF	46 (43.8)
Complications	
Hypertension	43 (41.0)
Diabetes mellitus	9 (8.6)
Coronary artery disease	12 (11.4)
Stroke	3 (2.9)
Heart failure	6 (5.7)
Echocardiography	0.19 ± 0.49
LAD, mm	39.5 ± 5.5
LVEF, %	62.0 ± 5.9
Procedure	
PVI only	67 (63.8)
Ablation points for PVI	65.6 ± 10.6
Ablation duration for PVI, min	30.4 ± 6.8
Fluoroscopy time for PVI, s	38.0 ± 27.7
Additional line ablation	38 (36.2)

The data are presented as the numbers (%) or the mean ± SD. BMI, body mass index; AF, atrial fibrillation; CHA2DS2-VASc score, congestive heart failure, hypertension, age (≥75 years), diabetes, stroke/transient ischemic attack, vascular disease, age (65-74 years), sex female; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation.

Gaps Distribution

PVs' conduction gaps were detected at 45 (0.7%) points in 7 (87.5%) PV segments in 23 (21.9%) patients. The distribution of gaps within each segment of the PVs is illustrated in **Figure 1A**. The greatest number of gaps was 16 (35.6%) in the anterior inferior segments of LPV, followed by 9 (20.0%) in the posterior superior segments of RPV and 8 (17.8%) in the anterior ridge segment of LPV, no gaps were found in the anterior inferior segments of RPV. Moreover, gaps were concentrated in the anterior segments of PVs (27, 60.0%), which was significantly more than gaps (18, 40.0%) in the posterior segments of PVs.

Ablation Parameters With and Without Gaps

The ablation characteristics with and without gaps are shown in **Table 3**. Although the min CF and mean Δ-Imp were not significantly different between the two groups, the max and mean CF, as well as max, min, and mean temperature, were significantly lower, the ablation duration per RF application was significantly

TABLE 2 | Ablation lesion results per segment.

		Left PV circle, $n = 105$ Left PV lesion, $n = 3269$				Left PV circle, $n = 105$ Left PV lesion, $n = 3573$			
	Overall	**L1 segment**	**L2 segment**	**L3 segment**	**L4 segment**	**R1 segment**	**R2 segment**	**R3 segment**	**R4 segment**
Lesions, n	6842	966	929	711	663	866	946	878	883
Max CF, g	29.3 ± 14.7	26.6 ± 14.6	22.4 ± 11.9*	27.0 ± 13.5	25.9 ± 10.7	30.1 ± 14.2*	26.5 ± 10.7*	38.5 ± 16.3	36.5 ± 16.3
Min CF, g	1.0 ± 1.5	0.9 ± 1.7*	1.2 ± 1.7	1.2 ± 1.5	1.2 ± 1.4	0.9 ± 1.3*	1.6 ± 1.7*	0.7 ± 1.1	0.8 ± 1.2
Mean CF, g	8.4 ± 2.8	6.8 ± 2.8*	7.5 ± 2.6*	7.9 ± 2.1	8.4 ± 2.0	9.8 ± 2.9*	9.8 ± 2.7*	8.5 ± 2.7	8.7 ± 2.5
Max temperature, °C	37.5 ± 3.2	37.4 ± 2.9*	39.0 ± 3.2*	36.2 ± 2.7	36.0 ± 2.6	39.4 ± 3.1*	39.1 ± 3.2*	35.7 ± 2.3	36.1 ± 2.6
Min temperature, °C	34.0 ± 2.9	33.8 ± 2.6*	35.3 ± 3.0	32.8 ± 2.4	32.8 ± 2.3	35.7 ± 2.9*	35.4 ± 2.9*	32.6 ± 2.1	32.9 ± 2.3
Mean temperature, °C	35.5 ± 2.6	35.3 ± 2.4*	36.6 ± 2.8*	34.5 ± 2.2	34.4 ± 2.2	37.0 ± 2.7*	36.8 ± 2.7*	34.4 ± 2.0	34.6 ± 2.1
Mean Δ-Imp, Ω	17.3 ± 6.9	19.7 ± 8.2*	18.3 ± 7.1*	17.4 ± 6.4	14.8 ± 5.3	17.4 ± 7.0	16.4 ± 6.9	17.5 ± 6.7	16.3 ± 5.6
Mean Δ-Imp, %	13.8 ± 4.4	15.6 ± 5.1*	14.5 ± 4.6*	13.6 ± 3.9	12.5 ± 3.6	13.7 ± 4.2	12.9 ± 4.3	13.7 ± 4.1	13.2 ± 3.8
RF duration, s	15.4 ± 6.4	18.1 ± 8.7*	19.2 ± 7.8*	15.0 ± 4.9	11.8 ± 3.7	15.1 ± 5.4	14.6 ± 5.0	14.7 ± 5.1	13.2 ± 4.5
ILD, mm	4.3 ± 0.4	4.4 ± 0.4*	4.4 ± 0.5*	4.3 ± 0.4	4.2 ± 0.3	4.3 ± 0.4*	4.6 ± 0.4*	4.1 ± 0.2	4.2 ± 0.3
FTI, gs	120.6 ± 40.4	111.5 ± 44.6	133.9 ± 44.0*	114.5 ± 36.4	96.8 ± 29.9	138.6 ± 38.9*	135.1 ± 38.1*	117.2 ± 34.6	109.6 ± 32.9
LSI	4.6 ± 0.4	4.7 ± 0.5*	4.8 ± 0.4*	4.4 ± 0.3	4.3 ± 0.3	4.9 ± 0.4*	4.9 ± 0.3*	4.5 ± 0.3	4.5 ± 0.3

*The data are presented as the numbers (%) or the mean ± SD. PV, pulmonary vein; CF, contact force; Δ-Imp, impedance drop; ILD, interlesion distance; FTI, force–time integral; LSI, lesion size index. *$p < 0.05$ (compared with ablation lesion parameters of respective left and right posterior segments). Abbreviations of pulmonary vein segments are as shown in **Figure 1**.*

TABLE 3 | Comparison of ablation lesion characteristics with and without gaps.

	Without gap ($n = 6797$)	**With gap ($n = 45$)**	***P*-value**
Max CF, g	29.3 ± 14.7	23.5 ± 13.0	0.008
Min CF, g	1.0 ± 1.5	0.8 ± 1.2	0.243
Mean CF, g	8.5 ± 2.8	5.7 ± 2.4	<0.001
Max temperature, °C	37.5 ± 3.2	36.0 ± 1.6	<0.001
Min temperature, °C	34.0 ± 2.9	32.7 ± 1.4	<0.001
Mean temperature, °C	35.6 ± 2.6	34.4 ± 1.4	<0.001
Mean Δ-Imp, Ω	17.3 ± 6.9	18.3 ± 8.5	0.329
Mean Δ-Imp, %	13.8 ± 4.3	13.9 ± 5.3	0.816
RF duration, s	15.4 ± 6.4	10.5 ± 3.6	<0.001
ILD, mm	4.3 ± 0.4	4.4 ± 0.3	0.031
FTI, gs	120.9 ± 40.4	82.6 ± 24.6	<0.001
LSI	4.6 ± 0.4	3.9 ± 0.4	<0.001

The data are presented as the mean ± SD. CF, contact force; Δ-Imp, impedance drop; ILD, interlesion distance; FTI, force–time integral; LSI, lesion size index.

shorter, and the mean ILD was significantly longer in the lesions with gaps than those without gaps. Furthermore, the LSI (3.9 ± 0.4 vs. 4.6 ± 0.4, $p < 0.001$) and FTI (82.6 ± 24.6 vs. 120.9 ± 40.4 gs, $p < 0.001$) were significantly lower in the gap group compared with the nongap group.

For anterior segments, the max, min and mean CF, and temperature were significantly lower, and the ablation duration per lesion was significantly shorter in the gap group compared with the nongap group. For posterior segments, mean CF was significantly lower, the ablation duration per lesion was significantly shorter, and the mean ILD was significantly longer in patients with gaps compared with those without gaps. Not only anterior segments but also posterior segments, both of the LSI and FTI, were significantly lower in the gap group compared with the nongap group (**Table 4**).

Relationships Between Ablation Parameters and Gap Formation

As shown in **Table 5**, after adjusting for confounding factors of the significant ablation parameters, the multivariable analysis has shown that LSI was identified as an independent predictor of acute conduction gap formation [odds ratio (OR): 0.62; 95% CI: 0.54 to 0.71, $p < 0.001$). **Figure 2A** presents the ROC curve analysis for LSI, FTI, CF, RF duration, Δ-Imp, and ILD to determine the thresholds for predicting the presence of acute conduction gap formation. The area under the curve (AUC) values for LSI, FTI, CF, RF duration, Δ-Imp, and ILD were 0.87, 0.79, 0.78, 0.75, 0.51, and 0.60, respectively. Compared to other ablation parameters, LSI showed the best predictive value with an AUC of 0.87 and the cutoff value of LSI on the ROC curve was 4.35 (sensitivity 80.0%; specificity 75.4%, $p < 0.0001$). Hence, the LSI of 4.35 showed the best predictive value for gap formation in all PVs' segments. In addition, following stratification by PVs' segments, the LSI of 4.55 had the highest predictive value for gap formation for the anterior segments (AUC 0.90; sensitivity 96.3%; specificity 75.8%, $p < 0.0001$) and the lower LSI of 3.95 showed a relatively high sensitivity of 72.2% and specificity of 92.3% for posterior segments (AUC 0.85, $p < 0.0001$), respectively, as shown in **Figures 2B,C**.

DISCUSSION

In this study, we explored the efficacy of LSI-guided HP ablation technique for PVI and further elucidated the relationship

TABLE 4 | Comparison of ablation lesion characteristics of anterior and posterior segments with and without gaps.

	Anterior segments			Posterior segments		
	Without gap (*n* = 3680)	**With gap (*n* = 27)**	***P*-value**	**Without gap (*n* = 3,117)**	**With gap (*n* = 18)**	***P*-value**
Max CF, g	26.5 ± 13.2	21.4 ± 12.9	0.049	32.7 ± 15.7	26.6 ± 12.8	0.100
Min CF, g	1.1 ± 1.6	0.5 ± 0.9	0.001	0.9 ± 1.3	1.2 ± 1.4	0.298
Mean CF, g	8.5 ± 3.1	4.8 ± 2.0	<0.001	8.4 ± 2.4	7.1 ± 2.5	0.020
Max temperature, °C	38.7 ± 3.2	36.2 ± 1.3	<0.001	36.0 ± 2.5	35.6 ± 1.9	0.437
Min temperature, °C	35.1 ± 2.9	32.9 ± 1.2	<0.001	32.7 ± 2.3	32.3 ± 1.7	0.182
Mean temperature, °C	36.4 ± 2.7	34.6 ± 1.2	<0.001	34.5 ± 2.1	34.1 ± 1.6	0.441
Mean Δ-Imp, Ω	18.0 ± 7.4	18.6 ± 8.7	0.638	16.6 ± 6.1	18.0 ± 8.5	0.324
Mean Δ-Imp, %	14.2 ± 4.7	14.3 ± 5.6	0.908	13.3 ± 3.9	13.4 ± 5.0	0.920
RF duration, s	16.9 ± 7.2	10.0 ± 3.5	<0.001	13.7 ± 4.8	11.2 ± 3.8	0.023
ILD, mm	4.4 ± 0.4	4.4 ± 0.3	0.721	4.2 ± 0.3	4.5 ± 0.3	0.001
FTI, gs	129.8 ± 42.9	86.4 ± 24.6	<0.001	110.3 ± 34.4	77.0 ± 24.3	<0.001
LSI	4.8 ± 0.4	3.9 ± 0.5	<0.001	4.4 ± 0.3	3.9 ± 0.4	<0.001

The data are presented as the mean ± SD. CF, contact force; Δ-Imp, impedance drop; ILD, interlesion distance; FTI, force–time integral; LSI, lesion size index.

TABLE 5 | The univariable and multivariable logistic regression analysis for predicting acute conduction gap formation.

	Univariable		Multivariable	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
LSI	0.58(0.52 - 0.62)	<0.001	0.62(0.54 - 0.71)	<0.001
FTI	0.94(0.93 - 0.95)	<0.001	1.02(0.99 - 1.05)	0.156
Mean CF	0.61(0.53 - 0.70)	<0.001	0.69(0.49 - 0.97)	0.031
RF duration	0.80(0.74 - 0.87)	<0.001	0.82(0.69 - 0.98)	0.028
Mean Δ-Imp	1.02(0.98 - 1.06)	0.328	1.02(0.97 - 1.07)	0.433
ILD	1.79(0.90 - 3.57)	0.095	1.08(0.99 - 1.18)	0.059

OR, odds ratio; CI, confidence interval; LSI, lesion size index; FTI, force-time integral; CF, contact force; RF, radiofrequency; Δ-Imp, impedance drop; ILD, interlesion distance.

between LSI and gap formation, as well as the best cutoff value, to predict gap formation following LSI-guided HP ablation for PVI in a Chinese AF cohort. The most important finding of this study was that LSI-guided HP ablation contributed to isolation of all targeted PVs with a higher first-pass PVI rate. Furthermore, most of the conduction gaps were concentrated in anterior wall while no or few gaps were observed in the posterior wall, and LSI was significantly lower in the gap group compared with the nongap group. In addition, our results showed that LSI turned out to be a strong independent predictor of acute conduction gap formation, and more than 4.35 of LSI for all PVs' segments showed the best predictive value to avoid gap formation for achieving effective first-pass PVI. The optimal LSI of 4.55 for the anterior wall and 3.95 for the posterior wall were the best cutoff values for detecting conduction gaps, respectively.

As is known, long-lasting, continuous, and transmural PVI has the greatest effect on the long-term atrial arrhythmia-free survival, and it is still a clinical challenge (1). Compared to conventional LP ablation, HP ablation distinctly increases resistive heating and decreases conductive heating, avoiding damage depth excessively and thus reducing the risk of adjacent tissue damage, especially esophageal injury (22, 23). Although HP ablation has already acted as a meaningfully efficient and safe strategy for treating AF, it did not significantly reduce the recurrence of AT/AFL compared with conventional LP ablation (24, 25). Recurrent AT/AFL was frequently associated with the reconnection of conduction gaps in the circumferential PVI lines, as well as extrapulmonary areas, following HP ablation (26, 27). Hence, optimization of procedural parameters, including power and duration for HP ablation, is critical for the creation of durable transmural lesions without collateral injury.

LSI is derived from a mathematical expression that incorporates power, CF, impedance, and time, which could predict accurately lesion dimensions by the experimental study and was reported to be related to higher single ablation success rate and lower rate of acute conduction gap formation, subsequently to minimize AT/AF recurrence following PVI (15, 28). Thus, it is important to note that combining the advantage of both HP ablation and LSI may preferably improve the procedural efficacy. Using LSI-guided HP ablation strategy for PVI in our study, despite a relatively low CF of 8.4 ± 2.8 g in our series, all targeted PVs were successfully isolated with a shortening ablation duration of 15.4 ± 6.4 s without severe complications other than steam pop. The first-pass PVI rate was 78.1% in our study, and the incidence of first-pass PVI was reasonably higher and the subsequent incidence of acute conduction gap formation was quite lower when compared to previous LP ablation studies with an average of 61.8% of first-pass PVI (29). The development of tissue edema and subsequent nontransmural lesion, as well as loss of proper tissue CF or catheter dislodgement during prolonged LP ablation, may lead to a lower incidence of first-pass PVI and a higher probability of gap formation. On the contrary, when following an LSI-guided HP ablation strategy, the use of higher power translates into

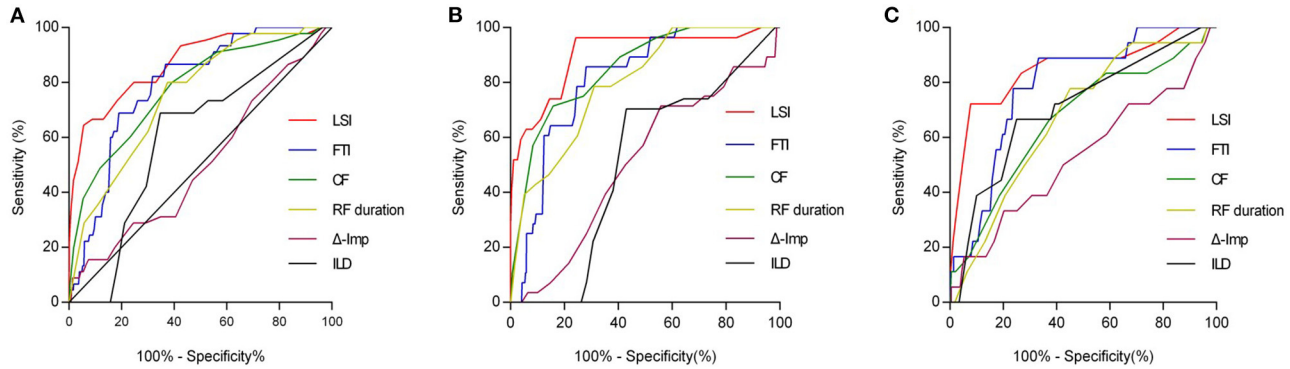

FIGURE 2 | ROC curve analysis for predicting acute conduction gap formation. **(A)** LSI showed the best predictive value with the AUC curve of 0.87 for all PVs segments. AUC values for FTI, CF, RF duration, Δ-Imp, and ILD were 0.79, 0.78, 0.75, 0.51, and 0.60, respectively. The optimal LSI threshold for predicting gap for all PVs segments was 4.35 (sensitivity 80.0%; specificity 75.4%, $p < 0.0001$). **(B)** For anterior wall of PVs, LSI showed the best predictive value with the AUC curve of 0.90. AUC values for FTI, CF, RF duration, Δ-Imp, and ILD were 0.81, 0.85, 0.80, 0.51, and 0.51, respectively. The optimal LSI threshold for anterior wall of PVs was 4.55 (sensitivity 96.3%; specificity 75.8%, $p < 0.0001$). **(C)** For posterior wall of PVs, LSI also showed the best predictive value with the AUC curve of 0.85. AUC values for FTI, CF, RF duration, Δ-Imp, and ILD were 0.79, 0.67, 0.67, 0.53, and 0.71, respectively. The optimal LSI threshold for posterior wall of PVs was 3.95 (sensitivity 72.2%; specificity 92.3%, $p < 0.0001$). ROC, receiver operating characteristic; LSI, lesion size index; AUC, area under the curve; PV, pulmonary vein; FTI, force-time integral; CF, contact force; RF, radiofrequency; Δ-Imp, impedance drop; ILD, interlesion distance.

distinctly shorter ablation duration, HP ablation could improve the catheter stability in a short time, achieve transmural injuries by predominant resistive heating, and reduce the conduction gaps, generating a higher first-pass PVI rate (23). Furthermore, in recent POWER-FAST PILOT and PILOT-AF study (17, 18), the first-pass PVI rate was 57% and 73.8% following LSI-guided HP ablation, respectively, which were relatively lower than that in this study. In spite of the similar ablation parameter settings as our study, including energy power output and target LSI, a higher incidence of first-pass PVI in our study may potentially be attributed to the more remarkably shorter RF duration per lesion and better stable tissue contact.

Although the role of LSI in PVI during LP ablation has been well recognized (14, 16, 30), and the optimal LSI in HP ablation to create transmural lesions and avoid conduction gaps remains unclear. In this study, to our knowledge, we are the first to elucidate the relationship between LSI and gap formation, as well as the best cutoff value, to predict gap formation following HP ablation for PVI. Theoretically, increasing LSI values could generate larger lesions and enhance a higher probability of contiguity and transmurality, but bring a higher potential risk of collateral damage (15). It is of great importance to identify the optimal target LSI value providing the best compromise between efficacy and safety. In line with a previous study conducted by Wang et al. (31), we found that more gaps were frequently concentrated in the anterior wall than those in the posterior wall. Moreover, we detected that the LSIs were significantly lower in the gap group compared with the nongap group and low LSI was significantly related to the formation of conduction gap regardless of anterior or posterior segments of PVs. When combined in a multivariable model, LSI represented a strong independent predictor of acute conduction gap formation. On ROC curve analysis, an LSI threshold level of 4.35 was identified to predict gaps in all PVs segments. Considering the wall thickness of the posterior wall of LA thinner than the nonposterior wall, excessive HP ablation of LA posterior wall may result in a rapid rise in tissue temperature and thermal latency to cause overheating of the myocardium and thermal injury to the adjacent tissues (16, 31, 32). Although a recent Frankfurt AI-HP ESO-I/II study demonstrated that the incidences of ablation-related esophageal lesion during HP ablation seem markedly low (33, 34), data from the POWER-FAST PILOT and PILOT-AF studies have shown that esophageal lesions were frequently found in patients with higher LSI when HP ablation on the LA posterior wall (17, 18). Referring to a previous study on LSI settings for ablation on LA posterior wall, minimal RF application was applied to the LA posterior in our study, giving rise to the optimal LSI for the posterior wall with the LSI of 3.95 for detecting conduction gaps, which was lower than the LSI of 4.55 for the anterior wall.

In an *ex vivo* model, when the RF application was delivered under the same LSI, it is worth noting that HP ablation resulted in similar lesion volumes but significantly wider lesion when compared to conventional LP ablation (7, 32). The essential mechanism of different lesion geometries when reaching the same target LSI may be that the HP ablation could quickly produce stronger resistive heating which could create a wider surface lesion area, while conductive heating on the tissue surface was weakened by convective cooling through the blood flow and catheter irrigation flow. Therefore, the larger the lesion surface diameter, the lower is the likelihood of gap formation between lesions in LSI-guided HP ablation. It may explain why a relatively lower LSI threshold under HP ablation could predict gaps in our patients compared with the optimal LSI threshold of 5.25 reported by Kanamori et al. using conventional LP ablation (16, 30). Consequently, our results showed a reduced LSI target value would provide a reasonable approach to LSI-guided HP ablation for PVI, which may improve the procedural efficacy and avoid excessive ablation to minimize the occurrence of complications.

LIMITATIONS

First, this study was a retrospective and single-center study in a relatively small sample size cohort, which was therefore subject to a myriad of biases, particularly selection bias and statistical power limitations. Hence, results from the current data need to be confirmed by further large-scale prospective randomized controlled studies. Second, the procedure in our study was performed under conscious sedation anesthesia rather than deep sedation, and RF ablation may cause discomfort such as chest pain or coughing, body movement, and respiratory instability, which may interfere catheter stability, motion correction reference, the accuracy of three-dimensional electroanatomic mapping, and circumferential PV antral ablation lines. Third, given that the thickness of the PVs antrum is significantly different and LSI does not take into account regional variations in underlying left atrial thickness (31), gap formation therefore may be associated not only with LSI value but also with wall thickness for each ablation point. Further study on the relationship among LSI, wall thickness, and gap formation in the LSI-guided HP ablation is warranted. Fourth, although we analyzed the association between LSI and acute conduction gap formation, the relationship between LSI and redo mapping, as well as long-term AF recurrence, was not performed in our study. The long-term efficacy of LSI-guided HP ablation performed with the optimal LSI settings should be performed and validated in future study. Fifth, as similar results were reported in the previous studies, LSI-guided HP may further minimize the collateral thermal injury (35), whereas the incidence and severity of esophageal injury in this study remain unrevealed due to lack of application of continuous luminal esophageal temperature monitoring. Sixth, the ablation catheter with high irrigation is very efficient at cooling the catheter tip and the adjacent atrial tissue, which may affect the catheter tip temperature, Δ-Imp, and subsequent LSI value (36). Therefore, the results of this study were based on the HP ablation using an ablation catheter with 6 irrigation holes (TactiCath Quartz; Abbott), the optimal LSI value for HP ablation using an ablation catheter with 66 or 56 irrigation holes cannot be derived from our data. Finally, the underlying biophysical and pathophysiological mechanisms of the interaction between LSI and gap formation in different PVs segments following HP ablation are also needed to elucidate in further *in vivo* and *ex vivo* studies.

CONCLUSION

This study on LSI-guided HP ablation for PVI demonstrated that LSI was correlated with gap formation at different PVs segments and could be utilized as a surrogate end point to guide PVI. To achieve a higher first-pass PVI without acute conduction gaps, more than 4.35 of LSI for all PVs segments showed the best predictive value to avoid gap formation. In addition, the optimal LSI of 4.55 for the anterior segments and 3.95 for the posterior segments of PVs were the best cutoff values for predicting gap formation in LSI-guided HP ablation, respectively.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW provided the design of the study, analyzed and interpreted data, drafted the manuscript, and approved the final version of the manuscript. CC participated in drafting the manuscript, analyzing and interpreting data. J-MC and YY assisted with the revising of the article. H-XN, WH, and SZ contributed to acquiring the patients' clinical data. All authors contributed to the article and approved the submitted version.

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Efficacy and Safety of Oral Anticoagulants for Atrial Fibrillation Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis

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Background: Data on different direct oral anticoagulants (DOACs) in atrial fibrillation (AF) patients with renal impairment are insufficient. We aimed to perform pairwise and network meta-analysis comparing oral anticoagulants (OACs) in AF patients with renal impairment, including advanced chronic kidney disease (CKD) with creatinine clearance <30 mL/min.

Methods: PubMed, Embase, Cochrane Database, and references of related articles were searched up to April 2021. We included randomized trials and non-randomized studies using propensity-score or multivariable-model adjustments that compared clinical outcomes among OACs. Hazard ratios (HRs) for stroke or thromboembolism, major bleeding, and all-cause death were pooled using random-effects model.

Results: From 19 studies, 124,628 patients were included. In patients with AF and CKD, DOACs presented significantly lower risks of stroke or thromboembolism [HR_{pooled} = 0.78, 95% confidence interval (CI) = 0.73–0.85, I^2 = 16.6%] and major bleeding [HR_{pooled} = 0.76 (0.64–0.89), I^2 = 85.7%] when compared with warfarin, regardless of the severity of renal impairment. Results were consistent in advanced CKD patients for stroke or thromboembolism [HR_{pooled} = 0.60 (0.43–0.85), I^2 = 0.0%] and major bleeding [HR_{pooled} = 0.74 (0.59–0.93), I^2 = 30.4%]. In the network meta-analysis, edoxaban and apixaban presented the highest rank probability to reduce the risk of stroke or thromboembolism (edoxaban, P-score = 94.5%) and major bleeding (apixaban, P-score = 95.8%), respectively. Apixaban remained the safest OAC with the highest rank probability for major bleeding (P-score = 96.9%) in patients with advanced CKD.

Conclusion: DOACs, particularly apixaban and edoxaban, presented superior efficacy and safety than warfarin in AF patients with CKD. Apixaban was associated with the lowest risk of major bleeding among OACs for patients with advanced CKD.

Systematic Review Registration: [PROSPERO], identifier [CRD42021241718].

Keywords: atrial fibrillation, anticoagulation, chronic kidney disease, meta-analysis, direct oral anticoagulant

INTRODUCTION

The presence of chronic kidney disease (CKD) increases both thromboembolic and bleeding risks in patients with atrial fibrillation (AF) (1–3), which makes anticoagulation therapy challenging in this patient group (3). Although the introduction of direct oral anticoagulants (DOACs) has led to safer oral anticoagulation (OAC) therapy in general (4, 5), there are areas of uncertainty in patients with AF and CKD. Notably, patients with advanced CKD [creatinine clearance (CrCl) <30 mL/min] have been excluded from the pivotal randomized controlled trials (RCTs), except for some patients on apixaban with CrCl of 25–30 mL/min (6–10). In addition, few studies have directly compared DOACs in patients with CKD (11, 12).

After publication of the practical guidelines on DOAC use in patients with CKD provided by the European Heart Rhythm Association (13), several observational studies have been published the comparing various OACs in patients with CKD (14–27). We thus aimed to evaluate the pooled efficacy and safety of DOACs compared with warfarin in AF patients with various stages of CKD, including advanced CKD with CrCl <30 mL/min. Second, we performed a network meta-analysis to comprehensively evaluate and rank different OAC strategies, including type of DOAC and warfarin, in patients with AF and CKD.

MATERIALS AND METHODS

A detailed description of the study methods is presented in the **Supplementary Materials**.

Data Sources and Search Strategies

We performed electronic searches of PubMed, Embase, Cochrane Central Register of Controlled Trials, and relevant websites, i.e., clinicaltrials.gov, clinicaltrialresults.com, tctmd.com, and esc365.escardio.org. We then searched conference proceedings from the American College of Cardiology, European Society of Cardiology, American Heart Association, and World Congress of Cardiology. We also performed a manual review of the reference lists of all included studies. References of recent narrative or systematic reviews, editorials, and meta-analyses were reviewed. We did not apply any restrictions on language, study period, or sample size. The last search was performed in November 2021.

Study Selection

We included studies that met the following criteria: (1) include patients with AF and CKD (defined by CrCl <60 ml/min) treated by OACs (warfarin or DOACs, including rivaroxaban, dabigatran, apixaban, or edoxaban) for the prevention of stroke or thromboembolic events; (2) clearly provide more than one of the outcomes of interest separately in CKD patients; (3) present comparative results of outcomes among two or more OACs as an extractable form. We did not apply any exclusion criteria regarding the estimation equation of glomerular filtration rate (GFR). However, we primarily incorporated studies using the Cockcroft-Gault formula, and results from other formulae [e.g., Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] were only used if we could not extract any result from Cockcroft-Gault formula. We excluded studies conducted on AF patients on dialysis [defined as an end-stage renal disease (ESRD)]. We also excluded single-arm studies or non-randomized controlled studies (NRSs) that did not provide comparative results adjusted for confounding factors by multivariable-regression or propensity score (PS)-based methods (i.e., PS matching or inverse probability of treatment weighting). NRSs that did not include age, sex, major cardiovascular risk factors, or components of the CHA_2DS_2-VASc score in the multivariable regression model were also excluded. Unpublished subgroup data of CKD patients from the study by Lee et al. (24) were added (data provided in the **Supplementary Materials**). Two investigators, T-M Rhee and S-R Lee, independently screened the titles and abstracts from the search results, identified duplicated search results, reviewed full articles, and determined the eligibility of candidate studies. Disagreements between investigators were resolved by discussion with the other authors, E-K Choi and GYH Lip.

Data Extraction and Quality Assessment

Summary data, as reported in the published articles, were used in the analysis. We used a standardized form to extract the comparative outcomes among OAC groups and detailed characteristics of each study. We assessed the quality of eligible studies using the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) (28) for RCT and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (29) for NRSs.

Study Outcomes and Definitions

The outcomes of interest in the present study were (1) stroke or thromboembolism, (2) major bleeding, and (3) all-cause death at the longest available follow-up. Stroke or thromboembolism included both ischemic or hemorrhagic stroke and systemic arterial thromboembolism confirmed clinically or radiologically. The definition of major bleeding varied slightly from study to study but was mostly consistent with the International Society on Thrombosis and Haemostasis (ISTH) major bleeding criteria.

Data Synthesis and Analysis

All results are presented according to the severity of renal impairment, i.e., all CKD with CrCl <60 mL/min, more than moderate CKD with CrCl <50 mL/min, and advanced CKD with CrCl <30 mL/min.

For pairwise direct comparisons for outcomes of interest between DOACs and warfarin, we established random-effects models and calculated pooled hazard ratios (HRs) with 95% confidence intervals (CIs) as summary statistics (30). Heterogeneity among studies was quantified using I^2 statistics (30). Publication bias was assessed qualitatively using funnel plot asymmetry and quantitatively using Egger's and Begg's tests (30). To discriminate the significance of heterogeneity caused

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; ISTH, International Society on Thrombosis and Haemostasis; NRS, non-randomized studies; OAC, oral anticoagulant; PS, propensity score; RCT, randomized controlled trial.

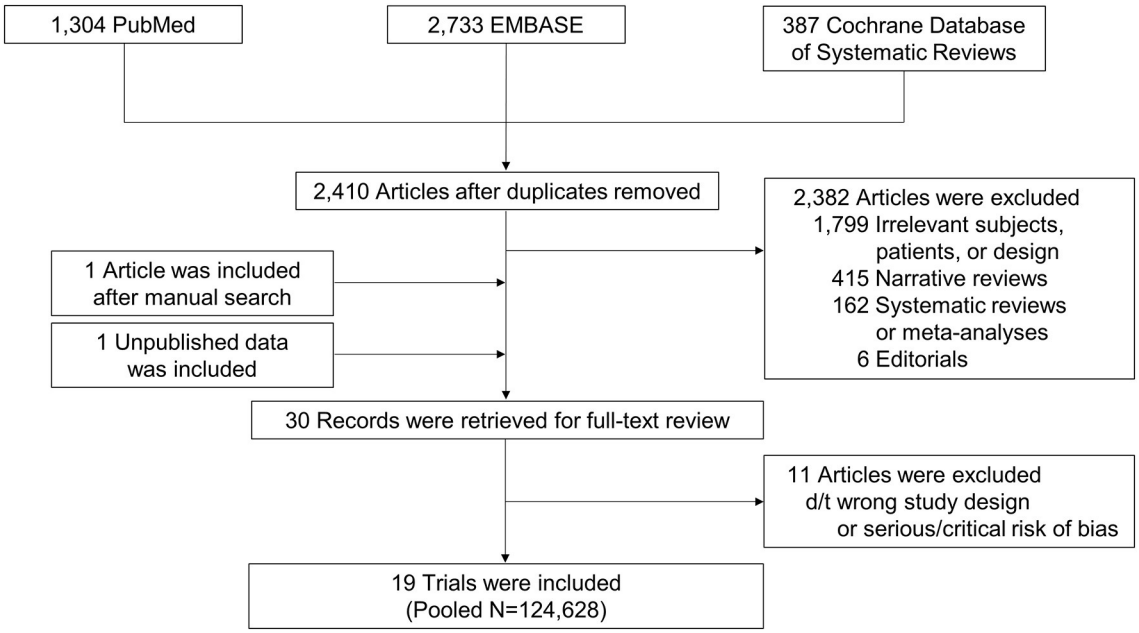

FIGURE 1 | Study flow. Flow of search and study selection are presented.

by including studies with different study types (RCT or NRS), various doses of DOAC (standard, reduced, or unspecified), and different GFR estimation equations (Cockcroft-Gault, MDRD, CKD-EPI, or unspecified), subgroup analyses were performed by (1) type of adjustment; (2) dose of DOAC; and (3) GFR estimation equation. The pooled HR and 95% CI in each subgroup was calculated and the heterogeneity was evaluated using I^2 statistics.

For the network meta-analysis to compare outcomes across all the different OACs, we established a random-effects model based on a frequentist approach for multiple treatment comparisons (31). Pooled HRs and 95% CIs were presented as summary statistics and forest plots. A network league table summary was used to present all possible combinations of comparisons (32). The ranking of OACs from most to least beneficial for two outcomes, i.e., stroke or thromboembolism and major bleeding, was obtained by calculating P-scores from the frequentist treatment ranking method and simultaneously presented in the clustered ranking plot (33). Heterogeneity and inconsistency were evaluated by Q statistics, a network heat plot, and the network node-splitting method. Potential publication bias was assessed using a comparison-adjusted funnel plot and Egger's test (31, 32).

Two-sided $p < 0.05$ were considered statistically significant. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (**Supplementary Table 1**) (34). The review protocol has been registered on the PROSPERO (CRD42021241718). Data were analyzed using Stata version 14.0 (StataCorp LP, College Station, Texas) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Search Results and Study Selection

We collected 2,410 articles and retrieved 30 studies for full-article review (**Figure 1**). Of these, 19 studies were included in the final analysis (6–10, 14–27). Five were subgroup analyses of previous RCTs (6–10). Direct comparisons between OACs were mostly conducted with warfarin as a reference group, while one study provided a direct comparison among DOACs (24). One study (14) did not report stroke or thromboembolism and 10 did not provide all-cause death (7, 14, 16, 17, 21–26).

Characteristics of Included Trials

The period of study publications ranged from 2011 to 2020. Of the 14 NRSs, 10 used PS-based methods (PS matching or inverse probability of treatment weighting) (14–16, 21–27) and four used a multivariable regression model (**Table 1** and **Supplementary Table 2**) (17–20). We incorporated 124,628 patients with AF and concomitant CKD (DOAC, $n = 71{,}390$; Warfarin, $n = 53{,}238$). The follow-up duration varied from 139 days to 5.5 years. The renal function of all pooled patients was CKD stage 3 or worse with CrCl <60 mL/min; five studies (6, 16, 17, 19, 25) provided outcomes for advanced CKD patients with CrCl <30 mL/min.

Assessment of Risk of Bias

The overall risk of bias was low for RCTs, except for one trial (8), which did not report a detailed randomization process. Although all NRSs had a moderate risk of bias due to their retrospective and observational nature, they showed low risk for most domains of bias (**Supplementary Figure 1**).

TABLE 1 | Characteristics of studies selected for analysis.

Study	Year	Study design	Adjustment method	DOAC group (*n*)	Warfarin group (*n*)	Renal function of enrolled patients	Duration of follow-up	Mean age (Y)	Male (%)	Mean CHA_2DS_2-VASc score	Mean HAS-BLED score
ROCKET-AF (7)	2011	Randomized trial (CKD subgroup)	N/A	1,474	1,476	CrCl 30–50 mL/min	Median 590 days	73	60.3	3.48/3.46 ($CHADS_2$)	NR
J-ROCKET AF (8)	2012	Randomized trial (CKD subgroup)	N/A	141	143	CrCl 30–50 mL/min	Up to 30 months	71.1	80.6	3.25 ($CHADS_2$)	NR
ARISTOTLE (6)	2012	Randomized trial (CKD subgroup)	N/A	1,493	1,512	CrCl 25–50 mL/min	Median 1.8 years	77.6	46.7	4.4	2.2
RE-LY (9)	2014	Randomized trial (CKD subgroup)	N/A	2,428	1,126	CrCl 30–50 mL/min	Median 2 years	75.2	53.4	81.2% ($CHADS_2$ ≥2)	NR
Hernandez et al. (14)	2015	Observational	Propensity-score based	428	2,536	CKD stage ≥3*	Median 177/228 days	75.1/75.6	42.1/41.0	80.9%/81.1% ($CHADS_2$ ≥2)	NR
Lee et al. (20)	2015	Observational	Multivariate model-based	59	174	CKD stage ≥3	Median 596 days	71.9/69.3	37.7/34.1	≥2	NR
Engage Af-Timi 48 (10)	2016	Randomized trial (CKD subgroup)	N/A	1,379	1,361	CrCl 30–50 mL/min	Median 2.8 years	79	46	5.0	2.8
Shin et al. (21)	2018	Observational	Propensity-score based	1,122	1,122	CKD stage ≥3	Mean 1.2 years	73/72	53/54	4/4	2/2
Yu et al. (15)	2018	Observational	Propensity-score based	741	839	CrCl 30–50 mL/min	Median 5 months	68.2/68.3 (E60) 72.8/72.6 (E30)	63.3/63.0 (E60) 52.0/53.3 (E30)	4.2/4.2 (E60) 4.9/4.8 (E30)	NR
Coleman et al. (16)	2019	Observational	Propensity-score based	1,896	4,848	CKD stage ≥4†	Median 1.4 years	72/72	58.4/61.6	4	NR
Chan et al. (22)	2019	Observational	Propensity-score based	21,081	6,264	CKD stage ≥3	Up to 16 months	74.7	57	3.6	2.6
Bonnemeier et al. (23)	2019	Observational	Propensity-score based	4,164	7,002	CKD stage ≥3	Mean 381/221 days	76.9/77.2	45.5/50.8	4.6/4.5	3.5/3.4
Lee et al. (24)	2019	Observational	Propensity-score based	11,633	4,056	CKD stage ≥3	Up to 18 months	72/73	55/54	3.5/3.6	2.7/2.7
Chang et al. (17)	2019	Observational	Multivariate model-based	280	520	CKD stage ≥4	Mean 3.2 years	79.8/76.6	43.9/44.6	4.7/4.6	3.7/4.0
Laugesen et al. (18)	2019	Observational	Multivariate model-based	552	1,008	CKD stage ≥3	Up to 1 year	80.0/78.0	56.9/64.0	NR	NR
Makani et al. (19)	2020	Observational	Multivariate model-based	4,748	5,895	CKD stage ≥3	Median 3.4 years	75.7	50.0	≥2	NR
Weir et al. (25)	2020	Observational	Propensity-score based	781	1,536	CKD stage ≥4	Mean 389/370 days	79.9	39.5	4.5	3.5
Chan et al. (26)	2020	Observational	Propensity-score based	4,780	1,291	CKD stage ≥3	Up to 5.5 years	74.6/74.5	53.7/53.5	4.5/4.4	3.1/3.0
Wetmore et al. (27)	2020	Observational	Propensity-score based	12,210	10,529	CKD stage ≥3	Median 139 days	78/78	49/49	5.3/5.3	3.3/3.3

**CKD stage ≥3 denotes estimated glomerular filtration rate below 60 mL/min/1.73 m^2 as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) classification.*

† CKD stage ≥4 denotes estimated glomerular filtration rate below 30 mL/min/1.73 m^2 as defined by the KDIGO classification.

CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; E30, edoxaban 30 mg; E60, edoxaban 60 mg; N/A, not applicable; NR, not reported.

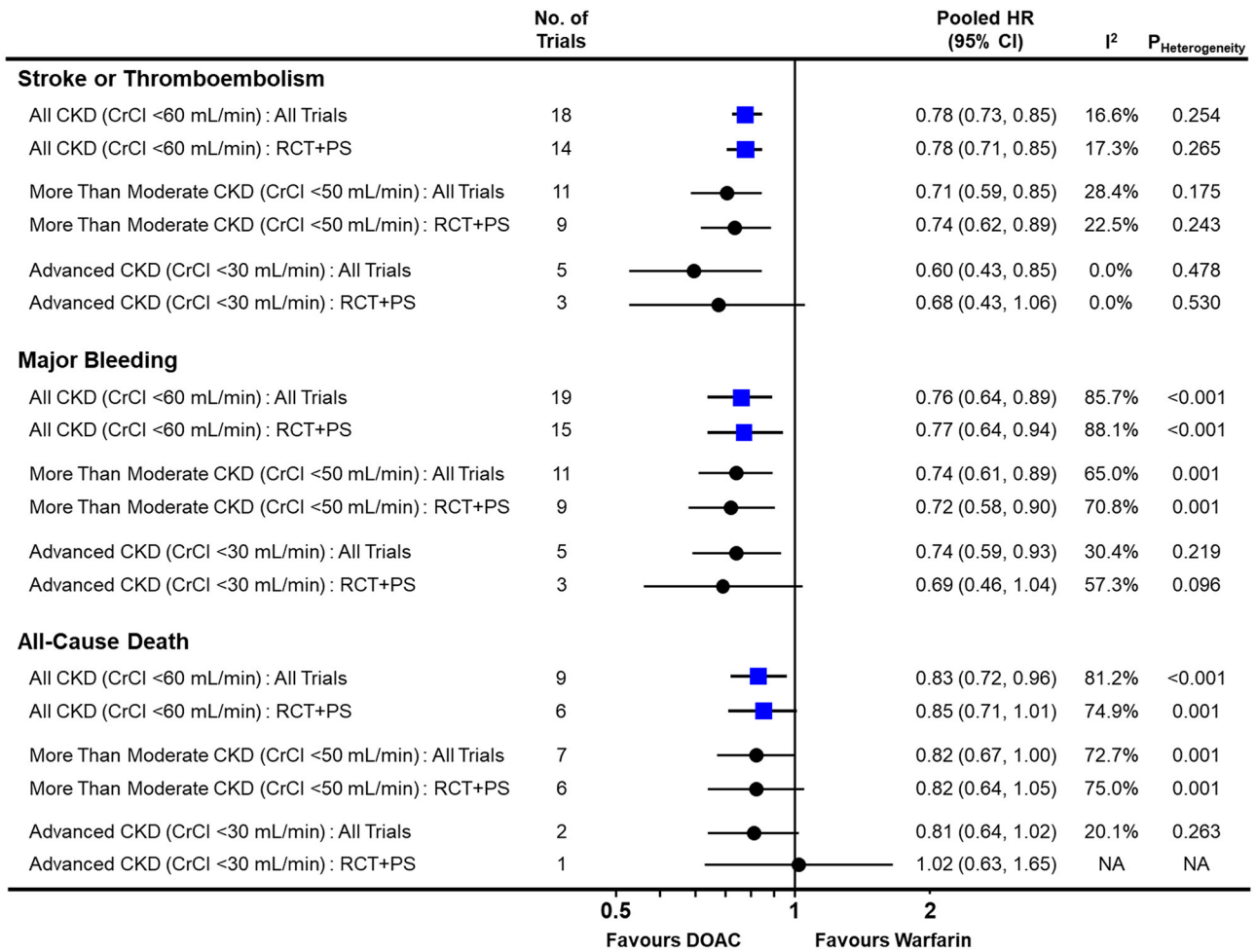

FIGURE 2 | Comparison of pooled treatment effects of oral anticoagulants on clinical outcomes in atrial fibrillation patients with concomitant chronic kidney disease. Pooled HR and 95% CI, I^2 and *P*-value for heterogeneity are presented for stroke or thromboembolism, major bleeding, and all-cause death according to the severity of renal impairment. CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; HR, hazard ratio; NA, not applicable; PS, propensity-score; RCT, randomized controlled trial.

Pairwise Comparison of DOAC vs. Warfarin in AF Patients With CKD

In the pairwise meta-analysis with random-effects model (**Figure 2** and **Supplementary Figures 2–4**), DOACs showed a significantly lower risk of stroke or thromboembolism [pooled HR = 0.78 (95% CI = 0.73–0.85), Heterogeneity I^2 = 16.6%], major bleeding [pooled HR = 0.76 (95% CI = 0.64–0.89), I^2 = 85.7%], and all-cause death [pooled HR = 0.83 (95% CI = 0.72–0.96), I^2 = 81.2%] in the total CKD population when compared with warfarin. This was consistent, except for all-cause death, when pooling only RCTs and NRSs that used PS-based adjustment. Regardless of the severity of renal impairment, DOACs were significantly favored over warfarin for both stroke or thromboembolism and major bleeding.

In advanced CKD with CrCl <30 mL/min, DOACs significantly lowered the risk of stroke or thromboembolism [pooled HR = 0.60 (95% CI = 0.43–0.85), I^2 = 0.0%] and major bleeding [pooled HR = 0.74 (95% CI = 0.59–0.93), I^2 = 30.4%] when compared with warfarin. Additionally, they showed a tendency to lower the risk of all-cause death [pooled HR = 0.81 (95% CI = 0.64–1.02), I^2 = 20.1%]. There was no evidence of publication bias for any of the outcomes (**Supplementary Figure 5**).

Subgroup Analysis for Pairwise Meta-Analysis

The pairwise meta-analysis according to various subgroups was generally consistent with the main results (**Figure 3** and **Supplementary Figures 6–8**). A similar trend was maintained in the RCTs, NRSs with PS-based adjustment, and NRSs with multivariable-model-based adjustment, while moderate heterogeneity in stroke or thromboembolism risk was observed among nine studies (15, 16, 21–27) that performed PS-based adjustment (I^2 = 42.4%). A significant risk reduction for stroke

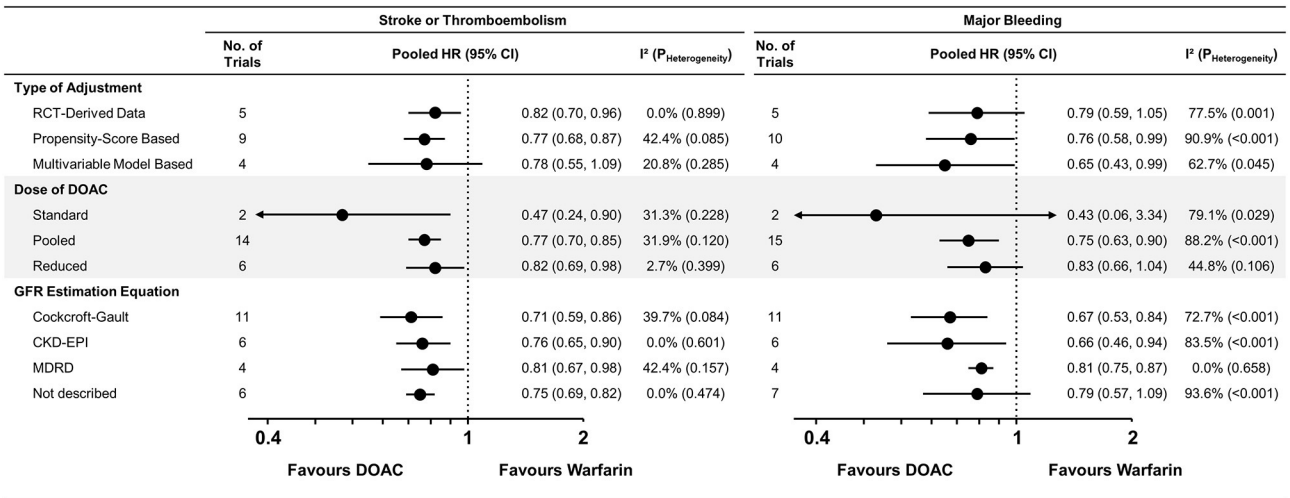

FIGURE 3 | Subgroup analysis for stroke or thromboembolism and major bleeding. Subgroup analysis across various subgroups are presented. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; HR, hazard ratio; NA, not applicable; PS, propensity-score; RCT, randomized controlled trial.

or thromboembolism was still observed with a reduced dose of DOACs [pooled HR = 0.82 (95% CI = 0.69–0.98), I^2 = 2.7%] when compared with warfarin. In the subgroups according to the GFR estimation equation, moderate heterogeneity was observed in studies using the Cockcroft-Gault (I^2 = 39.7%) and MDRD equations (I^2 = 42.4%), contrast to the studies using the CKD-EPI equation (I^2 = 0.0%).

Frequentist Network Meta-Analysis Comparing Efficacy and Safety of OACs for AF in Patients With CKD

In all CKD patients, all four DOACs showed significant risk reduction for stroke or thromboembolism with warfarin as a reference group (**Figures 4A,B**). Except dabigatran, all DOACs were significantly favored over warfarin in terms of major bleeding. Edoxaban showed a significantly lower risk of stroke or thromboembolism when compared with the other DOACs. For major bleeding, apixaban showed a significant benefit when compared with rivaroxaban and dabigatran, while dabigatran showed a significant increase of major bleeding risk when compared with all other DOACs (**Table 2**). A significant heterogeneity was observed for major bleeding (Heterogeneity Q = 70.92, $P < 0.001$), while there were possibilities of publication bias for both outcomes (**Supplementary Figures 9**, **10**). In the advanced CKD group, (**Figures 4C,D** and **Table 3**) the risk of major bleeding was significantly lower in apixaban [pooled HR = 0.34 (95% CI = 0.14–0.83)] compared to warfarin.

Figure 5 illustrates the ranking probability of OACs for both outcomes by a clustered ranking plot. For the total CKD population, apixaban and edoxaban showed higher rank probabilities than other OACs for both stroke or thromboembolism (P-score for ranking probability, apixaban = 82.7% and edoxaban = 94.5%) and major bleeding (P-score, apixaban = 95.8% and edoxaban = 73.0%). Warfarin showed the lowest ranking probability (P-score for stroke or thromboembolism = 0.4% and for major bleeding = 10.8%). In the advanced CKD group, apixaban showed the highest rank for major bleeding (P-score = 96.9%), while it was the second-best strategy in terms of stroke prevention (P-score = 64.5%).

DISCUSSION

By incorporating RCTs as well as high-quality NRS data, we performed a comprehensive meta-analysis on the anticoagulation in AF patients with renal impairment. Our major findings can be summarized as follows. First, DOACs were better OAC treatment options for AF patients with concomitant CKD when compared with warfarin. They showed significantly lower risks of stroke or thromboembolism and major bleeding, regardless of the severity of renal impairment. Second, apixaban and edoxaban presented higher ranks than the other DOACs in terms of stroke or thromboembolism and major bleeding in the total CKD population. Apixaban remained the best treatment option in advanced CKD patients, particularly to reduce the risk of major bleeding.

Optimal Anticoagulation Strategies in AF Patients With CKD

Although anticoagulant therapy in non-valvular AF lowers the risk of fatal stroke, bleeding, and mortality even for CKD patients (5, 35), starting OAC might be challenging in AF patients with CKD who are known to be associated with high risks of both thromboembolism and bleeding (3, 35–37). After the introduction of DOACs, a meta-analysis including pivotal RCTs showed consistent or accentuated clinical benefits of DOACs when compared with warfarin in this population (4).

In the present meta-analysis, we confirmed the superior safety and efficacy of DOACs compared with warfarin in all

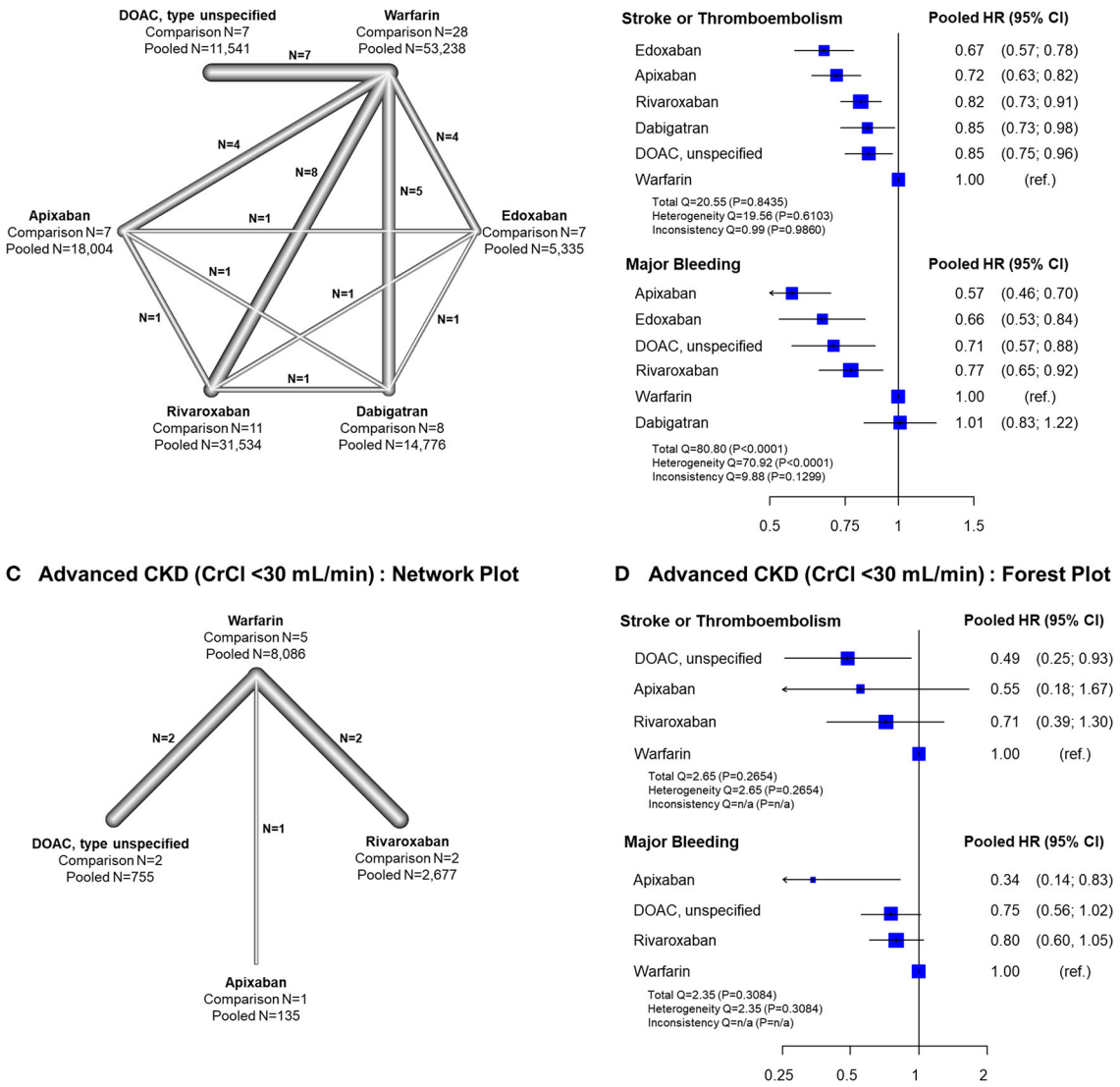

FIGURE 4 | Results of network meta-analysis comparing safety and efficacy of oral anticoagulants in all CKD and advanced CKD patients. Results of frequentist network meta-analysis for all CKD patients with CrCl <60 mL/min, **(A)** network plot **(B)** forest plot, and for advanced CKD patients with CrCl <30 mL/min, **(C)** network plot, and **(D)** forest plot, are presented. ref., reference; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; HR, hazard ratio; NA, not applicable; PS, propensity-score; RCT, randomized controlled trial.

CKD patients with CrCl <60 mL/min, which was in line with previous evidence. Reduced mortality was also expected in the DOAC group. Our results may suggest that physicians should not compare DOACs vs. warfarin anymore; rather, they should consider which DOAC to use in AF patients with CKD.

Efficacy and Safety of DOACs in Advanced CKD Patients With CrCl <30 mL/min

Data on the relative efficacy and safety of OACs in patients with advanced non-end stage CKD (stage 4 or worse without renal replacement therapy with CrCl <30 mL/min) are highly limited, mainly because these patients were excluded from pivotal RCTs except for the ARISTOTLE trial which covered 269 patients with CrCl 25–30 mL/min (6). By incorporating data from the recent observational studies covering the advanced CKD population (16, 17, 19, 25, 27), we found that DOACs significantly reduced the risk of stroke or thromboembolism as well as that of major bleeding compared to warfarin even in this population.

The increase of the area under the curve (AUC) for the plasma concentration of DOACs is predictable to some extent, except for dabigatran (13). In contrast, warfarin has a significantly suboptimal time in the therapeutic range as renal function

TABLE 2 | League table summary of network meta-analysis for oral anticoagulants in patients with chronic kidney disease (CrCl <60 mL/min).

	Apixaban	Dabigatran	Edoxaban	DOAC, unspecified	Rivaroxaban	Warfarin
Apixaban	-	0.56 (0.43, 0.73)	0.85 (0.64, 1.13)	0.80 (0.59, 1.09)	0.73 (0.57, 0.93)	0.57 (0.46, 0.70)
Dabigatran	0.85 (0.71, 1.01)	-	1.52 (1.15, 2.00)	1.43 (1.07, 1.92)	1.30 (1.03, 1.65)	1.01 (0.83, 1.23)
Edoxaban	1.07 (0.89, 1.29)	1.26 (1.04, 1.54)	-	0.94 (0.68, 1.29)	0.86 (0.66, 1.12)	0.66 (0.53, 0.84)
DOAC, unspecified	0.84 (0.70, 1.01)	0.99 (0.82, 1.20)	0.79 (0.64, 0.96)	-	0.91 (0.69, 1.21)	0.71 (0.57, 0.88)
Rivaroxaban	0.88 (0.76, 1.02)	1.04 (0.88, 1.22)	0.82 (0.69, 0.98)	1.04 (0.89, 1.23)	-	0.77 (0.65, 0.92)
Warfarin	0.72 (0.63, 0.82)	0.85 (0.73, 0.98)	0.67 (0.57, 0.78)	0.85 (0.75, 0.97)	0.82 (0.73, 0.91)	-
Pooled HR and 95% CI for stroke or thromboembolism (first column as the reference group)						
Pooled HR and 95% CI for major bleeding (first row as the reference group)						

CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; DOAC, direct oral anticoagulant.

TABLE 3 | League table summary of network meta-analysis for oral anticoagulants in patients with advanced chronic kidney disease (CrCl <30 mL/min).

	Apixaban	Dabigatran	Edoxaban	DOAC, unspecified	Rivaroxaban	Warfarin
Apixaban	-	Not available	Not available	0.45 (0.18, 1.15)	0.43 (0.17, 1.08)	0.34 (0.14, 0.83)
Dabigatran	Not available	-	Not available	Not available	Not available	Not available
Edoxaban	Not available	Not available	-	Not available	Not available	Not available
DOAC, unspecified	1.13 (0.31, 4.09)	Not available	Not available	-	0.95 (0.63, 1.43)	0.75 (0.56, 1.02)
Rivaroxaban	0.77 (0.22, 2.72)	Not available	Not available	0.68 (0.28, 1.64)	-	0.80 (0.60, 1.05)
Warfarin	0.55 (0.18, 1.67)	Not available	Not available	0.49 (0.25, 0.93)	0.71 (0.39, 1.30)	-
Pooled HR and 95% CI for stroke or thromboembolism (first column as the reference group)						
Pooled HR and 95% CI for major bleeding (first row as the reference group)						

CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; DOAC, direct oral anticoagulant.

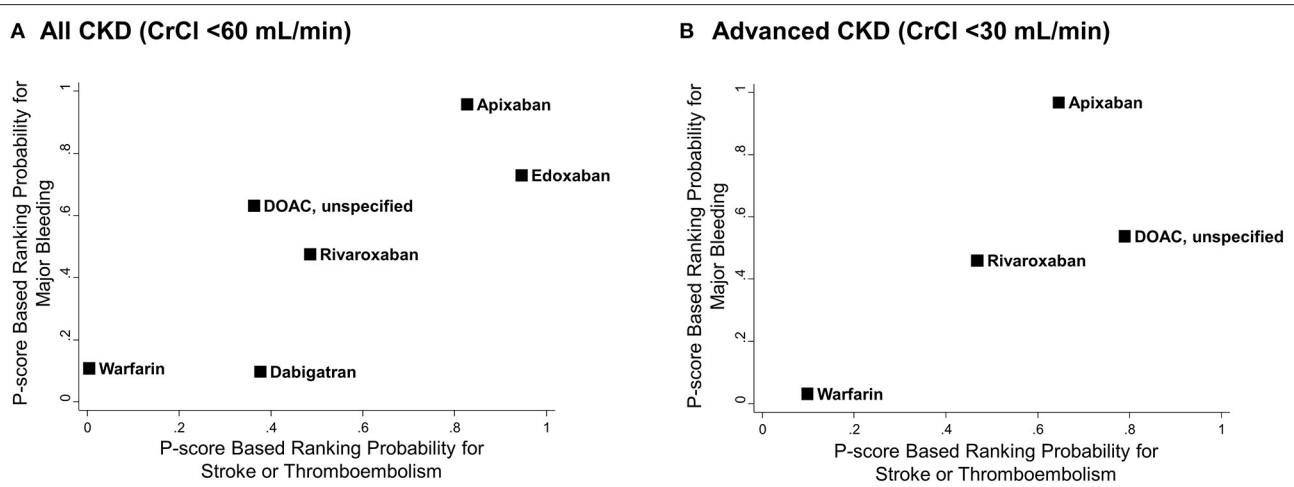

FIGURE 5 | Clustered ranking plots of oral anticoagulants for stroke or thromboembolism and major bleeding. P-score based rankings of various oral anticoagulants for stroke or thromboembolism and major bleeding are plotted. **(A)** All CKD with CrCl <60 mL/min and **(B)** advanced CKD with CrCl <30 mL/min. CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; HR, hazard ratio; NA, not applicable; PS, propensity-score; RCT, randomized controlled trial.

worsens (36). Along with the possibility of extensive drug–drug interactions of warfarin, this may explain the superiority of DOACs shown in patients with advanced CKD. Our results may be an important cornerstone that can emphasize the necessity of a large-scale randomized trial comparing the efficacy and safety of each DOAC in advanced CKD patients. Furthermore, investigation to determine the optimal dosing strategy of each DOAC in this population is warranted.

Comparison Among Different DOACs for AF Patients With CKD

Our network meta-analysis results showed that all four DOACs consistently showed significant risk reductions for stroke or thromboembolism and major bleeding compared with warfarin in AF patients with CKD, except dabigatran in terms of major bleeding. Among the DOACs, apixaban and edoxaban were ranked as the highest treatment recommendation. When compared with rivaroxaban and dabigatran, edoxaban showed significantly better efficacy in preventing stroke or thromboembolism, and apixaban significantly lowered the risk of major bleeding. Notably, dabigatran showed a risk of major bleeding similar to that of warfarin and thus showed significantly inferior results when compared with other DOACs. For patients with advanced CKD with CrCl <30 mL/min, we found that apixaban was the best DOAC treatment, especially in terms of reducing major bleeding risk. Although there is still a lack of evidence, these results are consistent with the consensus documented in current practical guidelines (13).

Differences in efficacy and safety according to DOAC types may be due to differences in the pharmacokinetic profiles of each DOAC. Apixaban has the lowest proportion of renal excretion; therefore, the AUC increase of plasma concentration is the most modest according to the decrease in renal function (13). The pharmacokinetic report from the ARISTOTLE substudy shows that the AUC of apixaban in the CrCl 25–30 mL/min patient group was similar to that of the group with CrCl 30–50 mL/min (6). The safety concern regarding high risk of major bleeding for dabigatran in CKD patients could also be explained by the excretion mostly dependent on the kidney. We found the best efficacy of edoxaban for the prevention of thromboembolism in the AF with CKD population. Further investigation is necessary for this novel finding. Better compliance of patients due to the once-daily regimen of edoxaban may have influenced the better outcomes, particularly in the observational study. The well-established dose reduction criteria of edoxaban may also explain the results of this study because the meticulous care of patients may have been possible in the edoxaban group.

Study Limitations

This study has several limitations. First, it was a study-level meta-analysis; therefore, it was impossible to consider individual patient-level confounders. In addition, bias due to unmeasured or inaccessible confounding factors from observational studies could not be completely excluded. Second, although inconsistency between direct and indirect evidence was not found, evidence through direct comparison between DOACs was relatively scant, and currently, there is no head-to-head randomized trial for DOACs. Third, we tried to minimize heterogeneity following the incorporation of NRSs, but a significant level of heterogeneity was still observed in terms of major bleeding and all-cause death, requiring attention in interpretation for these outcomes. Nevertheless, the meta-analysis of the advanced CKD group showed negligible heterogeneity for both stroke or thromboembolism and major bleeding; thus, we assume that the heterogeneity issue minimally affected the core results of the present study. Fourth, the efficacy and safety of DOACs in the patient group requiring dialysis due to ESRD were not covered in this study. Fifth, there were studies in which the dose of DOAC was not reported and in which the proportion of different types of DOACs used was not described. Considering the variable effects of off-label dosing (38, 39), this may have increased the possible heterogeneity of the overall study results. Finally, we could not properly address the comparative efficacy and safety of off-label dosing of DOACs in AF with CKD patients in this study, which needs to be elucidated in future studies.

In conclusion, in patients with AF and CKD, DOACs were safer and more effective than warfarin regardless of severity of renal impairment. Among DOACs, apixaban and edoxaban presented higher rank probabilities compared to other DOACs as well as warfarin for both stroke prevention and a reduced risk of major bleeding. For advanced CKD patients with CrCl <30 mL/min, apixaban should be the first choice, especially in terms of safety.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.885548/full#supplementary-material

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Clustering of Unhealthy Lifestyle and the Risk of Adverse Events in Patients With Atrial Fibrillation

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Background: Little is known regarding the risk of clinical outcomes depending on the clustering of lifestyle behaviors after atrial fibrillation (AF) diagnosis. This study evaluated the association between a cluster of healthy lifestyle behaviors and the risk of adverse outcomes in patients with AF.

Methods: Using the Korean National Insurance Service database, patients who were newly diagnosed with AF between 2009 and 2016 were included. A healthy lifestyle behavior score (HLS) was calculated by assigning 1 point each for non-current smoking, for non-drinking, and for performing regular exercise from the self-reported questionnaire in health examinations. The primary outcome was defined as major adverse cardiovascular event (MACE), including ischemic stroke, myocardial infarction, and hospitalization for heart failure.

Results: A total of 208,662 patients were included; 7.1% in HLS 0, 22.7% in HLS 1, 58.6% in HLS 2, and 11.6% in HLS 3 groups. Patients with HLS 1, 2, and 3 were associated with a lower risk of MACE than those with HLS 0 (adjusted hazard ratio [95% confidence interval (CI)]: 0.788 [0.762–0.855], 0.654 [0.604–0.708], and 0.579 [0.527–0.636], respectively). After propensity score weighting, consistent results were observed. The risk reduction of healthy lifestyle combinations was consistently observed in various subgroups, regardless of the CHA_2DS_2-VASc score and oral anticoagulant use.

Conclusion: Increased number of healthy lifestyle behaviors was significantly associated with lower MACE risk in patients with new-onset AF. These findings support the promotion of a healthy lifestyle to reduce the risk of adverse events in patients with AF.

Keywords: atrial fibrillation, lifestyle, stroke, myocardial infarction, heart failure

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Abbreviations: AF, atrial fibrillation; ASD, absolute standardized difference; CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular event; NHIS, National Health Insurance Service.

INTRODUCTION

Globally, the prevalence of atrial fibrillation (AF) is increasing with an aging population (1–3). AF is associated with an increased risk of stroke, heart failure, and death, and increases the overall healthcare burden (3–6). Therefore, the optimal management of AF, including AF burden reduction and stroke prevention, is crucial for improving outcomes and reducing the AF-related healthcare burden (7). Many studies have studied optimal oral anticoagulation treatment and better symptom care including rhythm and rate control in patients with AF; (8–10) however, lifestyle-related factors that play a role as modifiable risk factors in AF management are still generally underrecognized and understudied, especially in relation to clinical outcomes.

In previous studies, each component of unhealthy lifestyle behaviors such as smoking, alcohol consumption, and lack of regular exercise were individually associated with an increased risk of AF burden, thromboembolic events, and all-cause death (11–15). Although unhealthy or healthy lifestyle behaviors tend to be clustered, studies on the risk of clinical outcomes depending on how lifestyle behaviors are managed after AF diagnosis remain limited (16–19).

This study aimed to evaluate the clustering of healthy lifestyle behaviors in patients who were newly diagnosed with AF and the impact of such accumulation of multiple healthy lifestyle behaviors on the risk of AF-related adverse clinical outcomes.

MATERIALS AND METHODS

Data Source and Study Population

The National Medical Claims Database, linked with the National Health Screening Examination Database established by the Korean National Health Insurance Service (NHIS) was used (20, 21). Briefly, the Korean NHIS provides universal, comprehensive, and mandatory medical coverage for the entire Korean population (approximately 50 million). The Korean NHIS database includes all the information about enrollees' medical use, including demographic information, diagnoses, examinations, prescription records, procedures, and operations for inpatient and outpatient services. Diagnoses were coded based on the *International Classification of Diseases, Tenth Revision, Clinical Modification* codes. The Korean government provides a national health screening examination and recommends that all Korean adults receive examinations every 1 or 2 years. The health examination included anthropometric measurements, physical examinations, regular blood tests, and questionnaires on lifestyle behaviors and medical history.

Among the patients who were newly diagnosed with non-valvular AF between 1 January 2009 and 31 December 2016 (n = 576,077), we included patients who underwent a national health screening examination within 2 years after their AF diagnosis (n = 209,880) (**Figure 1**). After excluding patients aged < 20 years and those with missing values among health screening examinations, 208,662 patients were finally included in this analysis.

This study was exempt from review by the Seoul National University Hospital Institutional Review Board (E-2103-006-1200). All data and materials have been made publicly available at the National Health Insurance Sharing Service and can be accessed at http://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do.

Definition of Healthy Lifestyle Behavior Score (HLS)

Lifestyle behaviors were assessed using self-reported questionnaires during health screening examinations. Each lifestyle was classified as follows: (1) smoking status as currently smoking or not; (2) alcohol consumption as a current drinker or non-drinker; and (3) regular exercise as performing moderate physical activity ≥ 5 times per week or vigorous physical activity ≥ 3 times per week and lack of regular exercise in the absence of regular exercise (19, 22). The frequency and intensity of physical activity were assessed using questionnaires. Moderate intensity of physical activity was defined as ≥ 30 min per day of brisk walking, dancing, or gardening, and vigorous intensity of physical activity was defined as ≥ 20 min per day of running fast, cycling, or aerobics (23).

To estimate the impact of each unhealthy lifestyle behavior on the risk of MACE, we evaluated the association between each unhealthy lifestyle behavior (with various dose or intensity) and the risk of MACE in the study population using multivariable Cox analysis (**Supplementary Table 1**). Based on the results of preliminary analyses, current smoker, current drinker, and non-regular exerciser were defined as patients with unhealthy lifestyle behaviors who were at significantly higher risk of MACE. Thus, in the present study, a healthy lifestyle behavior score (HLS) was calculated by assigning 1 point each for non-current smokers, non-drinkers, and performing regular exercise. The study population was categorized into four groups according to HLS from patients with HLS 0 who did not have any healthy lifestyle behaviors to patients with HLS 3 who met all three healthy lifestyle behaviors.

Covariates

Demographic information including age and sex, comorbidities including hypertension, diabetes mellitus, dyslipidaemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, and chronic kidney disease were assessed based on the diagnoses of medical claims and health screening examination database. The CHA_2DS_2-VASc score was calculated based on comorbidities (7). Detailed definitions of the comorbidities are presented in **Supplementary Table 2** (2, 21, 24). Prescription records of claims database obtained medications including oral anticoagulants (warfarin or non-vitamin K antagonist oral anticoagulant), antiplatelet agents, and statins. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Systolic and diastolic blood pressure, fasting glucose, and glomerular filtration rate were obtained from the health screening examination. Low income was defined as household income lower than 25%.

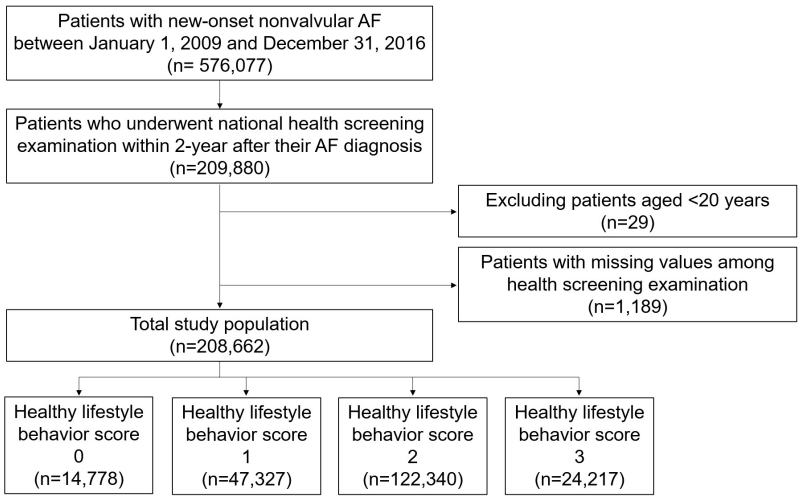

FIGURE 1 | Study flow. AF, atrial fibrillation.

Follow-Up and Study Outcomes

The primary outcome was the first occurrence of major adverse cardiovascular events (MACE), including ischemic stroke, myocardial infarction, and hospitalization for heart failure. Secondary outcomes included the individual components of MACE and all-cause deaths. Detailed definitions of the clinical outcomes are presented in **Supplementary Table 2** (21, 24, 25). Patients were followed up starting from the index date (at the health screening examination date) until the occurrence of the study outcomes, death, or 31 December 2017 whichever came first.

Statistical Analysis

Continuous variables were presented as mean and standard deviation and categorical variables were presented as number and percentage. Baseline characteristics across patient groups were compared using the Cochran-Armitage trend test for categorical variables and a linear trend test using a generalized linear model for continuous variables. The number of events was calculated as the incidence rate during the follow-up period divided by 100 person-years at risk. The risk of clinical outcomes with HLS was analyzed using the Cox proportional hazards regression model. The hazard ratio (HR) and 95% confidence intervals (CIs) for primary and secondary outcomes were analyzed using the HLS 0 group as the reference group. Model 1 was unadjusted; model 2 was adjusted for age and sex; and model 3 was further adjusted for hypertension, diabetes mellitus, dyslipidaemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulants, antiplatelet agents, and statins, BMI, and low income. The proportional hazards assumption was graphically evaluated with a log minus log graph and confirmed with Schoenfeld residuals for Cox models. Parallel log minus log survival curves and random patterns in Schoenfeld residuals were found, indicating no major deviation from the proportionality assumption, and the test was not statistically significant. The variance inflation factor (VIF) was used to assess multi-collinearity. Between the covariates, there was no significant collinearity (VIF = 1.005–2.492).

To provide complementary analyses for balancing among patient groups with different HLS, we performed inverse probability of treatment weighting (IPTW) using stabilized weights calculated from the propensity scores as a sensitivity analysis (26). The covariates included in model 3 were used for the propensity score calculation. We evaluated the maximum absolute standardized difference (ASD) of covariates to confirm the balance of the different groups. A maximum ASD of > 0.1 (10%) indicates an imbalance in a covariate (27, 28). The weighted incidence rate (per 100 person-years) and weighted cumulative incidence curves using the Kaplan–Meier method and log-rank test for primary and secondary outcomes were evaluated. The risk for primary and secondary outcomes of the different HLS groups was evaluated using weighted Cox proportional hazards models with IPTW. When the maximum ASD was > 0.1, the covariate was included in the Cox proportional hazard model for further adjustment.

For the primary outcome, subgroup analyses were performed for age (< 65, 65 to < 75, and ≥ 75 years), sex, CHA_2DS_2-VASc score (< 3 and ≥ 3), presence of prior history of ischemic stroke, and use of oral anticoagulants.

All analyses were two-tailed, and statistical significance was defined as $P < 0.05$. Statistical analyses were conducted using SAS (version 9.4; ASA Institute Inc., Cary, NC, United States).

RESULTS

Baseline Characteristics

A total of 208,662 patients with AF who were available for national health screening exam data were included

TABLE 1 | Baseline characteristics of the study population.

	Before IPTW					After IPTW				
	Healthy lifestyle behavior score				Maximum ASD	Healthy lifestyle behavior score				Maximum ASD
	0 (*n* = 14,778)	1 (*n* = 47,327)	2 (*n* = 122,340)	3 (*n* = 24,217)		0 (*n* = 14,363)	1 (*n* = 45,841)	2 (*n* = 123,866)	3 (*n* = 23,905)	
Age, years										
Mean ± SD	54.3 ± 12.4	59.6 ± 12.8	66.3 ± 12.1	64.6 ± 10.8	0.97	63.2 ± 12.6	63.0 ± 12.7	63.3 ± 13.4	63.8 ± 11.7	0.06
< 65	79.6	63.2	40.4	45.8		53.4	51.8	50.0	46.5	
65 to < 75	15.7	25.5	33.9	38.3		26.2	28.8	30.1	36.6	
≥ 75	4.7	11.3	25.7	16.0		20.4	19.4	19.9	16.9	
Sex (male)	95.7	92.3	87.9	54.4	1.30	60.6	62.0	60.0	59.6	0.04
CHA_2DS_2-VASc										
Mean ± SD	2.15 ± 1.52	2.66 ± 1.71	3.81 ± 1.99	3.43 ± 1.78	0.94	3.33 ± 1.88	3.3 ± 1.89	3.34 ± 2	3.4 ± 1.83	0.05
0	9.8	6.0	2.1	2.3		3.6	3.5	4.1	3.0	
1	30.9	23.3	11.0	11.9		15.6	16.2	16.2	12.8	
2	25.3	23.6	16.2	19.6		19.7	19.8	18.7	19.3	
≥ 3	65.9	47.1	70.7	66.2		61.1	60.5	61.0	64.9	
Comorbidities										
Hypertension	81.9	83.3	85.9	84.4	0.11	83.2	84.1	84.5	84.9	0.04
Diabetes mellitus	22.9	22.0	24.6	23.5	0.06	20.9	22.8	23.3	23.9	0.07
Dyslipidaemia	38.1	41.7	47.3	48.8	0.22	44.3	44.8	45.1	45.7	0.02
Heart failure	24.5	28.0	36.3	31.1	0.26	34.0	33.0	32.7	33.3	0.02
Prior ischemic stroke	14.1	19.2	29.3	27.0	0.38	25.1	25.1	25.3	25.7	0.01
Prior MI	9.1	10.5	12.5	11.8	0.11	11.4	11.7	11.6	11.9	0.01
PAD	16.5	19.2	23.4	21.4	0.17	21.3	21.6	21.5	21.9	0.01
COPD	14.4	17.3	22.0	19.3	0.20	21.2	20.2	19.9	20.1	0.03
Cancer	2.0	3.8	6.3	8.7	0.30	6.0	6.1	5.7	5.8	0.01
CKD	7.3	11.1	20.2	16.9	0.38	17.2	16.7	16.6	16.9	0.01
Health examination										
BMI (kg/m^2)										
Mean ± SD	24.5 ± 3.4	24.6 ± 3.3	24.4 ± 3.5	24.4 ± 3.3	0.08	24.3 ± 3.5	24.4 ± 3.3	24.4 ± 3.4	24.5 ± 3.1	0.04
≥ 25	42.1	44.4	41.0	40.7		40.7	41.5	41.8	40.8	
Antithrombotic treatment and other medications										
Oral anticoagulants	19.2	23.7	28.1	29.6	0.24	26.2	26.9	26.5	27.0	0.01
Warfarin	14.6	16.9	18.8	20.1	0.17	20.3	20.2	20.4	20.5	0.00
NOAC	4.6	6.8	9.3	9.5	0.19	7.8	8.9	8.2	8.5	0.03
Antiplatelet agent	23.8	26.2	26.7	25.0	0.07	24.5	26.0	26.0	26.4	0.04
Aspirin	21.1	22.8	22.5	20.8	0.05	20.2	22.1	22.0	22.1	0.04
P2Y12 inhibitor	5.3	6.7	7.8	7.4	0.10	7.4	7.0	7.4	7.7	0.03
Statin	13.3	15.9	19.2	19.3	0.16	16.5	17.7	17.9	18.1	0.04
Low income	18.4	17.5	18.0	16.8	0.04	19.5	18.7	17.9	18.0	0.03

Categorical variables were presented as a percentage and continuous variables were presented as mean and standard deviation.
ASD, absolute standardized difference; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; SBP, systolic blood pressure.

in this analysis (**Figure 1**). The mean duration between AF diagnosis and the national health screening exam was 333 ± 203 days. The proportions of patients with 0, 1, 2, and 3 HLS were 7.1%, 22.7%, 58.6%, and 11.6%, respectively, and the baseline characteristics according to HLS are presented in **Table 1**. The baseline characteristics of the study population are summarized in **Supplementary Table 3**.

Patients in the HLS 0 group who had a cluster of three unhealthy lifestyles, including current smoking, current

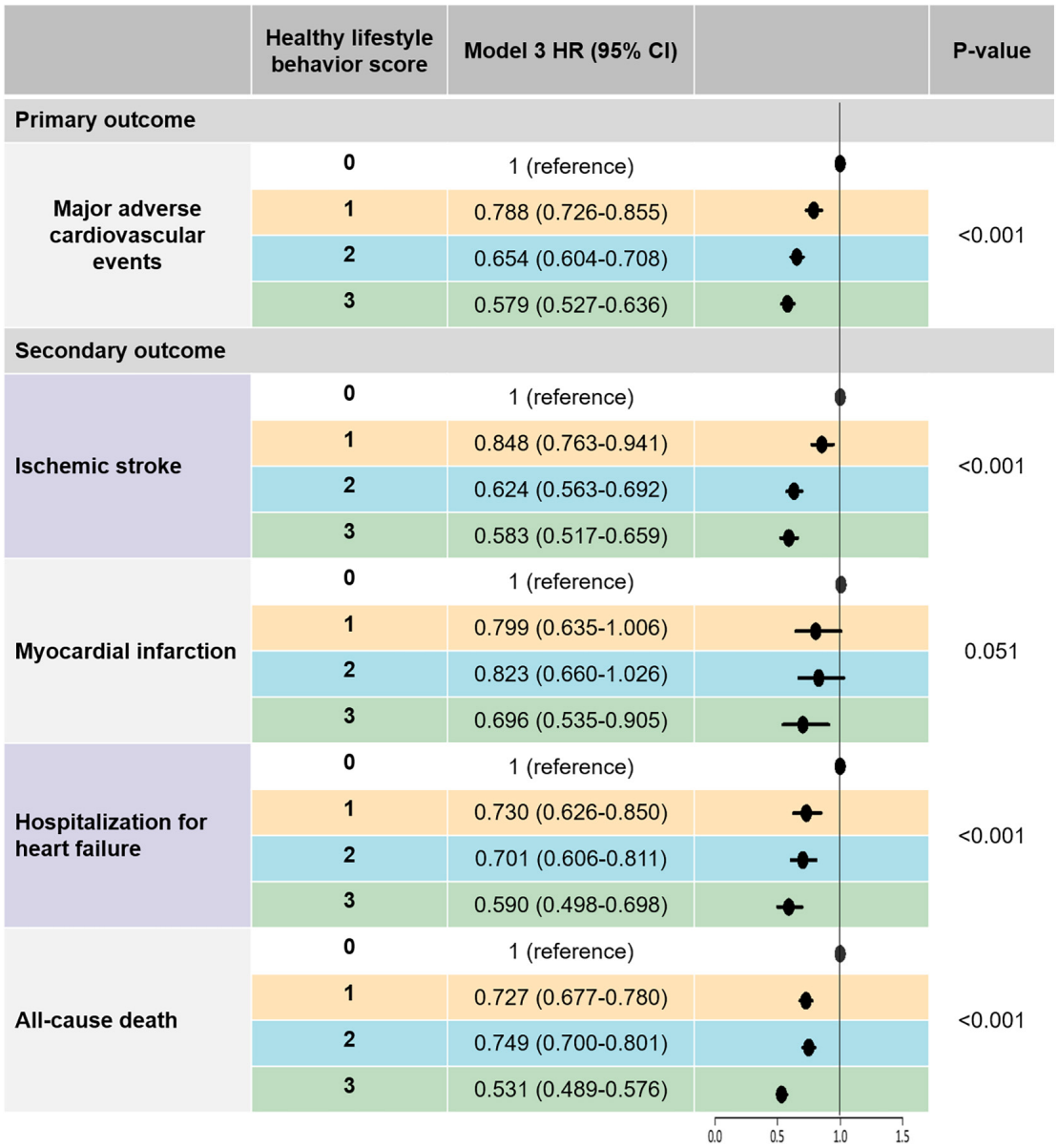

FIGURE 2 | The risk of primary and secondary outcomes according to healthy lifestyle behavior scores: a multivariable-adjusted Cox analysis. Model 3 was adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, BMI, and low income. Major adverse cardiovascular events was defined as the composite outcomes of ischemic stroke, myocardial infarction, and hospitalization for heart failure. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

drinking, and lack of regular exercise, were younger, more likely to be men, had lower CHA_2DS_2-VASc scores, and had a lower prevalence of comorbidities such as hypertension, diabetes, dyslipidaemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, and chronic kidney disease than those in the HLS 3 group who had a cluster of three healthy lifestyles. The HLS 0 group showed a lower proportion of patients with obesity (BMI $\geq$ 25 kg/m^2) than the HLS 3 group. The proportion of patients receiving oral anticoagulation treatment was higher in the HLS 1, 2, and 3 groups than in the HLS 0 group.

Risk of Clinical Outcomes According to Healthy Lifestyle Score

During a median of 3.5-year follow-up (interquartile range 1.7–5.6), ischemic stroke, myocardial infarction, hospitalization for heart failure, MACE, and all-cause death occurred in 7,110 (3.4%), 1,460 (0.7%), 4,378 (2.1%), 12,298 (16.4%), and 18,318

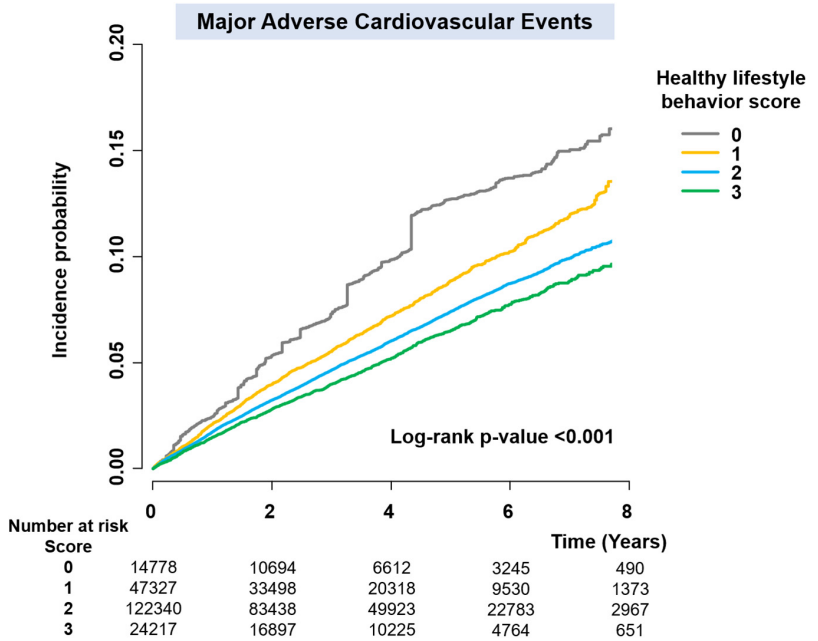

FIGURE 3 | Weighted Kaplan–Meier curves for major adverse cardiovascular events.

(8.8%), respectively. **Supplementary Table 4** and **Figure 2** show the unadjusted and adjusted HRs for clinical outcomes according to HLS groups.

After multivariable adjustment (model 3), patients with HLS 1, 2, and 3 were associated with a lower risk of MACE by 21%, 35%, and 42%, respectively, than those with HLS 0. Consistent results were observed for secondary outcomes. HLS 1, 2, and 3 groups were associated with lower risks of ischemic stroke by 15, 38, and 42%, respectively, compared to the HLS 0 group. The HLS 3 group showed a statistically significant risk reduction for myocardial infarction compared to the HLS 1 group. Compared to the HLS 0 group, the HLS 1, 2, and 3 groups were associated with lower risks of hospitalization for heart failure by 27%, 30%, and 41%, respectively. An increased number of healthy lifestyle behaviors was associated with a lower risk of all-cause death.

Sensitivity Analysis

Since the baseline characteristics of each group stratified by HLS were significantly different, we performed a sensitivity analysis to compare HLS groups for the risk of clinical outcomes using the IPTW method. The baseline covariates were well balanced among the different HLS groups after IPTW (**Table 1**). **Figure 3** and **Supplementary Figure 1** reveal weighted Kaplan–Meier curves for clinical outcomes, and **Figure 4** shows the weighted incidence rates and HRs for clinical outcomes after IPTW. The results were largely consistent with those of the multivariable Cox analysis (Model 3).

Subgroup Analyses

The results of subgroup analyses were consistent with the main analysis. For the primary outcome, there was no significant interaction between each subgroup and the risk of MACE according to HLS (**Table 2**), except for the age subgroups. Although p for interaction was 0.019 in the age subgroup analyses and the HRs were slightly different in different age subgroups, the trends and directionality of HRs of HLS 1, 2, and 3 compared to HLS 0 were consistent in all age subgroups.

DISCUSSION

In this analysis of a large-scale nationwide population-based cohort study, we sought to determine whether the accumulation of healthy lifestyle behaviors was associated with a lower risk of MACE. Our principal findings were as follows: (1) although the study patients were newly diagnosed with AF, 7% of patients had a cluster of three unhealthy lifestyles, including current smoking, current drinking, and lack of regular exercise, whereas 12% of patients had all three healthy lifestyle behaviors; (2) healthy lifestyle behaviors as a composite score were associated with a substantially lower risk of MACE, including ischemic stroke, myocardial infarction, and hospitalization for heart failure, and all-cause death; and (3) there was an inverse dose-response relationship in which an increased number of healthy lifestyle behaviors were associated with lower risks of MACE.

Considering that healthy lifestyle factors are not isolated but often occur in a cluster with other healthy lifestyle factors, we suggest that an integrated approach to lifestyle modification is needed to improve the clinical outcomes in patients with AF.

Traditionally, the management of patients with AF has been particularly focused on the prevention of stroke with anticoagulation and control rate and rhythm for symptom relief. A more integrated care approach that addresses modifiable

TABLE 2 | Subgroup analyses for major adverse cardiovascular events.

Subgroup	HLS	Number	Events	IR	HR (95% CI)	*p*-value	p-for-interaction
Age (years)							
< 65	0	11,760	429	0.96	1 (reference)	< 0.001	0.019
	1	29,903	945	0.83	0.774 (0.690–0.868)		
	2	49,419	1,398	0.72	0.626 (0.558–0.703)		
	3	11,080	259	0.60	0.503 (0.429–0.59)		
65 to < 75	0	2,323	216	2.61	1 (reference)	< 0.0001	
	1	12,071	977	2.29	0.868 (0.749–1.006)		
	2	41,522	2,982	1.98	0.710 (0.616–0.819)		
	3	9,269	575	1.74	0.666 (0.568–0.780)		
≥ 75	0	695	105	4.95	1 (reference)	< 0.001	
	1	5,353	617	3.89	0.765 (0.621–0.941)		
	2	31,399	3,457	3.87	0.673 (0.552–0.820)		
	3	3,868	338	3.03	0.593 (0.475–0.739)		
Sex							
Male	0	14,144	720	1.36	1 (reference)	< 0.001	0.380
	1	40,104	2,202	1.51	0.810 (0.744–0.882)		
	2	56,528	3,354	1.72	0.683 (0.628–0.742)		
	3	13,171	684	1.49	0.626 (0.563–0.697)		
Female	0	634	30	1.37	1 (reference)	< 0.001	
	1	7,223	337	1.26	0.657 (0.452–0.954)		
	2	65,812	4,483	1.88	0.521 (0.363–0.747)		
	3	11,046	488	1.17	0.452 (0.313–0.655)		
CHA_2DS_2-VASc score							
≤ 3	0	12,081	472	1.01	1 (reference)	< 0.001	0.135
	1	33,796	1,242	0.96	0.760 (0.683–0.846)		
	2	57,417	1,874	0.84	0.614 (0.552–0.684)		
	3	13,315	394	0.77	0.541 (0.471–0.621)		
> 3	0	2,697	278	3.16	1 (reference)	< 0.001	
	1	13,531	1,297	2.97	0.825 (0.725–0.940)		
	2	64,923	5,963	2.84	0.699 (0.617–0.791)		
	3	10,902	778	2.15	0.617 (0.537–0.709)		
Prior ischemic stroke							
No	0	12,698	540	1.12	1 (reference)	< 0.001	0.691
	1	38,262	1,706	1.20	0.776 (0.704–0.855)		
	2	86,472	4,494	1.41	0.639 (0.581–0.704)		
	3	17,671	720	1.10	0.571 (0.509–0.641)		
Yes	0	2,080	210	2.94	1 (reference)	< 0.001	
	1	9,065	833	2.75	0.796 (0.684–0.927)		
	2	35,868	3,343	2.89	0.669 (0.579–0.774)		
	3	6,546	452	2.03	0.576 (0.487–0.680)		
OAC							
No	0	11,940	604	1.31	1 (reference)	< 0.001	0.376
	1	36,122	1,894	1.38	0.764 (0.696–0.838)		
	2	87.923	5,629	1.70	0.643 (0.588–0.703)		
	3	17,058	805	1.23	0.558 (0.501–0.622)		
Yes	0	2,838	146	1.60	1 (reference)	< 0.001	
	1	11,205	645	1.85	0.895 (0.747–1.072)		
	2	3,4417	2,208	2.17	0.720 (0.604–0.857)		
	3	7,159	367	1.66	0.671 (0.552–0.816)		

Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, BMI, and low income. CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate; OAC, oral anticoagulant.

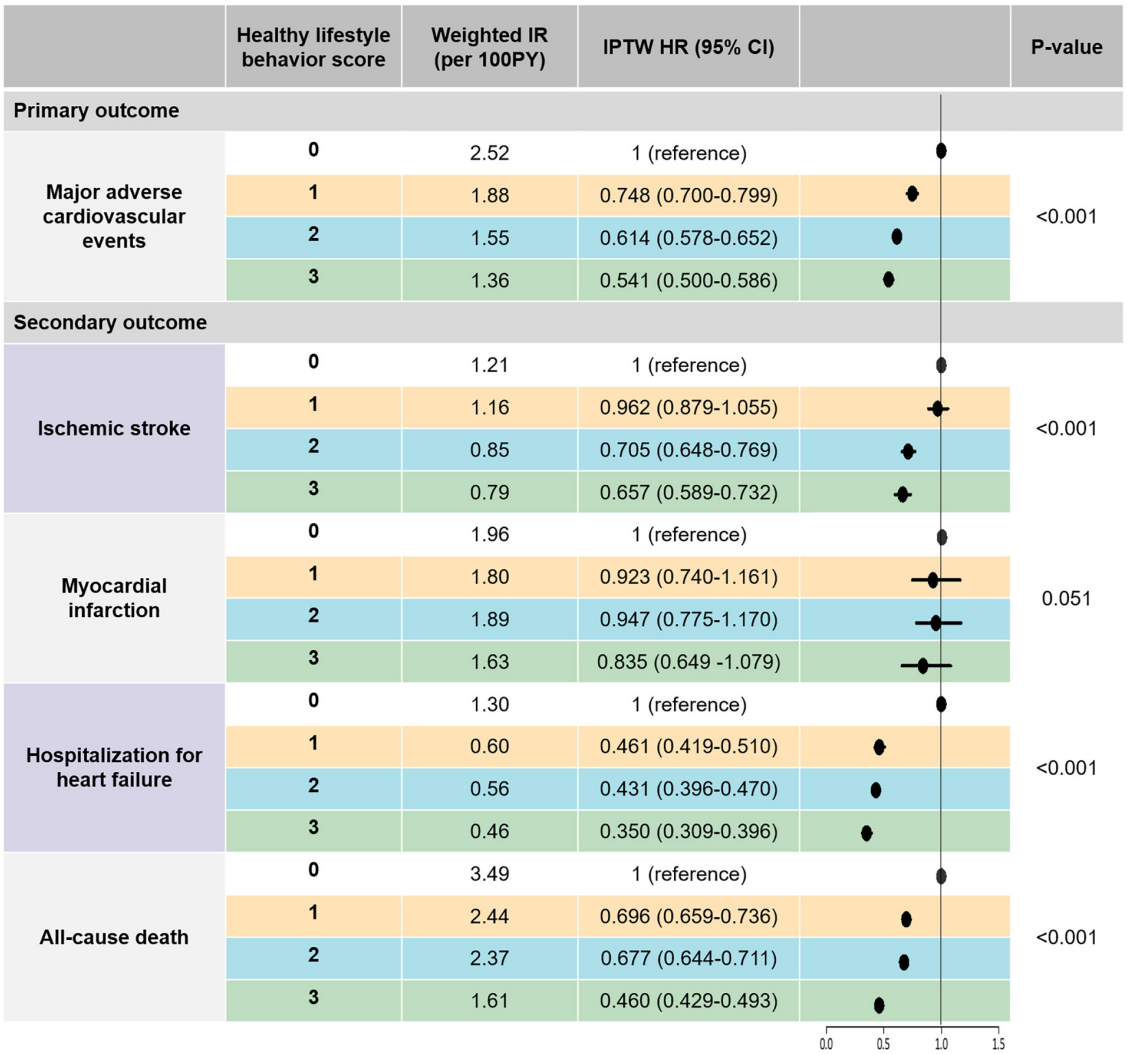

FIGURE 4 | The risk or primary and secondary outcomes according to healthy lifestyle behavior scores: an IPTW analysis. Major adverse cardiovascular events was defined as the composite outcomes of ischemic stroke, myocardial infarction, and hospitalization for heart failure. CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; PY, person-years.

risk factors, including coexisting cardiovascular comorbidities and unhealthy lifestyle behaviors, has been promoted in recent guidelines (7, 29). A recent scientific statement from the American Heart Association comprehensively summarizes the modifiable risk factors for primary and secondary prevention of AF, similar to the statement from the European Heart Rhythm Association (29, 30). Moderate exercise, smoking cessation, and alcohol intake reduction are recommended to reduce the risk of AF occurrence and reduce the AF burden (29).

Several previous observational studies have established that healthy lifestyle behaviors are associated with reducing the AF burden and lower risks of adverse clinical outcomes (11, 12, 14, 15, 31, 32). Subsequently, well-designed randomized controlled trials (RCTs) have strengthened previous findings in observational studies (13, 33). Although an RCT could not be conducted for smoking, several observational studies have shown that smoking was associated with an increased risk of stroke and death, and smoking cessation after AF diagnosis might reduce the risk of stroke and MACE (11, 12, 32). Alcohol is a well-known risk factor for the development of AF (34) and is associated with an increased risk of thromboembolic events, including ischemic stroke and AF hospitalization (14). Indeed, a recent RCT further confirmed the impact of abstinence from alcohol on reducing AF recurrence and its burden (13). In patients with AF, performing regular exercise is associated with a lower risk of all-cause death (15). In addition, higher physical activity and cardiorespiratory fitness have been associated with a lower long-term risk of death from cardiovascular disease (a composite of myocardial infarction, heart failure, and stroke) and all-cause death (31). Of note, cardiorespiratory fitness was also closely related to AF recurrence risk, with a significant dose-response relationship (33).

It must be emphasized that much of the evidence in previous studies has focused on an isolated component of lifestyle behaviors (11–15, 31–33). However, healthy (or unhealthy) lifestyle behaviors tend to cluster (16–19, 35, 36). Two RCTs have shown that intensive implementation of integrated care for modifiable risk factors significantly reduced AF recurrence (37, 38). Aggressive risk factor management, including blood pressure control, weight management, lipid management, glycemic control, sleep-disordered breathing management, smoking cessation, and alcohol reduction by the physician-directed clinic after AF catheter ablation reduced AF recurrence and symptom severity with left atrial reverse remodeling (37). In patients with early persistent AF and mild-to-moderate heart failure, optimal medical therapy combined with cardiac rehabilitation, including physical activity, dietary restriction, and counseling, improves sinus rhythm maintenance (38). In these studies, the study population was perhaps more selected from the general AF population. The components of lifestyle intervention were slightly different from our study, and the primary outcome was AF recurrence, not a hard adverse clinical outcome.

According to our results (**Supplementary Table 1**), current smoking is the most powerful factor to be associated with a higher risk of MACE [adjusted HR 1.479, 95% confidence interval (CI) 1.393–1.571]. Followed by current smoking, current drinking was associated with a higher risk of MACE by 16–32% [adjusted HR 1.159 (95% CI 1.082–1.241), 1.261 (1.139–1.397), and 1.317 (1.183–1.466) for mild, moderate, and heavy drinker, respectively]. In the case of regular physical activity, although it depends on the degree (or amount) of exercise, lack of exercise was associated with a higher risk of MACE by 10–20%. In this analysis, we did not weight each lifestyle behavior due to primarily exploring the impact of the combination of unhealthy lifestyle behavior on the risk of MACE. Further study is needed to weight each lifestyle behavior by considering the dose-response relationship of each factor and develop a more sophisticated lifestyle score for predicting AF-related adverse.

In subgroup analyses, among relatively low-risk patients with CHA_2DS_2-VASc ≤ 3, a cluster of healthy lifestyle behaviors was associated with a significantly lower risk of MACE. In addition, the benefit of a healthy lifestyle cluster was consistently observed regardless of whether the patients were anticoagulated or not. According to a recent study, current smoking was a predictor for future ischemic stroke in low-risk patients who were not indicated oral anticoagulation (male with CHA_2DS_2-VASc 0 or female with CHA_2DS_2-VASc 1) (39). Hence, proactive lifestyle risk evaluation and promotion of a healthy lifestyle in the early period of AF diagnosis would also be beneficial to prevent stroke in low-risk patients who are not indicated for oral anticoagulation treatment immediately.

The European Hypertension Guidelines regarded AF as an equivalent of cardiovascular disease risk (40). Hence, the comprehensive management of AF patients should include not only oral anticoagulation therapy but also general control or cardiovascular risk factors and comorbidities (7). The time point of immediate after the new diagnosis of AF could be the best chance to promote healthy lifestyle behaviors, including smoking cessation, reducing alcohol consumption, and initiating regular exercise, to improve clinical outcomes and reduce AF-related adverse events in the future. Physician-directed proactive management of modifiable lifestyle risk factors should be more emphasized in a holistic approach to AF care, as recommended in the guidelines (7). Indeed, lifestyle optimization is the C of the ABC (Atrial fibrillation Better Care) pathway whereby ABC pathway compliant care has been shown in numerous studies to be associated with better clinical outcomes (15, 41–43).

Study Limitations

This study included a large number of patients with incident AF. It comprehensively analyzed the association between an increased number of healthy lifestyle behaviors and the risk of MACE with sufficient statistical power. However, there are several limitations to this study. First, we classified healthy lifestyle behaviors using self-reported questionnaires. Although several studies have reported the association between lifestyle factors and adverse clinical outcomes using self-reported questionnaires, recall bias could be one of the major potential limitations (19, 22, 23, 31, 33). Second, although we performed multivariable adjustment and balanced the baseline characteristics of the different groups using IPTW, we cannot exclude the possibility of unmeasured confounding factors. For example, the types of AF, such as the paroxysmal and persistent, or the actual burden of AF at baseline could not be measured in this database. Third, changes in baseline variables during follow-up, including lifestyle factors and medication use, were not considered in this analysis. Lastly, in this study, covariates and study outcomes were defined based on the diagnostic codes, which could be affected by the physicians' clinical practice, thus, might have resulted in an underestimation and overestimation. To overcome this limitation, we used a well-established and widely used operational definition in previous studies, or a validated definition through our own data (21, 44).

CONCLUSION

Increased number of healthy lifestyle behaviors, including quitting smoking, abstaining from alcohol consumption, and performing regular physical activity, were significantly associated with lower risks of MACE and all-cause death in patients with new-onset AF. These findings support the promotion of a healthy lifestyle and a more holistic or integrated approach to reduce the risk of adverse events in patients with AF.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Seoul National University Hospital Institutional

Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-RL, E-KC, and GL: conceptualization. S-WL and K-DH: methodology and data curation. K-DH: software and resources. S-RL, S-WL, S-HP, and E-KC: validation. S-WL: formal analysis. S-RL: investigation, writing—original draft preparation, and visualization. S-RL, S-HP, E-KC, and GL: writing—review and editing. SO: supervision. E-KC: project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.885016/full#supplementary-material

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Tailored Target Ablation Index Guided Pulmonary Vein Isolation in Treating Paroxysmal Atrial Fibrillation: A Single Center Randomized Study in Asian Population (AI-Asian-I)

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Objective: To evaluate the efficacy and safety of lower ablation indexes (AI) guided pulmonary vein isolation (PVI) in treating paroxysmal atrial fibrillation (AF).

Methods: Ninety patients with paroxysmal AF scheduled for radiofrequency ablation were randomly divided into three groups. The AI targets for PVI were as follows: In group A/B/C, 550/500/450 for roof and anterior wall, and 400/350/300 for posterior/inferior wall. The first-pass PVI rate, ablation time, complications and recurrence of atrial tachyarrhythmia (ATa) were compared.

Results: The mean age was 62.5 years (male: 63.0%), mean body mass index (BMI): 24.35 ± 3.66 kg/m^2. The baseline characteristics were comparable. There was no significant difference in the first-pass PVI rate among the three groups (left-sided-PV: 66.7% vs. 80% vs. 73.3%, P = 0.51; right-sided-PV: 70% vs. 83.3% vs. 73.3%, P = 0.64), also with similar gap rate during the procedural waiting time. At 1-year follow-up there was no significant difference in the recurrence rate of ATa among the three groups (10% vs. 13.3% vs. 13.3%, P = 1.00). The ablation time in the Group C was significantly less than that in the other two groups (47.8 min. vs. 47.0 min. vs. 36.6 min, $P < 0.001$). Higher AI seemed to link a non-significant trend toward higher rate of pericardial effusion (group A + B vs. group C:6.7% vs. 0%, P = 0.30), although the rate of overall complications was not different among the three groups.

Conclusion: This randomized study shows that, a relatively lower target AI guided ablation may be similarly effective to achieve PVI with significantly reduced ablation time and obtain similar clinical outcome in treating paroxysmal AF in Asian population.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [NCT:04549714].

Keywords: atrial fibrillation, ablation index, pulmonary vein isolation, randomized, recurrence

INTRODUCTION

Catheter ablation is an effective treatment option for patients with symptomatic atrial fibrillation (AF) (1–5). Electrical reconnection between the pulmonary veins and left atrium has been recognized as an important factor responsible for AF recurrence after ablation (6, 7). Radiofrequency ablation is conventionally performed with or without contact-force technology, usually not guided by standardized quantitative criteria. Lower ablation energy delivery may result in non-transmural damage, but over-shooting increases ablation time and may increase risk of complications (8, 9).

The ablation index (AI) which integrates catheter contact force, ablation power, and ablation duration is an algorithm to guide radiofrequency ablation, and the AI can be used to quantify the ablation energy and predict lesion formation (10–12). Previous studies have shown the efficacy of AI guided ablation for AF, and the target AI values adopted are generally 550 for the anterior wall and the roof and 400 for the inferior/posterior wall (13, 14).

However, (1) the target AI 550/400 was mainly obtained from European-American population; (2) The lesion depth caused by ablation guided by target AI of 550/400 can be deeper than the atrial thickness *per se* and may therefore potentially increase the risk of complications, particularly among Asian population, an ethnic group normally with smaller atrial size (15, 16). The aim of this randomized study was to investigate the feasibility, safety, efficacy and clinical outcome of catheter ablation guided by predefined lower target AI for pulmonary veins isolation (PVI) in treating paroxysmal AF in Asian population.

MATERIALS AND METHODS

Study Design

The study was designed as a prospective randomized, single blind, non-placebo controlled clinical study with the primary objective of assessing the optimal ablation index to achieve effective pulmonary vein isolation. A total of 90 patients with paroxysmal AF were randomly assigned to group A, B, and C by using a randomization envelope. Group A was designed with target AI value of 550 at the roof and anterior wall and 400 at the posterior and inferior wall; Group B was designed with target AI value of 500 at the roof and anterior wall and 350 at the posterior and inferior wall; Group C was designed with target AI value of 450 at the roof and anterior wall, and 300 at the posterior and inferior wall (**Figure 1**). The study was approved by ethics committee of Second Affiliated Hospital of Chongqing Medical University and complied with the declaration of Helsinki. Written informed consent was obtained from all patients.

Study Population and Exclusion

Study population: (1) Patients with symptomatic paroxysmal AF; (2) Age 18–80 years; (3) Without contraindication to anticoagulant therapy; (4) Transoesophageal ultrasonography excluded atrial/left atrial appendage thrombi. Exclusion criteria: (1) Patients who had undergone prior catheter ablation for AF; (2) Left ventricular ejection fraction (LVEF) $<$ 35%; (3) Pregnant, prepared pregnant or lactating women; (4) Left atrial appendage thrombus detected by transesophageal or intracardiac ultrasonography; (5) Severe abnormalities of hematologic or hepatic and renal function; (6) Combined with other heart disease (congenital heart disease, valvular heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy); (7) Acute myocardial infarction or patients who had undergone PCI or CABG within 1 year; (8) Pulmonary vein stenosis, occlusion, or thrombus.

Pre-procedure

Pre-operative Transesophageal ultrasonography was completed to exclude intracardiac thrombi. Cardiac Computed tomography (CT) or magnetic resonance imaging (MRI) was performed to assess the anatomy. All patients received anticoagulant therapy according to the recommendation (17). To reduce the risk of bleeding during ablation, oral anticoagulant drugs were suspended on the day of ablation. All patients discontinued antiarrhythmic drugs 5 half-life period.

Ablation

Procedures were performed by two operators; both of them have had more than 5 years of ablation experience and more than 50 procedures per year. All ablation were under local anesthesia, and fentanyl was used to reduce pain during ablation. Heparin was administered at 100–120 U/kg and activated prothrombin time (ACT) was maintained at 300–400 S. After the puncture of the bilateral femoral veins, a 7F vascular sheath was placed through the left femoral vein and a diagnostic electrode catheter (SinusFlex^{TM}, APT Medical, China) was placed in the coronary sinus. Two 8.5F Swartz transseptal sheaths (St. Jude) were advanced through the right femoral vein, and transseptal puncture was performed under the guidance of fluoroscopy. A spiral diagnostic mapping catheter (Lasso, Biosense-Webster Inc., Diamond Bar, CA) was positioned in left atrium *via* the transseptal sheath to document the pulmonary vein ostia potential. A 3.5 mm irrigated tip ablation catheter (Thermocool SmartTouch; Biosense-Webster Inc., Diamond Bar, CA) was advanced in the left atrium *via* the other transseptal sheath. Anatomical model of left atrial, pulmonary vein, and mitral annulus was constructed under the guidance of the 3D mapping system (CARTO 3 V6; Biosense-Webster, Inc., Diamond Bar, CA). Wide-area circumferential pulmonary vein antrum isolation (PVI) was performed under the guidance of carto mapping system and automated lesion tagging (VisiTag^{TM}, Biosense Webster Inc., DiamondBar, CA, United States). The following Visitag settings were used: 3 mm stability for 3 s. Inter-lesion distance (ILD) targets $\leq$ 5 mm. Ablation power was set at 35 W, target contact force between 5 and 15 g, irrigation rate of 25 ml/min. The target AI for ablation was determined according to randomization (**Figure 2**). The ablation endpoint was reached if disappearance (or dissociation) of all pulmonary vein potential after completion of the ablation circles. Otherwise, the gaps were searched and ablated until successful PVI. If patient remained in AF after PVI, electrical cardioversion was performed to restore sinus rhythm. 30 min waiting time was required for all patients

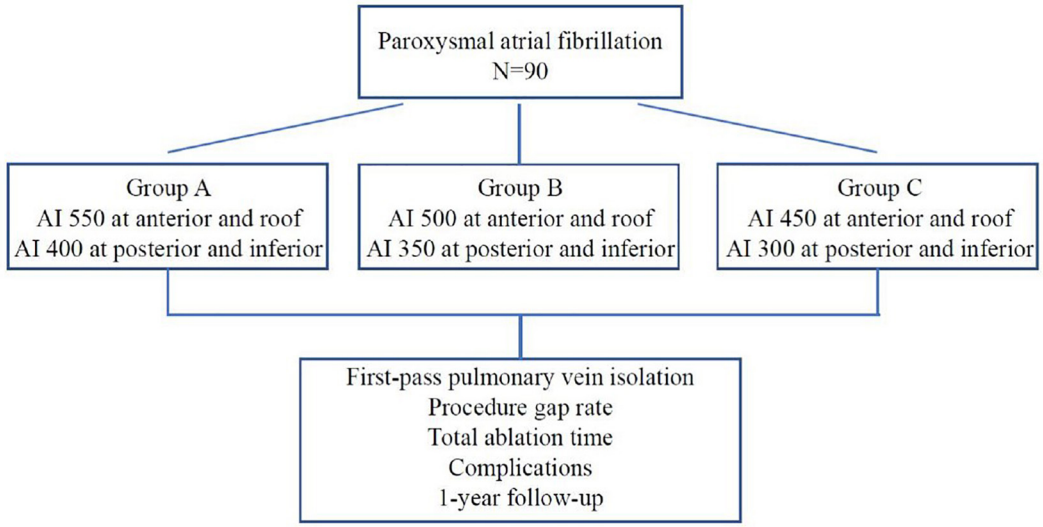


FIGURE 1 | The study flowchart.

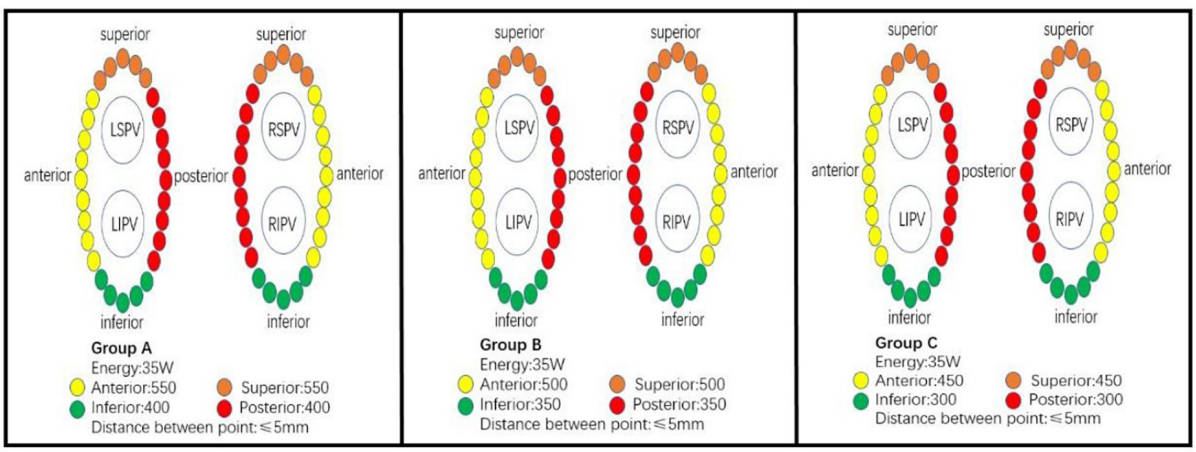


FIGURE 2 | Pulmonary vein segments and ablation protocol in Group A/B/C.

TABLE 1 | Baseline characteristics.

Characteristics	Total(*n* = 90)	Group A(*n* = 30)	Group B(*n* = 30)	Group C(*n* = 30)	*P*-value
Age, years ± *SD*	62.5 ± 10.5	61 ± 10	63 ± 13	63 ± 13	0.74
Male gender, *n* (%)	57 (63.3)	18 (60)	19 (63.3)	20 (66.7)	0.87
Diabetes mellitus, *n* (%)	12 (13.3)	4 (13.3)	5 (16.7)	3 (10)	0.93
Hypertension, *n* (%)	44 (48.9)	11 (36.7)	18 (60)	15 (50)	0.19
Stroke/TIA (including lacunar), *n* (%)	16 (17.8)	4 (13.3)	9 (30)	3 (10)	0.95
Heart failure, *n* (%)	10 (11.1)	2 (6.7)	5 (16.7)	3 (10)	0.59
CHD, *n* (%)	16 (17.8)	5 (16.7)	4 (13.3)	7 (23.3)	0.59
BMI, kg/m^2, mean ± *SD*	24.35 ± 3.66	25.17 ± 2.78	23.88 ± 4.43	24.01 ± 3.66	0.12
Smoke, *n* (%)	33 (36.7)	10 (33.3)	11 (36.7)	12 (40)	0.87
LA diameter (mm), mean ± *SD*	36.1 ± 3.8	35.9 ± 3.5	35.8 ± 4.4	36.6 ± 3.5	0.45
LVEF (%), mean ± *SD*	68.6 ± 7.0	67.9 ± 6.2	69.2 ± 6.7	68.6 ± 8.1	0.77
CHA_2DS_2-VASc, mean ± *SD*	2.2 ± 1.5	1.9 ± 1.4	2.1 ± 1.4	2.7 ± 1.5	0.06

BMI, body mass index; LA, left atrium; CHD, coronary heart disease; LVEF, left ventricular ejection fraction.

TABLE 2 | Comparison of first-pass PVI among three groups.

	Group (AI)	Total (circle)	First-pass PVI (*n*, %)	*P*-value
LPV	Group A (550/400)	30	20 (67.7)	0.51
	Group B (500/350)	30	24 (80)	
	Group C (450/300)	30	22 (73.3)	
RPV	Group A (550/400)	30	21 (70)	0.64
	Group B (500/350)	30	25 (83.3)	
	Group C (450/300)	30	22 (73.3)	

RPV, Right-sided pulmonary vein; LPV, left-sided pulmonary vein; PVI, pulmonary vein isolation.

after PVI, each pulmonary vein was re-examined to confirm procedural success.

Follow-Up

All patients returned to the hospital for follow-up at 1, 3, 6, and 12 months after discharge. The main contents included: 12-channel electrocardiography(ECG), 24-h Holter ECGs, and clinical symptoms. Three-month after the procedure was defined as a blank period. Oral antiarrhythmic drugs remained discontinued after the procedure, cardioversion or AADs were allowed if early recurrence during the blanking period. In case of any symptoms suggestive of an arrhythmia recurrence, 24 h Holter ECGs were performed or patient received an external event monitor. Arrhythmia recurrence was defined as ECG documented atrial arrhythmias longer than 30 s after 3 months without AADs. Oral preventive PPI inhibitors were used for 1 month after the ablation. The primary outcomes were the rate of first-pass PVI and clinical recurrence, and secondary outcomes referred to procedural data, including ablation time, procedure time, rate/location of gaps and procedural complications.

Statistics

The sample size calculation was primarily based on the rates of first-pass PVI guided by different AIs reported in previous literatures, i.e., the rate of first-pass PVI ranged from ca. 70% guided by lower target AI to ca. 95% guided by higher target AI. At α level of 0.05, the sample size of 64 patients (32 in each group) could provide 80% statistical power to estimate the differences between two groups.

Normally distributed continuous data were expressed as mean ± standard deviation. Non-normally distributed data were presented as median with interquartile range. Categorical data were presented as frequencies and percentages. The normality of variable distribution was tested using the Shapiro–Wilk test. The *t*-test was used to compare continuous variables with normal distribution; otherwise the Mann–Whitney test was used. For categorical variables, comparisons between groups were performed using the chi square test or Fisher's exact test. Kaplan – Meier analysis and log rank test were used for event free survival analysis. For all calculations, two tailed tests were used, and the level of significance was set at a *p*-value of 0.05. All calculations were performed using SPSS 25 (IBM Corp., Armonk, NY, United States).

RESULTS

Population Baseline Characteristics

The study recruited the first patient on June 18, 2019 and the last patient on June 29, 2020. All 90 patients completed 1 year follow-up and were included in the data analysis. **Table 1** reports the demographic information of all included patients. The three groups were balanced in terms of basic characteristics, mean age 62.5 years, 63.3% male, mean left atrial diameter 36.1 mm by TTE, and left ventricular ejection fraction 68.6%.

First Pass Pulmonary Vein Isolation

As shown in **Table 2**, The first-pass isolation rate of left-sided pulmonary vein was 73.3% in 90 patients, and there was no significant statistical difference among the three groups (67.7% vs. 80% vs. 73.3, $P = 0.51$). The first-pass isolation rate of the right-sided pulmonary vein was 75.6%, with no significant difference between the three groups (70% vs. 83.3% vs. 73.3, $P = 0.64$) (**Table 2**).

For patients who did not have first-pass isolation, the location of gap was searched. **Figure 3** summarizes the procedural gap rate and the distribution of the gaps. In details, for the left pulmonary veins, in group A, 3 gaps were located at the anterior wall, 3 gaps at the posterior wall and 1 gap at the inferior; in Group B, 2 gaps at the posterior wall and 3 gaps at the anterior wall; in group C, there were 6 gaps at anterior wall, 1 gap at inferior wall, and 1 gap at posterior wall. For the right pulmonary veins, in group A, 2 gaps were located at the anterior wall, 3 gaps at the posterior wall, 1 gap at the inferior wall; in Group B, 1 gap at the posterior wall and 5 gaps at the anterior wall; in group C, 8 gaps were at the posterior wall. **Table 3** compares the procedural gaps rate (including the 30 min waiting time) among the three groups, and no significant difference was observed.

Recurrence

All patients completed 1-year follow-up. The results showed that 3 patients had recurrent AF after ablation in group A, 4 patients in group B (1 patient had recurrent left atrial flutter), and 4 patients recurrent AF in group C. The rate of ATa recurrence was similar among the three groups (10% vs. 13.3% vs. 13.3%, $P = 1.00$), and **Figure 4** shows the Kaplan Meier Curve for freedom from ATa recurrence. In univariate and multivariate regression analysis, no factor related to the recurrence of ATa was found (**Table 4**).

Ablation Time and Complications

The procedure was successfully completed in all 90 patients, the procedure duration (172.4 ± 41.1 min vs. 176.2 ± 36.2 min vs. 168.3 ± 46.7 min, $p = 0.37$) and fluoroscopy time (21.17 ± 5.59 min vs. 18.42 ± 5.18 min vs. 18.42 ± 5.62 min, $p = 0.71$) reached no significant difference, but the ablation time was significantly reduced in the low AI group (group C) compared with the other two groups (47.8 ± 14.6 min. vs. 47.0 ± 15.6 min vs. 36.6 ± 8.9 min, $P < 0.001$), and there was no statistical difference between groups A and B. Four patients had pericardial effusion, 3 in group A, 1 in group B, and 0 in group C (10% vs. 3.3% vs. 0%,

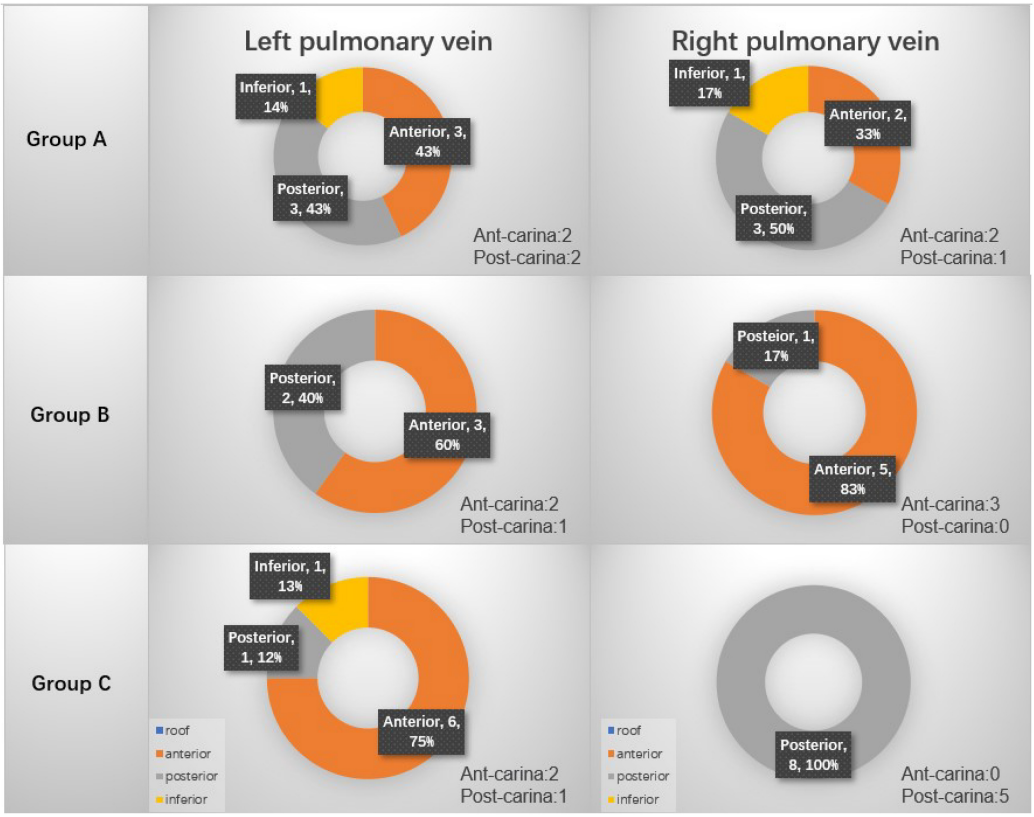


FIGURE 3 | Procedural gap distribution among three groups.

TABLE 3 | Comparison of gap rate after first-around ablation circles and during waiting time.

1) Group/segment	Gap/N (per circle) (After first around circles)	*P*
Group A Gap roof/anterior	5/60	0.66
Group B Gap roof/anterior	8/60	
Group C Gap roof/anterior	6/60	
Group A Gap inferior/posterior	8/60	0.12
Group B Gap inferior/posterior	3/60	
Group C Gap inferior/posterior	10/60	
2.) Total gap rate	Gap/N (per circle) (After first around circles)	P
Group A	13/60	0.54
Group B	11/60	
Group C	16/60	
3). Gap rate	Gap/N (per circle) (Waiting time)	P
Group A	0/60	NS
Group B	0/60	
Group C	0/60	

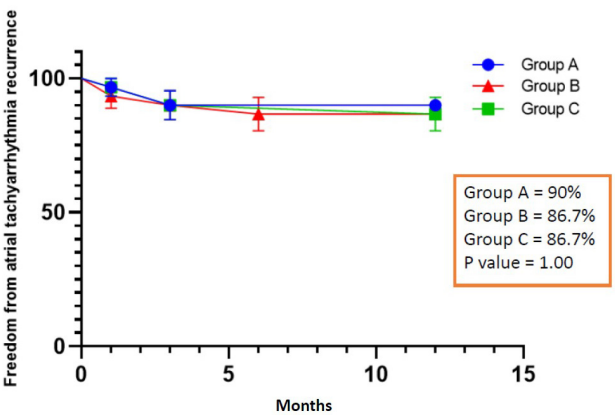


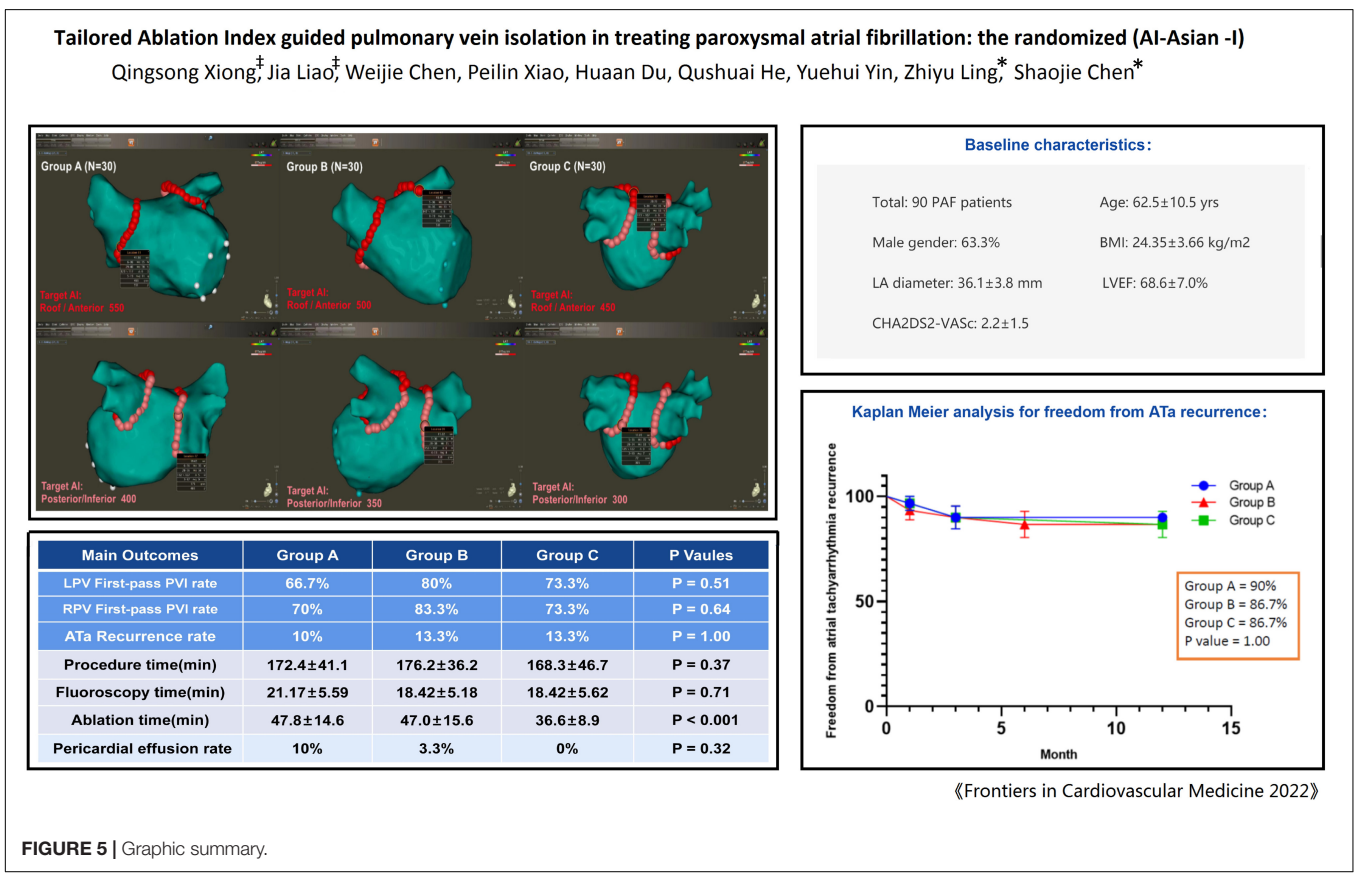
FIGURE 4 | Freedom from atrial tachyarrhythmia recurrence.

P = 0.32) (group A + B vs. group C: 6.7% vs. 0%, *P* = 0.30), all pericardial effusions were treated with pericardiocentesis (aspiration of fluid volume: 100–200 ml) without surgery. There was no steam pop in all procedures. One arteriovenous fistula occurred in group A, the patient was asymptomatic and without hematoma at the puncture site. Other complications, such as death, thromboembolic events, major bleeding, PV stenosis, phrenic nerve palsy, or symptoms suggestive of esophageal injury were not observed during the study period.

TABLE 4 | Univariate and multivariate Cox regression analysis for ATa recurrence.

Factor	Patients without ATs recurrence	Patients with ATs recurrence	Univarite analysis		Multivariable	
			P	HR	*P*	HR
Lower AI (Group C, %)	26 (32.9)	4 (36.4)	0.84	1.06 (0.58–1.97)	0.65	1.17 (0.59–2.32)
Age	62.53	62.95	0.48	1.02 (0.96–1.09)	0.10	1.07 (0.99–1.16)
CHA_2DS_2-VASc	2.23	2.27	0.50	0.86 (0.57–1.32)	0.42	0.77 (0.41–1.45)
HAS-BLED	0.92	0.99	0.69	0.85 (0.40–1.84)	0.49	0.69 (0.23–2.03)
LA	36.12	36.34	0.71	1.03 (0.88–1.20)	0.16	1.14 (0.95–1.37)
BMI	23.35	24.14	0.70	0.97 (0.82–1.14)	0.81	0.98 (0.80–1.19)
Male	50.00	7	0.96	1.03 (0.30–3.05)	0.79	0.81 (0.17–3.81)
Diabetes	12	0	0.39	0.04 (0.00–67.4)	0.98	0.00 (0.00–)
Hypertension	49	4	0.39	0.58 (0.17–1.99)	0.22	0.37 (0.07–1.84)
CHD	15	1	0.46	0.46 (0.06–3.61)	0.74	0.67 (0.06–7.39)
Smoke	29	4	1.00	1.00 (0.29–3.41)	0.36	2.32 (0.38–14.21)
CKD	14	1	0.51	0.52 (0.06–3.92)	0.89	1.21 (0.09–16.76)
LVEF	68.56	68.76	0.50	1.03 (0.94–1.14)	0.32	1.07 (0.94–1.21)

AI, ablation index; Ata, atrial tachyarrhythmia; LA, left atrium; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction.



Main Outcomes	Group A	Group B	Group C	P Vaules
LPV First-pass PVI rate	66.7%	80%	73.3%	P = 0.51
RPV First-pass PVI rate	70%	83.3%	73.3%	P = 0.64
ATa Recurrence rate	10%	13.3%	13.3%	P = 1.00
Procedure time(min)	172.4±41.1	176.2±36.2	168.3±46.7	P = 0.37
Fluoroscopy time(min)	21.17±5.59	18.42±5.18	18.42±5.62	P = 0.71
Ablation time(min)	47.8±14.6	47.0±15.6	36.6±8.9	P < 0.001
Pericardial effusion rate	10%	3.3%	0%	P = 0.32

FIGURE 5 | Graphic summary.

DISCUSSION

The main findings are summarized in **Figure 5**. In this randomized study, we compared different target AI guided PVI in treating paroxysmal AF. The overall rate of first-pass PVI was 73.3%, and the rate of first-pass PVI did not significantly differ between the three groups, also with similar gap rate during the procedural waiting time. Lower AI guided PVI (group C) was associated with significantly less ablation time than that in the other two groups, whereas higher AI guided PVI seemed to link a non-significant trend toward higher rate of pericardial effusion/tamponade, although

the rate of overall complications was not different. One-year follow-up showed single-procedural similar freedom from ATa recurrence among the three groups. To the best of our knowledge, this is the first randomized study investigating different target ablation index to guide pulmonary vein isolation in Asian population.

Previous studies showed that AI guided AF ablation may improve the procedural efficacy (18); however, studies to define optimal AI value remains limited. According to the anatomy, the thickness of atrial tissue is about 2–4 mm. *In vitro* experiments showed that, every 100 increase of the AI caused lesion-depth increase by 1 mm. Thus theoretically, the transmural lesion can be achieved when the AI reaches 200–400 depending on the thickness of atrial wall. From the literature, the mostly adopted target AI was around 500–550/350–400, mainly from European-American population, and such target AI led to a first-pass rate of PVI around 70–90% (19–24).

Notably, the patients enrolled in our study appeared to have significantly lower BMI (24 kg/m^2) and smaller LA (36 mm). Consistent with previous studies, the overall rate of first-pass PVI in our study was 73.3%, and interestingly the rate of first-pass PVI did not significantly differ between the three groups, indicating that relatively lower AI guided ablation might be effective to achieve procedural PVI among Asian population. Such assumption seemed to be further supported by the similar procedural gap rate (even during the waiting time) and the similar ATa recurrence rate during follow-up.

Indeed, the 70–80% first-pass PVI observed in our study was not high. A relatively lower power (35W) adopted in our study may play a role since it has been known that high-power ablation may form wider ablation lesion. Second, the target inter-lesion distance of 5 mm was employed in our study, as previous randomized study found that a relatively wider inter-lesion distance (5–6 mm) was associated with significantly lower rate of first-pass PVI as compared with that with closer inter-lesion distance (3–4 mm), when using conventional power ablation for PVI (25).

In general, effective lesion formation with short ablation time indicates an efficient procedure, or even may be safe procedure. Longer ablation time can be potentially associated with increased risk of procedural complication. In our study, four (4/90) patients had pericardial effusion after the AI guided PVI without evidence of notable steam-pop, all pericardial effusion occurred in higher AI groups (3 in group A, 1 in group B), and no pericardial effusion occurred in group C. More specifically, all pericardial effusions were detected after the PVI during routine echocardiography, and all these patients had additional ablation due to no first-pass isolation. For the four patients who had pericardial effusion: three were female, one male patient had known renal dysfunction, all four patients were in older age (mean 70 years old) with relatively low BMI (mean 24 kg/m^2), procedural ACTs were between 300 and 350, and no audible steam-pop was noticed during the procedures. The four patients with pericardial effusion were treated with pericardiocentesis (aspiration of fluid volume: 100–200 ml), without needing surgery. These observations may indicate that, (1) pericardial effusion could still occur regardless of steam-pop; (2) repeated or additional ablation to achieve the target AI thereby to close the gap sites due to failure of first-pass isolation appears to be a risk factor of pericardial effusion; (3) the recommended target AI derived from the European-American population might not be necessarily suitable for Asian population, and should be performed with cautions, e.g., in small, older, female patients.

In our study, lower AI guided ablation (group C) was associated with significantly less ablation time. However, we did not count overall procedure and fluoroscopic time for every patient because some patients also had concomitant electrophysiological examination, and some patients had concomitant coronary angiography. Although this was a randomized study, as an initial validation study, the sample size in each group was rather small. We could only investigate the procedural efficacy of the different AI guided PVI, and the long-term durable PVI could not be assessed in the present study. The ATa recurrence was only assessed by Holter-ECG, without continuous heart rhythm monitoring, thus some episodes of ATa recurrences may not be diagnosed in all the three groups. Conventional power instead of high power was used, thus our result cannot be generalized to high power ablation strategy. Due to unavailability our patients could not receive esophageal temperature monitoring during ablation. As preventive strategy, the atrial esophageal anatomical relationship was carefully assessed by pre-procedural cardiac CT or MRI and integrated in the 3D mapping system, energy delivery at those potential adjacent sites were maximally avoided. In addition, all patients received 4 weeks preventive PPI therapy after the ablation, and no patients had symptoms or signs suggestive of esophageal injury during clinical follow-up.

CONCLUSION

This randomized study shows that, a relatively lower target AI guided AF ablation may be similarly effective to achieve PVI with significantly reduced ablation time and obtain similar clinical outcome in treating paroxysmal atrial fibrillation in Asian population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was approved by Ethics Committee of Second Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL: study design. QX, JL, WC, PX, HD, QH, YY, and ZL: data collection. QX and JL: data analysis. QX, ZL, and SC: first draft. QX, JL, WC, PX, HD, QH, YY, ZL, and SC: review and approval. ZL and SC were co-mentors for the dissertation. SC dedicated intellectual contribution to the dissertation, interpreted the study results, and made critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Oral anticoagulant decreases stroke recurrence in patients with atrial fibrillation detected after stroke

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Background: Atrial fibrillation detected after stroke (AFDAS) has a lower risk of ischemic stroke recurrence than known atrial fibrillation (KAF). While the benefit of oral anticoagulants (OAC) for preventing ischemic stroke recurrence in KAF is well established, their role in patients with AFDAS is more controversial. This study aimed to evaluate the association between OAC use and the risk of recurrent ischemic stroke in patients with AFDAS in a real-world setting.

Methods: This nationwide retrospective cohort study was conducted using the Taiwan National Health Insurance Research Database. Patients hospitalized with a first-ever ischemic stroke and AFDAS confirmed within 30 days after hospitalization were assigned to OAC and non-OAC cohorts. Inverse probability of treatment weighting was applied to balance the baseline characteristics of the cohorts. The primary outcome was ischemic stroke recurrence. Secondary outcomes were intracranial hemorrhage (ICH), death, and the composite outcome of "ischemic stroke recurrence, ICH, or death." Multivariate Cox proportional hazard models were used to estimate adjusted hazard ratios (aHR) and 95% confidence intervals (CI).

Results: A total of 4,508 hospitalized patients with stroke and AFDAS were identified. Based on OAC use, 2,856 and 1,652 patients were assigned to the OAC and non-OAC groups, respectively. During the follow-up period (median

duration, 2.76 years), the OAC cohort exhibited a lower risk of ischemic stroke recurrence (aHR, 0.84; 95% CI, 0.70–0.99), death (aHR, 0.65; 95% CI, 0.58–0.73), and composite outcome (aHR, 0.70; 95% CI, 0.63–0.78) than did the non-OAC cohort. The risk of ICH (aHR, 0.96; 95% CI, 0.62–1.50) was not significantly different between the two cohorts.

Conclusion: OAC use in patients with AFDAS was associated with reduced risk of ischemic stroke recurrence, without an increased risk of ICH. This supports current guidelines recommending OACs for secondary stroke prevention in patients with AF, regardless of the time of diagnosis.

KEYWORDS

atrial fibrillation, atrial fibrillation detected after stroke, anticoagulant, ischemic stroke, intracranial hemorrhage

Introduction

Stroke can be the initial clinical manifestation of previously undetected atrial fibrillation (AF) (1). Up to 58.7% of patients with AF-related acute ischemic stroke have AF detected after stroke (AFDAS) (2, 3). The prognosis and management of stroke patients with AFDAS have recently attracted more attention (3–9) owing to the increased utilization of advanced monitoring technology for AF screening after a stroke (10, 11). According to current guidelines (9, 12), newly detected AF in patients who suffered a stroke should prompt anticoagulation unless contraindicated. However, compared to patients with AF known before stroke (KAF), AFDAS seems to have a more benign profile (5, 6, 8, 13). A recent systematic review and meta-analysis showed that patients with AFDAS have a lower burden of risk factors, a lower CHA_2DS_2-VASc score, a smaller left atrium, and 26% lower risk of stroke recurrence than patients with KAF (14). Furthermore, another systematic review and meta-analysis of randomized controlled trials has shown that although prolonged cardiac monitoring in patients with stroke results increased AF detection and use of oral anticoagulants (OACs), it is not associated with reduced risk of stroke recurrence (15). These recent studies suggest that given the relatively benign risk profile of AFDAS, the use of OACs in these patients may not be as beneficial as it is for patients with KAF. However, to our knowledge, no prior randomized controlled trials or observational studies have confirmed the benefits of OACs in patients with AFDAS (16). Therefore, we conducted this nationwide population-based cohort study to examine the association between OAC use and ischemic stroke recurrence, as well as with intracranial hemorrhage (ICH) and death, in stroke patients with AFDAS.

Materials and methods

Data sources

The present study was conducted using data from Taiwan's National Health Insurance Research Database (NHIRD) between 2000 and 2018. The NHIRD is derived from the electronic claims data of Taiwan's National Health Insurance program, which enrolls more than 99% of the Taiwanese population (approximately 23.6 million). The NHIRD is currently stored and managed by the Health and Welfare Data Science Center of Taiwan's Ministry of Health and Welfare (17). It provides comprehensive healthcare information, including medication prescriptions, medical device usage, and emergency, inpatient, or outpatient visits. Information on individual beneficiaries can be linked and longitudinally followed using an encrypted identification number. The study protocol was approved by the Institutional Review Board of Hualien Tzu Chi Hospital (IRB-107-152C). The requirement for obtaining informed consent was waived, as personal identifiers of patients were encrypted in the NHIRD.

Study design, population, and definitions

In this retrospective cohort study, we identified consecutive adult patients hospitalized due to first-ever ischemic stroke with AFDAS between 2012 and 2017 (**Figure 1**). Each patient's index date and year were defined as the admission date and year of the index stroke event, respectively. Ischemic stroke was defined based on ICD-9-CM codes 433 and 434 before 2016, and ICD-10-CM code I63 thereafter (18–20). ICH was defined

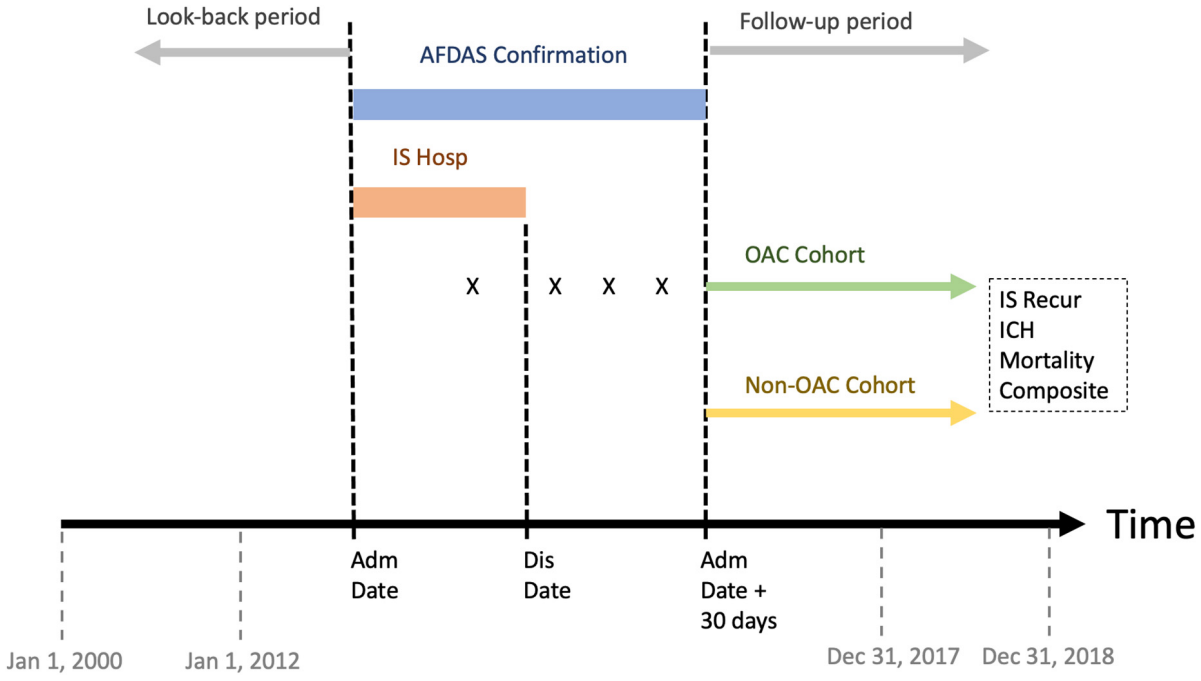

FIGURE 1
Study design. AFDAS, atrial fibrillation detected after stroke; Hosp, hospitalization; X, prescription of oral anticoagulant; Adm, admission; Dis, discharge; OAC, oral anticoagulant; IS Recur, ischemic stroke recurrence; ICH, intracranial hemorrhage.

by applying ICD-9-CM codes 430, 431, and 432 before 2016 and ICD-10-CM codes I60, I61, and I62 thereafter (21). Only patients with available brain imaging during hospitalization for their index stroke event were included.

We established a 10-year lookback window to identify and exclude patients with a previous diagnosis of stroke or related cerebral vascular disease (ICD-9-CM codes 430–438 or ICD-10-CM codes I60–I69), in either inpatient and outpatient claims, to avoid reporting bias based on outcomes and indication bias based on anticoagulant use. AF was identified by using ICD-9-CM codes 427.31 and ICD-10-CM code I48.0–I48.2 or I48.9 (22, 23). AFDAS was defined as a new diagnosis of AF in either the inpatient or outpatient claims within 30 days after the index date. For this purpose, we applied the same 10-year look-back window before the index date to exclude patients with a previous diagnosis of AF. In Taiwan, prolonged cardiac monitoring is not reimbursed by the National Health Insurance, so the vast majority of the AFDAS diagnoses are made on admission electrocardiography (ECG) or 24-h Holter. The diagnostic codes for ischemic stroke (18–20) and AF (22, 23) have been previously validated In Taiwan's NHIRD.

We excluded patients with a previous diagnosis of severe valvular heart disease such as rheumatic heart disease (ICD-9-CM codes 393–398 or ICD-10-CM codes I00-I09), congenital heart disease (ICD-9-CM codes 746–747 or ICD-10-CM codes Q20-Q28), or those who had undergone valvular replacement surgery (NHI procedure code: 68016B, 68017B, 68018B). We also excluded patients who died or had new ischemic stroke or ICH within 30 days after the index date, prolonged hospitalization beyond 30 days, or age younger than 20 years (**Supplementary Figure 1**).

Allocation of cohorts

The OAC cohort consisted of patients with first-ever ischemic stroke with AFDAS who received OACs within 30 days following the index date. The non-OAC cohort consisted of patients with AFDAS who never received OACs during the same 30-day period (**Figure 1**).

Covariates

The baseline characteristics of both cohorts were listed in **Table 1**. The monthly income was defined based on the insurance premium, which was income-dependent and recorded on a graduated scale. It was categorized as dependent, USD 567–1,076, USD 1,077–1,615, and > USD 1,615. Comorbidities were defined as diagnostic codes recorded in at least one inpatient diagnosis or at least two outpatient diagnoses within 1 year before the index stroke event (23). These variables were also used to calculate the pre-stroke CHA_2DS_2-VASc scores (24). The timing of AFDAS was categorized as

TABLE 1 Baseline characteristics before and after IPTW.

	Original cohorts			IPTW cohorts		
	OAC *N* = 2,856	Non-OAC *N* = 1,652	SMD	OAC *N* = 2,496	Non-OAC *N* = 1,434	SMD
Age						
Age, years *	71.7 (11.7)	75.2 (11.9)	0.298	72.5 (10.8)	73.9 (11.2)	0.123
< 65	762 (26.7)	330 (20.0)	0.159	598 (24.0)	325 (22.7)	0.030
65–75	823 (28.8)	386 (23.4)	0.124	739 (29.6)	371 (25.9)	0.083
≥ 75	1,271 (44.5)	936 (56.7)	0.245	1,160 (46.5)	738 (51.4)	0.100
Sex						
Male	1,680 (58.8)	863 (52.2)	0.133	1,433 (57.4)	790 (55.1)	0.047
Female	1,176 (41.2)	789 (47.8)	0.133	1,063 (42.6)	644 (44.9)	0.047
Index year†						
2012	389 (13.6)	331 (20.0)	0.172	363 (14.6)	245 (17.1)	0.070
2013	396 (13.9)	318 (19.3)	0.145	379 (15.2)	237 (16.5)	0.036
2014	454 (15.9)	308 (18.6)	0.073	427 (17.1)	264 (18.4)	0.035
2015	524 (18.4)	273 (16.5)	0.048	469 (18.8)	271 (18.9)	0.002
2016	541 (18.9)	208 (12.6)	0.175	424 (17.0)	204 (14.2)	0.076
2017	552 (19.3)	214 (13.0)	0.174	433 (17.4)	213 (14.8)	0.069
Monthly income (USD)‡						
Dependent	762 (26.7)	468 (28.3)	0.037	676 (27.1)	403 (28.1)	0.023
567–1,076	1,364 (47.8)	853 (51.6)	0.077	1,229 (49.2)	728 (50.7)	0.030
1,077–1,615	373 (13.1)	187 (11.3)	0.053	323 (12.9)	170 (11.9)	0.032
> 1,615	357 (12.5)	144 (8.7)	0.123	268 (10.8)	133 (9.3)	0.049
Comorbidities						
Hypertension	1,513 (53.0)	919 (55.6)	0.053	1,334 (53.4)	775 (54.1)	0.013
Diabetes mellitus	580 (20.3)	349 (21.1)	0.020	514 (20.6)	300 (20.9)	0.008
Dyslipidemia	576 (20.2)	296 (17.9)	0.057	497 (19.9)	264 (18.4)	0.038
CAD	476 (16.7)	282 (17.1)	0.011	406 (16.3)	236 (16.4)	0.004
CHF	79 (2.8)	25 (1.5)	0.087	51 (2.0)	22 (1.6)	0.037
MI	37 (1.3)	38 (2.3)	0.075	28 (1.1)	24 (1.6)	0.044
Pre-stroke CHA_2DS_2-VASc score§						
Score*	2.4 (1.4)	2.7 (1.4)	0.217	2.5 (1.4)	2.6 (1.4)	0.082
Low risk‡	394 (13.8)	168 (10.2)	0.112	300 (12.0)	166 (11.6)	0.013
Intermediate risk	560 (19.6)	244 (14.8)	0.129	483 (19.3)	253 (17.6)	0.045
High risk	1,902 (66.6)	1,240 (75.1)	0.187	1,713 (68.6)	1,016 (70.8)	0.047
Timing of AFDAS diagnosis						
Inpatient	2,541 (89.0)	1,427 (86.4)	0.079	2,219 (88.9)	1,264 (88.2)	0.024
Outpatient	315 (11.0)	225 (13.6)	0.079	277 (11.1)	170 (11.8)	0.024
Stroke severity‖						
eNIHSS*	9.0 (6.1)	10.9 (7.1)	0.289	9.1 (6.0)	9.9 (6.6)	0.128
Mild§	1,525 (53.4)	741 (44.9)	0.172	1,297 (52.0)	718 (50.1)	0.038
Moderate	666 (23.3)	319 (19.3)	0.098	606 (24.3)	290 (20.2)	0.098
Severe	665 (23.3)	592 (35.8)	0.278	593 (23.8)	427 (29.8)	0.136
Length of hospitalization						
Days*	11.6 (7.5)	12.3 (8.0)	0.091	11.6 (7.4)	12.0 (7.9)	0.060
Physician specialty						
Neurology	2,517 (88.1)	1,348 (81.6)	0.183	2,208 (88.5)	1,228 (85.6)	0.086
Others	339 (11.9)	304 (18.4)	0.183	288 (11.5)	207 (14.4)	0.086

(*Continued*)

TABLE 1 (Continued)

	Original cohorts			IPTW cohorts		
	OAC *N* = 2,856	Non-OAC *N* = 1,652	SMD	OAC *N* = 2,496	Non-OAC *N* = 1,434	SMD
Hospital level						
Tertiary center	1,179 (41.3)	554 (33.5)	0.160	980 (39.3)	518 (36.1)	0.065
others	1,677 (58.7)	1,098 (66.5)	0.160	1,516 (60.7)	916 (63.9)	0.065
Anticoagulant type						
NOAC	1,855 (65.0)	n/a	n/a	1,585 (63.5)	n/a	n/a
Warfarin	1,001 (35.1)	n/a	n/a	912 (36.5)	n/a	n/a
Antiplatelet use						
Yes	1,687 (59.1)	1,055 (63.9)	0.099	1,492 (59.8)	939 (65.4)	0.117
No	1,169 (40.9)	597 (36.1)	0.099	1,004 (40.2)	496 (34.6)	0.117
24-h Holter monitoring						
Yes	1,226 (42.9)	614 (37.2)	0.118	1,055 (42.3)	565 (39.4)	0.059
No	1,630 (57.1)	1,038 (62.8)		1,441 (57.7)	869 (60.6)	0.059

Data are expressed as n (%) unless otherwise indicated.
*Expressed as mean (SD).
†Index year: the year of admission for the index stroke event.
‡1 NTD = 0.036 USD as of Nov 2021.
§CHA_2DS_2-VASc score: low stroke risk was defined as a score of 1 or 0 for women and 0 for men; intermediate stroke risk was defined as a score of 2 for women and 1 for men; high stroke risk was defined as a score of ≥ 3 for women and ≥ 2 for men.
‖Severity of stroke: mild severity was defined as a score of ≤ 5; moderate severity was defined as a score of ≥ 6 and ≤ 13; severe severity was defined as a score of > 13.
AFDAS, atrial fibrillation detected after stroke; CAD, coronary artery disease; CHF, congestive heart failure; eNIHSS, estimated National Institutes of Health Stroke Scale; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SMD, standardized mean difference.

during the inpatient (before discharge) or the outpatient period (after discharge). Stroke severity was determined using a claims-based stroke severity index, which was further transformed to the estimated National Institutes of Health Stroke Scale (eNIHSS) score (25). We categorized the eNIHSS as mild (≤ 5), moderate (≥ 6 and ≤ 13), and severe (> 13) (26, 27). Other important covariates regarding the index stroke included length of hospitalization, physician specialty (neurology or others), and hospital level (tertiary referral center or others). To investigate anticoagulant use in the OAC cohort, we further classified patients into those treated with non-vitamin K antagonist oral anticoagulants for ≥ 1 day within the 30 days following the index date, and the others were defined as being treated with warfarin. Antiplatelet use was defined as the use of antiplatelet therapy for ≥ 1 day within the 30 days following the index date. 24-h Holter monitoring was defined as whether the patients received 24-h Holter monitoring within the 30 days following the index date.

Follow-up and outcomes

The date of follow-up onset was defined as 30 days after the index date (**Figure 1**). This approach has been previously used (28) to avoid immortal time bias (29). That is, patients in both OAC and non-OAC cohorts have to survive up to the same starting time point to be included in the analysis of outcomes.

The primary outcome was ischemic stroke recurrence, defined as an inpatient diagnosis of ischemic stroke after an examination of brain imaging. The secondary outcomes included ICH, death, and a composite endpoint of "ischemic stroke recurrence, ICH, or death." Death was defined by using the National Death Registry, linked to the Taiwan's NHIRD (30).

Statistical analysis

Categorical variables were expressed as counts and percentages, while continuous variables were expressed as means and standard deviations (*SD*). To minimize the selection bias inherent to a non-randomized controlled study, we used propensity score (PS) matching with a stabilized IPTW approach to create more homogeneous OAC and non-OAC groups with balanced baseline characteristics to facilitate comparisons. We calculated the PS using the logistic regression model and including covariates of age, sex, monthly premium level, pre-stroke CHA2DS2-VASc score, timing of AFDAS diagnosis, eNIHSS, length of hospitalization, physician specialty, hospital level, and comorbidities (listed in **Table 1**). The weights for the stabilized IPTW approach were defined as Z/PS for OAC group and (1-Z)/(1-PS) for the non-OAC group. Z and 1-Z were the marginal prevalence of OAC and non-OAC in the overall population, respectively. To avoid extreme weights, we removed patients whose PS

were < 5% or > 95% of the population. Using PS with the stabilized IPTW approach could generate two interchangeable groups with the same treatment assignment probabilities, thus allowing for comparisons based on the average treatment effects of the entire population (31). Standardized mean differences were used to determine differences in baseline characteristics between the two cohorts, and a value of < 0.1 was considered no difference.

The probability of ischemic stroke event-free was estimated using the Kaplan-Meier method, and the difference between the event-free curves was examined using the log-rank test. The association between OAC use and primary and secondary outcomes was evaluated by applying multivariate Cox proportional hazard models and reported as hazard ratios (HR) and 95% confidence intervals (CI) (32). Multivariate models were adjusted for age, sex, income, comorbidities listed in **Table 1**, pre-stroke CHA_2DS_2-VASc score, timing of AFDAS diagnosis, eNIHSS, length of hospitalization, specialty of the treating physician (neurology or others), and hospital level (tertiary center or others).

Two sensitivity analyses were performed. First, a time-varying analysis was performed to account for crossovers in treatment groups during follow-up. Second, the Fine and Gray competing risk model was applied to account for the competing risk of ICH and death (33). Additionally, stratified analyses for age, sex, pre-stroke CHA_2DS_2-VASc score, timing of AFDAS diagnosis, eNIHSS, physician specialty, or hospital level were performed to estimate their interaction with the association between OAC use and the primary outcome. Statistical significance was defined as a two-tailed probability value of < 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and Stata version 14.0 (StataCorp, College Station, TX).

Results

Baseline characteristics

A total of 4,508 hospitalized patients with both stroke and AFDAS were identified. Based on OAC use, 2,856 and 1,652 patients were assigned to the OAC and non-OAC groups, respectively. Patients in the OAC group tended to be younger, to have higher incomes and lower pre-stroke CHA_2DS_2-VASc and eNIHSS scores, and were more likely to be male, and to receive medical care from a neurologist or at a tertiary center (**Table 1**). In the IPTW cohorts, the baseline characteristics were well balanced between the two groups, except that the OAC group tended to be younger, had lower eNIHSS scores, and lower proportions of severe stroke, antiplatelet use than did the non-OAC group.

Primary and secondary outcomes in IPTW cohorts

In the non-adjusted analysis, the risk of ischemic stroke recurrence was lower in the OAC cohort than in the non-OAC cohort (log-rank test, $p = 0.018$; **Figure 2**). At a median follow-up of 2.76 and 2.53 years, respectively (**Table 2**), the numbers (annualized event rates) of ischemic stroke recurrences in the OAC and non-OAC cohorts were 321 (4.29%) and 209 (5.33%), respectively. The univariate Cox proportion hazard model indicated a significantly lower risk of ischemic stroke recurrence in the OAC cohort than in the non-OAC cohort (HR, 0.81; 95% CI, 0.69–0.97; $p = 0.018$). This association remained significant in the multivariate model (adjusted HR, 0.84; 95% CI, 0.70–0.99; $p = 0.042$) (**Table 2**). Patients in the OAC cohort had a similar risk of ICH (adjusted HR, 0.96; 95% CI, 0.62–1.50; $p = 0.864$), and had a lower risk of death (adjusted HR, 0.65; 95% CI 0.58–0.73; $p < 0.001$) and the composite outcome (adjusted HR, 0.70; 95% CI, 0.63–0.78; $p < 0.001$), compared to patients in the non-OAC cohort.

Sensitivity analyses

In the time-varying sensitivity analysis accounting for treatment group crossovers, OAC use was associated with a nearly 50% lower risk of ischemic stroke recurrence (adjusted HR, 0.52; 95% CI, 0.43–0.63; $p < 0.001$) (**Table 3**). In Fine and Gray's competing risk model, OAC use was also associated with a similar trend of lower risk of stroke recurrence compared with non-OAC use (adjusted HR, 0.91; 95% CI, 0.76–1.06; $p = 0.305$) (**Table 3**).

Stratified analysis

In stratified analysis, there was no significant interaction for age, sex, pre-stroke CHA_2DS_2-VASc score, timing of AFDAS diagnosis, 24-h Holter monitoring, eNIHSS, physician specialty, or hospital level with the association between OAC and stroke recurrence (**Supplementary Table 1**).

Discussion

In this large population-based retrospective cohort study, the use of OACs in patients with first-ever ischemic stroke and AFDAS was associated with a 16% lower risk of ischemic stroke recurrence during a median follow-up of 2.76 years. Results were consistent in sensitivity analyses accounting for treatment group crossovers and the compering risk of ICH and death. There were no differences in the risk of ICH between treatment groups. There were no significant interactions identified for age, sex,

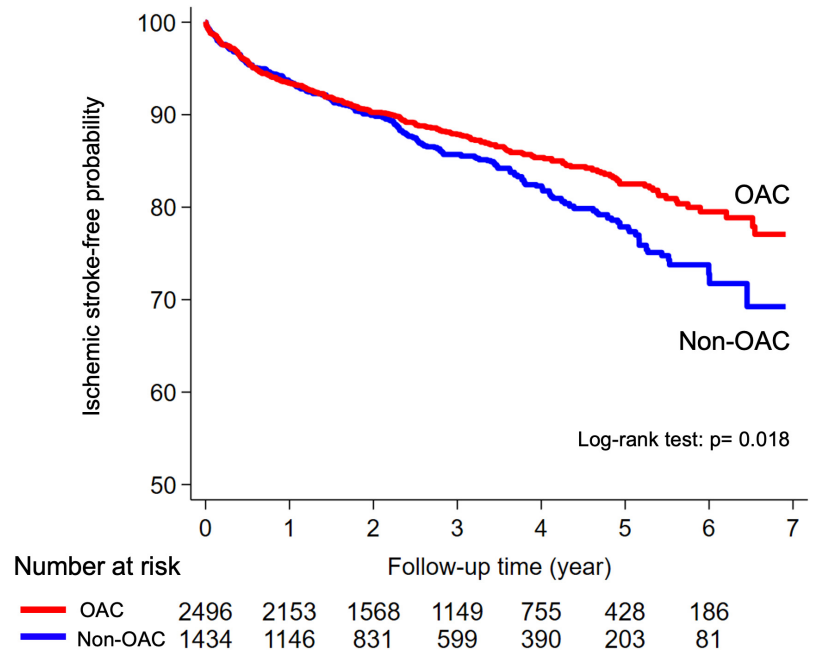

FIGURE 2
Kaplan–Meier curves for ischemic stroke event-free probability in the OAC and non-OAC cohorts among patients with AFDAS. AFDAS, atrial fibrillation detected after stroke; OAC, oral anticoagulant.

TABLE 2 Risk of ischemic stroke and secondary outcomes in IPTW cohorts.

	Event	FU*	AER†	Univariate model			Multivariate model‡		
				HR	95% CI	*p*	aHR	95% CI	*p*
Ischemic stroke									
OAC	321	2.76	4.29	0.81	0.69–0.97	0.018	0.84	0.70–0.99	0.042
Non-OAC	209	2.53	5.33				Ref.		
Intracranial hemorrhage									
OAC	55	2.76	0.73	0.96	0.62–1.49	0.861	0.96	0.62–1.50	0.864
Non-OAC	30	2.53	0.76				Ref.		
Death									
OAC	600	3.11	7.29	0.57	0.51–0.64	<0.001	0.65	0.58–0.73	<0.001
Non-OAC	557	2.84	12.90				Ref.		
Composite outcome§									
OAC	825	2.76	11.02	0.64	0.58–0.71	<0.001	0.70	0.63–0.78	<0.001
Non-OAC	680	2.53	17.29				Ref.		

*Expressed as median duration of follow-up (years).
†Expressed as annualized event rate (%).
‡Hazard ratios were calculated using multivariate Cox regression models with adjustment for age, sex, index year, monthly income, comorbidities listed in Table 1, pre-stroke CHA_2DS_2-VASc score, diagnosis of AFDAS, eNIHSS score, length of hospitalization, physician specialty, and hospital level.
§Composite outcome defined as development of ischemic stroke, intracranial hemorrhage, or mortality.
aHR, adjusted hazard ratio; AER: annualized event rate; CI, confidence interval; eNIHSS, estimated National Institutes of Health Stroke Scale; FU, follow-up; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; OAC, oral anticoagulant.

CHA_2DS_2-VASc score, timing of AFDAS diagnosis, 24-h Holter monitoring, eNIHSS, physician specialty, or hospital level.

Currently, major guidelines suggest the use of OAC in patients with stroke and AF, without differentiating between KAF or AFDAS (9, 12). This is mainly based on the fact that AFDAS is a fairly novel concept (13, 15), and that there have not been any specific randomized clinical trials of OACs vs. antiplatelet agents or no antithrombotic therapy in patients

TABLE 3 Sensitivity analyses in the risk of ischemic stroke in IPTW cohorts.

	Univariate model			Multivariate model		
	HR	95% CI	*p*	aHR†	95% CI	*p*
Sensitivity analysis A*						
OAC	0.55	0.47–0.66	<0.001	0.52	0.43–0.63	<0.001
Non-OAC		Ref.			Ref.	
Sensitivity analysis B†						
OAC	0.90	0.76–1.07	0.240	0.91	0.76–1.09	0.3050
Non-OAC		Ref.			Ref.	

*Sensitivity analysis A: we used time-varying analysis to evaluate the effect of OAC on the primary outcome.
†Sensitivity analysis B: we used the Fine and Gray's competing risk model to evaluate the effect of OAC on primary outcome.
aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant.

with AFDAS. The results of the present real-world population-based study represent the closest possible approach to filling this knowledge gap, since a randomized controlled trial of OACs would be ethically unfeasible.

It is important to note that not all AFDAS have the same embolic risk. It has been proposed that AFDAS identified on the admission ECG or on short-term monitoring (e.g., 24-h Holter) may entail a higher burden and embolic risk, whereas lower-burden AFDAS detected on prolonged cardiac monitoring (e.g., 30-day external loop recorders or 2 or 3-year implantable loop recorders) may lower the risk of stroke recurrence (15). In the present study, AFDAS was diagnosed on admission with ECGs or 24-h Holter monitoring within 30 days after stroke in usual care settings. As a result, most AFDAS may have been high-burden and may have occurred asymptomatically before stroke occurrence. Although this assumption is hypothetical, the likely high-burden nature of most AFDAS in our cohorts may explain the association between OAC use and lower risk of stroke recurrence.

In sensitivity analysis, the time-varying analysis accounting for changes in OAC exposure during the follow-up period found that there was an even greater risk reduction (nearly 50% reduction in HR, $p < 0.001$) in ischemic stroke recurrence than there was in the main analysis (16% reduction, in HR, $p = 0.042$). However, this association was not statistically significant after taking into account the competing risks of ICH and death using Fine and Gray's method in sensitivity analysis (9% reduction in HR, $p = 0.305$). This highlights the importance of adherence to OAC treatment for patients with AFDAS, and this information might provide physicians more confidence to initiate and maintain OAC treatment for post-stroke care in these patients. As only 37.1% and 39.3% of patients with stroke and newly confirmed AFDAS on serial ECGs or 24-h Holter monitoring, respectively, were prescribed with OACs at discharge (34), our real-world evidence lends support to current guidelines and indicates that physicians could prescribe OAC early with confidence once AFDAS has been confirmed.

Limitations

Our study has several limitations. First, the diagnosis of AFDAS in the present study was mainly based on ECGs at admission and 24-h Holter monitoring. As such, the results are not generalizable to patients with AFDAS on prolonged Holter monitoring or implantable loop recording, who may have a different (and probably lower) AF burden. Results are awaited from those ongoing randomized trials, such as the FIND-AF2 trial (35), which is expected to provide more definitive information on this subject. Second, the use of a limited time window (30 days after the index stroke event) to identify the OAC and non-OAC cohorts is a limitation of the current study, because there could be cross-overs between the specified time windows. Third, unmeasured confounders such as hemorrhagic transformation, the size of cerebral infarctions, cerebral microbleeds, or comorbidities associated with high embolic or hemorrhagic risk may have influenced the results. However, the application of IPTW, as well as the consistency of the results of multivariate models and sensitivity analyses, suggest that our results are unlikely to be explained by selection bias. Fourth, the proportion of severe stroke (eNIHSS > 13) was higher in the non-OAC group, even after the application of IPTW. Nevertheless, the *p*-value for this interaction was insignificant ($p = 0.224$) for the severe stroke subgroup (**Supplementary Table 1**). Fifth, the use of a 10-year lookback period to exclude patients with a previous stroke and/or a previous AF diagnosis may have led to misclassification. However, this risk might be negligible (5, 36). Sixth, it would be more accurate to consider a certain proportion of patients who were re-admitted within the first 30-day period after index stroke admission as experiencing a continuation of the same stroke episode, instead of having an early stroke recurrence. Excluding these patients from the current study may have caused a selection bias. Lastly, we did not apply a cut-off value for AF duration for it to be considered as clinically relevant. AF was identified retrospectively based on claims records (22, 23). Such AF was likely to be high burden, because it was diagnosed on admission ECGs or short-term monitoring in usual care; therefore, it was probably a fairly homogenous group of AFDAS from a prognostic perspective.

Conclusion

For acute patients with ischemic stroke with AFDAS, OAC initiation within 30 days after stroke was associated with a reduced risk of ischemic stroke recurrence but without

a significantly increased risk of ICH. This finding might support current guidelines that recommend the use of OAC for secondary stroke prevention in patients with AF, regardless of AFDAS or KAF.

Data availability statement

Taiwan's NHIRD is maintained and regulated by the Health and Welfare Data Science Center at the Ministry of Health and Welfare in Taiwan. The dataset only could be utilized in the division of the Health and Welfare Data Science Center. Researchers who are interested to analyze this dataset can request access to the Taiwan Ministry of Health and Welfare. Requests to access the datasets should be directed to Taiwan Ministry of Health and Welfare (website: https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html).

Ethics statement

The studies involving human participants were reviewed and approved by the Hualien Tzu Chi Hospital. Written informed consent for participation was not required for this study because personal identifiers of patients were encrypted in the NHIRD.

Author contributions

J-YH: manuscript preparation, study conception and design, data extraction, and interpretation. PP-SL: study design and data extraction statistical analysis. LAS and S-JL: critical revision of the manuscript. H-KH: study conception and design and data interpretation. A-BL: study conception and data interpretation. EC-CL: statistical consultation and data interpretation. C-YH: study conception and design, data interpretation, and critical revision of the manuscript. C-HL: study conception and design and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.929304/full#supplementary-material

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Contemporary survival and anticoagulation of patients with atrial fibrillation: A community based cohort study in China

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Backgrounds: The understanding of death in patients with atrial fibrillation (AF) in China is limited. This study aimed to assess the contemporary survival of AF patients in China and to explore risk factors for deaths.

Methods: This was a prospective community-based cohort study including 559 AF patients, who were followed-up from July 2015 to December 2020.

Results: During 66-month follow-up, there were 200 deaths (56.5% cardiovascular, 40.0% non-cardiovascular, and 3.5% unknown causes) among 559 AF patients with the median age of 76 years. The top three causes of death were heart failure (33.0%), ischemic stroke (17.0%) and cancer (16.5%). Multivariate Cox regression analysis indicated baseline variables positively associated with all-cause death were age (HR: 1.10, 95% CI: 1.08–1.13), AF subtype (HR: 1.37, 95% CI: 1.08–1.73), prior myocardial infarction (HR: 3.40, 95% CI: 1.48–7.78), previous tumor (HR: 2.61, 95% CI: 1.37–4.98), hypoglycemic therapy at baseline (HR: 1.81, 95% CI: 1.13–2.91), but body weight (HR: 0.98, 95% CI: 0.97–1.00) and use of calcium channel blocker (CCB) (HR: 0.62, 95% CI: 0.41–0.95) played a protective role to all-cause death. Of patients who were alive at the end of follow-up, 24.0% were on oral anticoagulants (OAC) alone, 4.5% on dual antithrombotic therapy, 33.1% on antiplatelet agents alone and 38.4% weren't on any antithrombotic medication.

Conclusion: Ischemic stroke still remains one of the leading causes of death and OAC is seriously underused in AF patients in China. Independent risk factors for death are age, AF subtype, previous tumor, prior myocardial infarction, hypoglycemic therapy, low body weight and no CCB use.

Clinical Trial Registration: http://www.chictr.org.cn/ (ChiCTR-ICR-15007036).

KEYWORDS

atrial fibrillation, survival, anticoagulation, mortality, stroke

Introduction

Atrial fibrillation (AF) is the most common arrhythmia for the elderly and associated with a high risk of stroke and heart failure (1). Several studies reported AF independently increased the risk of all-cause mortality by 1.5–2.0-fold (1). With the aging of population, AF has become a new global public health problem. However, great challenges exist in the prevention and treatment of AF in China, such as high morbidity, low awareness and poor management (2, 3). Both our and Du X's community-based surveys showed a great gap in anticoagulation in Chinese AF patients, for only 6.0% of them received oral anticoagulants (OAC) (2, 4).

To reduce the AF-related mortality, it is of great importance to study specific categories of deaths and to identify their risk factors for developing effective targeted interventions. However, the understanding of the mechanisms of death in patients with AF in China is limited at present. This study aimed to assess the temporal trends in survival of patients with AF in the contemporary clinical practice in China, and to identify clinical factors independently associated with deaths of specific causes. Meanwhile, to characterize the extent to which anticoagulation rate improves in Chinese community patients with AF in the latest 5 years.

Methods

Organization and management

In 2015, we investigated the prevalence of AF among residents over 60 years old in seven towns such as Xinbang, Chedun, Maogang, Shihudang, Dongjing, Xiaokunshan and Yexie in Shanghai China, and identified 828 AF patients from 36,734 individuals (2). Of these patients with AF, 622 agreed to receive baseline data collection and questionnaire. We informed all the 622 subjects in detail of the purpose and nature of this prospective observational study, and 90% of them signed and agreed to participate in this study. Protocols for this study are showed in Supplementary Figure 1. This study was approved by the Ethical Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China and Songjiang Central Hospital, Shanghai, China. It was in line with the declaration of Helsinki.

Participants

The inclusion criteria were as follows: (1) aged over 60 years old, (2) registered residents in the seven above-mentioned towns, and (3) diagnosed with AF by the resting 12-lead electrocardiogram (ECG) obtained during the physical examination in 2015. Those who did not volunteer to sign an informed consent were excluded. A total of 559 AF patients were eligible and separated into paroxysmal AF, persistent AF and permanent AF groups on the basis of clinical history and previous ECG recordings in the community health care centers. All selected subjects were followed up from July 2015 to December 2020.

Data collection

The socio-demographic characteristics [age, sex, body weight, height, body mass index (BMI)], smoking and alcohol consumption, cardiovascular disease history, other comorbidities [diabetes mellitus, stroke, tumor, chronic gastrointestinal disease (CGD), liver diseases, and renal dysfunction], drugs being used at entry, and previous intervention treatment for AF were collected at baseline for each cohort participant. The CHA_2DS_2-VASc score [Congestive heart failure, Hypertension, Age $\geq$75 years (doubled), Diabetes, Stroke/transient ischemic attack/thromboembolism (doubled), Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), Age 65–75 years, Sex category (female)] was used for stroke risk stratification. The HAS-BLED (Hypertension, Abnormal renal/liver Function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, elderly, Drugs/alcohol) score was calculated to estimate OAC-related bleeding risk. Smoking was defined as current smoking every day or some days and having smoked at least 100 cigarettes during the lifetime. Alcoholism was defined as self-reported drinking at least 5 days per week. Hypertension was defined as systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$90 mmHg, or current antihypertensive therapy.

The history of heart failure was made due to the patient's symptoms, signs, previous diagnosis or treatment of heart failure, elevated brain natriuretic peptide or N-terminal pro-brain natriuretic peptide, and echocardiography.

The diagnosis of coronary heart disease (CHD) was made primarily according to clinical symptoms of angina pectoris, ECG manifestations of myocardial ischemia and coronary stenosis showed by contrast-enhanced coronary CT angiography or percutaneous coronary angiography.

Stroke was defined as a history of cerebral thromboembolism or bleeding manifested by brain computed tomography (CT) or magnetic resonance imaging. Renal dysfunction was defined as the estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2 at baseline or having a history of chronic renal failure. Diabetes mellitus was defined as having a previous diagnosis of diabetes mellitus, receiving oral hypoglycemic agents or insulin treatment, or having a fasting plasma glucose $\geq$126 mg/dL (7.0 mmol/L) or hemoglobin A1c level $\geq$6.5%. Liver disease was defined as a set of chronic liver diseases (e.g., liver cirrhosis) or significant biochemical

abnormalities of liver function (e.g., bilirubin more than twice the upper limit of normal, or aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase over 3 times the upper limit of normal).

Follow-up

All subjects were followed up every six months after enrollment and follow-up was censored on the date of death. The patient and family were contacted if the patient failed to return for appointments. The cause of death was independently determined by two members of the Endpoint Assessment and Adjudication Committee (EAAC) after reviewing the medical record and death certificate. Each death was attributed to a specific cause. If there was a discrepancy between the two investigators, a meeting would be held by the EAAC for discussing and voting on the cause of death. All deaths were preliminarily divided into three categories, such as cardiovascular death, non-cardiovascular death and undetermined death. Cardiovascular death was defined as any death due to cardiovascular causes (for example, myocardial infarction, heart failure, sudden death, fatal arrhythmia, pulmonary embolism, stroke). Non-cardiovascular causes of death included cancer, respiratory failure, infection/sepsis, renal failure, trauma/accidental and others. Death of unknown cause was defined as undetermined. The primary outcome of this study was all-cause death. Secondary outcomes included cause specific mortality as cardiovascular death, non-cardiovascular death and ischemic stroke-related death.

Statistical analysis

For numerical variables, the normality test was conducted. If each group met the normality, the mean (standard deviation) was used for statistical description (BMI), and the *t*-test was performed for inter-group comparison. Otherwise, the median [interquartile interval (IQR)] was used for statistical description (age, body weight, height, SBP, DBP, HR, CHA_2DS_2-VASc score and HAS-BLED score), and the non-parametric test was used for inter-group comparison. Categorical data were compared between groups with Chi-Square test. And Wilcoxon rank sum test was used to compare ranked data (symptom pattern of AF and AF subtype). The relation of baseline variables with mortality was assessed using Kaplan-Meier analysis. Multivariate Cox proportional hazards models were constructed using the stepwise selection technique to identify independent predictors of deaths. All statistical analyses were performed with SPSS 13.0. Two-tailed $P < 0.05$ was considered of statistical significance.

Results

Baseline characteristics of participants

The media age of the 559 subjects was 76 (70–81) years and 47.9% were female. AF was paroxysmal in 18.4%, persistent in 61.2% and permanent in 20.4% of the patients.

The media CHA_2DS_2-VASc score was 3 (2–4), with congestive heart failure in 16.1%, hypertension in 56.2%, diabetes mellitus in 12.2%, and previous stroke in 11.1%. Detailed patient characteristics are summarized in Table 1.

Temporal survival of atrial fibrillation patients in China

During the follow-up, 200 patients died (35.8%). The rest 359 subjects all finished the 66-month follow-up. The survival rates from the first to the fifth year of follow-up were 93.5, 87.5, 80.5, 75.3 and 67.5%, respectively (Figure 1).

Descriptive analysis of causes of death

A total of 200 deaths were adjudicated. The majority of deaths were cardiovascular (56.5%), whereas non-cardiovascular deaths (principally cancer) accounted for 40.0, and 3.5% of deaths were due to unknown causes. Table 2 presents death causes of the entire study population. The top three causes of death were heart failure (accounting for 33.0%), ischemic stroke (accounting for 17.0%) and cancer (accounting for 16.5%). Among cardiovascular deaths, cardiac mortality, ischemic stroke-related death and fatal cerebral hemorrhage represented 65.5, 30.1 and 4.4%, respectively.

Cumulative incidences of deaths for specific causes

Cumulative mortality of patients with AF in the entire cohort during the follow-up is presented in Figure 2. With the follow-up of 2,562 patient-years, all-cause mortality was 7.8 per 100 person-years (%/P-Y) and the rates of cause-specific deaths were 4.4 %/P-Y for CV death, 3.1 %/P-Y for NCV death, 2.9 %/P-Y for cardiac death, and 1.3 %/P-Y for ischemic stroke-related death.

Independent risks of death in AF patients

Among various baseline variables, only age, body weight, height, BMI, CHA_2DS_2-VASc score, AF type, baseline use of diuretic, CCB or statin, were of significant difference between

TABLE 1 Patient characteristics at baseline.

Characteristics	Overall ($n = 559$)	Alive ($n = 359$)	Dead ($n = 200$)	*P*-value
Demographics				
Age, years old, median (IQR)	76 (70–81)	74 (68–79)	81 (76–84)	<0.001
Female gender, *n* (%)	268 (47.9)	166 (46.2)	102 (51.0)	0.280
SBP, mmHg	130 (122–136)	130 (122–136)	130 (121–136)	0.764
DBP, mmHg	80(74–82)	80 (76–83)	80 (74–82)	0.163
Heart rate, bpm	80 (74–86)	78 (74–86)	80 (74–86)	0.442
Body weight, kg	60 (51–67)	62 (55–68)	55 (48–64)	<0.001
Height, cm	160 (155–166)	161 (156–168)	159 (152–164)	<0.001
BMI, kg/m^2	23.3 ± 3.7	23.8 ± 3.6	22.4 ± 3.6	<0.001
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)	3 (3–4)	<0.001
HAS-BLED score	2 (1–3)	2.0 ± 1.0	2.1 ± 0.95	0.162
Baseline lifestyle				
Smoking, *n* (%)	173 (30.9)	113 (31.5)	60 (30.0)	0.717
Alcoholism, *n* (%)	35 (6.3)	22 (6.1)	13 (6.5)	0.862
History of cardiovascular disease				
Hypertension, *n* (%)	314 (56.2)	207 (57.7)	107 (53.5)	0.342
Heart failure, *n* (%)	90 (16.1)	55 (15.3)	35 (17.5)	0.502
CHD, *n* (%)	210 (37.6)	128 (35.7)	82 (41.0)	0.211
Myocardial infarction	10 (1.8)	4 (1.1)	6 (3.0)	0.201
Comorbidities				
Diabetes mellitus, *n* (%)	68 (12.2)	43 (12.0)	25 (12.5)	0.856
Previous stroke, *n* (%)	62 (11.1)	34 (9.5)	28 (14.0)	0.102
Tumor, *n* (%)	18 (3.2)	8 (2.2)	10 (5.0)	0.075
CGD, *n* (%)	50 (8.9)	30 (8.4)	20 (10.0)	0.514
Liver disorders, *n* (%)	9 (1.6)	4 (1.1)	5 (2.5)	0.370
Renal dysfunction, *n* (%)	11 (2.0)	5 (1.4)	6 (3.0)	0.320
Symptom pattern of AF				0.267
Obvious symptoms	78 (14.0)	52 (14.5)	26 (13.0)	
Minor symptoms	264 (47.2)	174 (48.5)	90 (45.0)	
No symptoms	217 (38.8)	133 (37.0)	84 (42.0)	
AF subtype				0.033
Paroxysmal AF	103 (18.4)	74 (20.6)	29 (14.5)	
Persistent AF	34 (61.2)	219 (61.0)	123 (61.5)	
Permanent AF	114 (20.4)	66 (18.4)	48 (24.0)	
Treatments at baseline				
OAC, *n* (%)	31 (5.5)	22 (6.1)	9 (4.5)	0.420
Antiplatelet agent, *n* (%)	189 (33.8)	117 (32.6)	72 (36.0)	0.414
ARB, *n* (%)	154 (27.5)	100 (27.9)	54 (27.0)	0.828
ACEI, *n* (%)	20 (3.6)	12 (3.3)	8 (4.0)	0.688
Diuretic, *n* (%)	86 (15.4)	47 (13.1)	39 (19.5)	0.044
β-blocker, *n* (%)	118 (21.1)	81 (22.6)	37 (18.5)	0.259
CCB, *n* (%)	107 (19.1)	81 (22.6)	26 (13.0)	0.006
Digoxin, *n* (%)	66 (11.8)	40 (11.1)	26 (13.0)	0.514
Statin, *n* (%)	96 (17.2)	51 (14.2)	45 (22.5)	0.013
Insulin and/or oral hypoglycemic, *n* (%)	54 (9.7)	33 (9.2)	21 (10.5)	0.616
Previous intervention treatment for AF				
AF ablation, *n* (%)	3 (0.5)	3 (0.8)	0 (0.0)	0.489
Pacemaker implantation, *n* (%)	16 (2.9)	9 (2.5)	7 (3.5)	0.500

IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CHD, coronary heart disease; CGD, chronic gastrointestinal disease; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; OAC, oral anticoagulants.

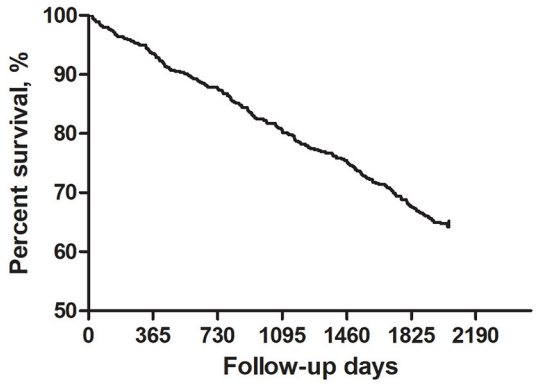

FIGURE 1
Survival of patients with atrial fibrillation.

patients who were alive at the end of follow-up and patients who had died during the follow-up (Table 1).

Multivariate Cox regression analysis indicated baseline variables associated with all-cause death independently were age (HR: 1.10, 95% CI: 1.08–1.13), AF subtype (HR: 1.37, 95% CI: 1.08–1.73), body weight (HR: 0.98, 95% CI: 0.97–1.00), prior myocardial infarction (HR: 3.40, 95% CI: 1.48–7.78), previous tumor (HR: 2.61, 95% CI: 1.37–4.98), CCB use at baseline (HR: 0.62, 95% CI: 0.41–0.95) and hypoglycemic therapy at baseline (HR: 1.81, 95% CI: 1.13–2.91) (Table 3).

The strongest independent predictor of cardiovascular death was prior myocardial infarction (HR: 5.64, 95% CI: 2.22–14.35), followed by alcoholism (HR: 2.26, 95% CI: 1.16–4.40), statin use at baseline (HR: 1.59, 95% CI: 1.02–2.48), age (HR: 1.07, 95% CI: 1.04–1.11), body weight (HR: 0.96, 95% CI: 0.94–0.98) and CCB use at baseline (HR: 0.48, 95% CI: 0.26–0.88) (Table 3). Meanwhile, age, diabetes mellitus, symptom pattern of AF, AF subtype, previous tumor, liver diseases were found

TABLE 2 Causes of death in patients with atrial fibrillation.

Events	*n*	%
All-cause death	200	-
Cardiovascular death	113	56.5
Cardiac death	74	37.0
Heart failure	66	33.0
Sudden death/dysrhythmia	4	2.0
Myocardial infarction	3	1.5
Other cardiac death	1	0.5
Vascular death	39	19.5
Ischemic stroke	34	17.0
Hemorrhagic stroke	5	2.5
Non-cardiovascular death	80	40.0
Cancer	33	16.5
Respiratory failure	13	6.5
Infection/sepsis	12	6.0
Renal failure	2	1.0
Trauma/accidental	8	4.0
Other non-vascular death	12	6.0
Undetermined causes	7	3.5

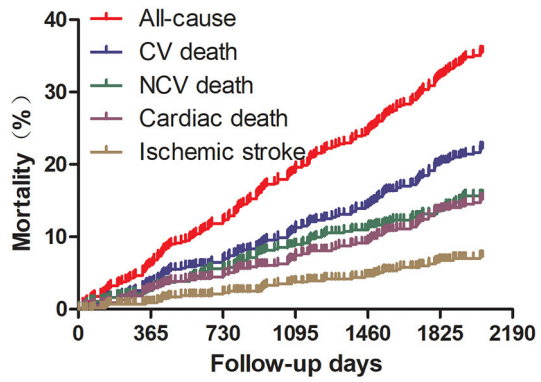

FIGURE 2
Cumulative incidences of death for specific causes. CV, cardiovascular; NCV, non-cardiovascular.

to be independently associated with non-cardiovascular death (Table 3).

Current status of OAC use among AF patients alive at the end of the follow-up

Of patients who were alive at the end of follow-up, 4.5% were on dual antithrombotic therapy (OAC plus antiplatelet agents), 24.0% on OAC alone, 33.1% on antiplatelet agents (most aspirin), and 38.4% were not on any antithrombotic medication

TABLE 3 Independent predictors for all-cause mortality and deaths of specific causes in patients with atrial fibrillation (cox proportional hazard model, multivariate analysis).

Baseline variables	HR	95% CI	*P*-value
All-cause mortality			
Age	1.10	1.08–1.13	0.000
AF subtype	1.37	1.08–1.73	0.010
Body weight	0.98	0.97–1.00	0.009
Prior myocardial infarction	3.40	1.48–7.78	0.004
Previous tumor	2.61	1.37–4.98	0.003
CCB use at baseline	0.62	0.41–0.95	0.027
Hypoglycemic therapy at baseline	1.81	1.13–2.91	0.014
Cardiovascular death			
Age	1.07	1.04–1.11	0.000
Alcoholism	2.26	1.16–4.40	0.017
Body weight	0.96	0.94–0.98	0.000
Prior myocardial infarction	5.64	2.22–14.35	0.000
CCB use at baseline	0.48	0.26–0.88	0.018
Statin use at baseline	1.59	1.02–2.48	0.041
Non-cardiovascular death			
Age	1.123	1.084–1.164	0.000
Diabetes mellitus	2.064	1.161–3.670	0.014
Symptom pattern of AF	1.414	1.005–1.990	0.047
AF subtype	1.619	1.101–2.380	0.014
Previous tumor	5.041	2.280–11.145	0.000
Liver disease	5.572	1.992–15.584	0.001

AF, atrial fibrillation; CCB, calcium channel blocker.

(Figure 3). The rate of anticoagulation was 28.5%. Of patients who received anticoagulants, warfarin was prescribed in 83.3% and non-vitamin K antagonist oral anticoagulants (NOAC) in 16.7% (dabigatran in 6.9% and rivaroxaban in 9.8%).

Discussion

The principal findings of this study were as follows: (1) the underutilization of anticoagulants of these eligible high-risk patients was observed in this community-based AF cohort in China; (2) the predominant cause of death is cardiovascular in the elderly community patients with AF in China, and ischemic stroke still remains one of the leading causes of death; (3) independent risk factors for death in these AF patients include age, AF subtype, low body weight, previous tumor, prior myocardial infarction, CCB use and hypoglycemic therapy at baseline; and (4) anticoagulantion therapy for AF patients from Chinese communities has improved in the recent 5 years, but it's still far from the recommendations of AF management guidelines.

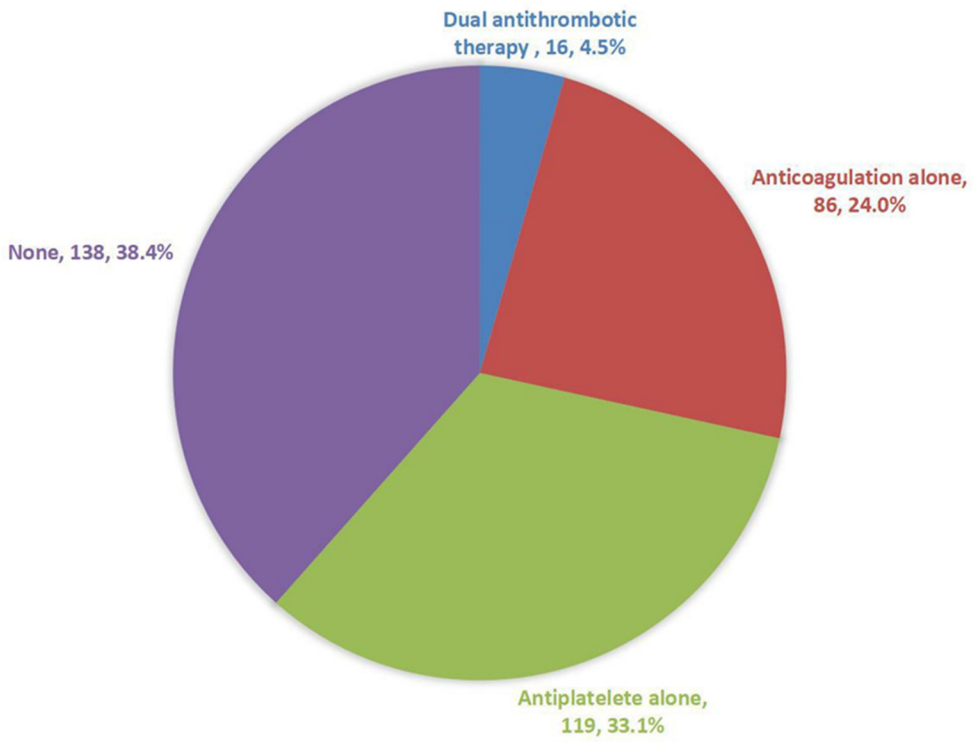

FIGURE 3
Current status of antithrombotic treatment in patients with atrial fibrillation who were alive at the end of the follow-up.

Mortality of AF patients

AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men (1). All-cause mortality and cause-specific deaths among AF patients have been examined in both randomized control trials and cohort studies. In contemporary anticoagulated AF population, the average annual mortality rates reported in four randomized control trials (RCTs) were 4.38 %/P-Y for the RE-LY study (5), 5.42 %/P-Y for the ROCKET AF study (6), 3.82 %/P-Y for ARISTOLE study (7) and 4.99 %/P-Y for the ENGAGE AF-TIMI 48 study (8). Although significant heterogeneity existed across these studies, a meta-analysis indicated their adjusted mortality rate was 4.72%/year (9). The real-world cohort studies indicated a great variation in mortality of AF patients, with 3.83 %/P-Y in a global hospital-based AF cohort (GARFIELD-AF) (10), 5.5 %/P-Y r in a Japanese community-based AF cohort (Fushimi AF Registry) (11), 6.3 %/P-Y in a nationwide population-based study in Korea (12), and 16.48 %/P-Y in the largest and comprehensive study on AF from India (KERALA-AF Registry) (13). Data describing the mortality of AF patients in China are limited. To our knowledge, this is the first prospective community-based study to investigate mortality of AF patients in China, with a long-term follow-up over 5 years. We found all-cause mortality in our study population was 7.8 %/P-Y. Mortality rates varied widely among different studies due to differences in study design, population, region, patient characteristics, enrollment period, health management level, and treatment option, etc.

Causes of death in AF patients

Our data indicated cardiovascular events were the most common cause of death, accounting for 56.5% of all deaths. Such proportion was similar to a large retrospective, real-world study of hospitalized patients with AF (14), which indicated 54% were cardiovascular and 43% were non-cardiovascular among all deaths. Both RCTs (5–8) and real-world cohorts (10) indicated stroke-related death represented no more than 7% of the overall mortality. However, in our study, the death due to ischemic stroke accounted for 17.0% of all deaths. This proportion was much higher than that in the previously published reports. The only plausible explanation is that only 6% of the enrolled AF patients were treated with OAC at the baseline in our study. The significance of OAC for AF patients with high risk of stroke is evident. Underuse of anticoagulants might cause high rate of AF-related stroke and stroke-related death. This result emphasizes that it's still of great significance to develop targeted approaches to improve anticoagulation rate for further reducing mortality in Chinese AF population.

Independent risk factors for death in AF patients

Various covariables are reported to be associated with the risk of death in AF patients. This study indicated the independent predictors of all-cause death were age, AF subtype, low body weight, previous tumor, prior myocardial infarction, CCB use and hypoglycemic therapy at baseline. Prior myocardial infarction was identified as the strongest indicator of all-cause death and cardiovascular death, which was consistent with the sub-analysis from the RE-LY trial (5). Previous studies indicated pre-existing heart failure was associated with an increased risk of all-cause death and cardiovascular death (5–7, 10), but this study didn't show such association. One potential explanation for this different finding is that patients were diagnosed with heart failure if they had a history of heart failure in the present study, regardless of heart function classification. So, many AF patients with pre-existing heart failure might have received optimal treatment of heart failure, resulting in an improved prognosis.

It's controversial whether sustained AF was associated with higher mortality than paroxysmal AF (10, 11, 14, 15). This study indicated permanent AF was independently associated with an increased risk of all-causeortality and non-cardiovascular mortality, but not cardiovascular mortality. Such correlation needs more research to verify in the future. Some studies indicated OAC use was independently associated with a lower risk of all-cause mortality and cardiovascular mortality (10, 11, 14, 15). However, our study did not show this correlation, and it may be attributed to the very low rate of anticoagulant therapy at baseline. The Fushimi AF registry demonstrated that statin use was associated with better all-cause mortality (11). However, on the contrary, we found that statin use at baseline was positively (HR: 1.59, 95% CI: 1.02–2.48) associated with cardiovascular death. Patients using statins in China usually have severe dyslipidemia or atherosclerotic cardiovascular disease, which are well-known risk factors for cardiovascular death. In addition, we also found that patients who died during follow-up had a significantly lower rate of prescription of CCB. Of note, CCB use was independently associated with a decrease of 38% in the risk of overall death and 52% in the risk of cardiovascular death in our studied patients. It's well-known that CCB is not recommended to patients with heart failure and the elderly are prone to heart failure, so elderly patients using CCB may not have heart failure, selecting a population with good prognosis.

Current status of OAC use among AF patients in China

Although anticoagulation is recommended by all guidelines of AF management to reduce the risk of AF-related stroke, both our and other studies indicated OAC remained seriously underused in AF patients in China (2, 4). This study indicated the baseline anticoagulation rate of the studied population was only 6% in 2015, which was consistent with the previous community-based study on anticoagulation status of AF patients in China (4). Meanwhile, hospital-based studies indicated the rate of OAC use were 35.6% in Jiangshu in 2017 (16), 11.5% in Chongqing in 2013 (17), 28.8% in Xinjiang in 2015 (18) and 31.7% nationwide in 2012 (19) in China. Though great variations of OAC treatment in Chinese patients with AF were explored among different studies, the anticoagulation rate of community patients with AF tended to be much lower than that of out-patients or in-patients with AF in China. To our opinion, the community-based study can better reflect the real-world anticoagulation status of AF patients than the hospital-based study.

Several studies have forecasted a growing improvement of OAC treatment for hospitalized or outpatient patients with AF in China (20, 21). This study first described contemporary anticoagulation in AF patients in Chinese communities. The anticoagulation rate of these studied AF patients increased from 6% in 2015 to 28.5% in 2020. So, application of anticoagulants according to the AF management guidelines is still far from expected in China. It's essential to develop target measures to improve clinicians' compliance with AF management guidelines as well as AF patients' adherence to OAC. Before the onset of NOAC in China, many physicians were unwilling to prescribe warfarin to AF patients mainly for their excessive worry about bleeding and patients' poor adherence to INR monitoring in China (22). Though NOAC is currently available in China and preferentially recommended to AF patients when compared with warfarin, high cost is the main reason for limiting its use, especially for AF patients in the impoverished areas in China. In order to reduce the financial burden of AF patients, more efforts should be paid to reduce the selling price of NOAC in China and increase the proportion of expenses paid by the China Medical Insurance Fund to over 90%. Left atrial appendage occlusion (LAAO) is an alternative treatment for preventing stroke. However, this cohort showed no one had received LAAO before enrollment, and none of them received LAAO during follow-up. Not only low anticoagulation rate, but also less willing to undergo catheter ablation in AF patients in China. Our data showed only 3 cases undergoing catheter ablation during the follow-up, of which one case recurred.

Conclusion

In conclusion, the predominant cause of death is cardiovascular and ischemic stroke still remains one of the leading causes of death for community patients with AF in China. The independent predictors of all-cause death included age, AF subtype, low body weight, previous tumor, prior myocardial infarction, CCB use and hypoglycemic

therapy at baseline. Distinct clinical factors are associated with cardiovascular and non-cardiovascular deaths. OAC is still seriously underused in the contemporary clinical practice in China in spite of a growing improvement. These findings provide important information for the optimal management of AF patients in China.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China and Songjiang Central Hospital, Shanghai, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SL and SC: concept and design. YL, JX, LC, XWa, BW, CS, CL, CW, YS, and SY: acquisition and analysis, or interpretation of data. SL: critical revision of the manuscript for important intellectual content. GZ and XWu: statistical analysis. XL: administrative and technical, or material support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.911393/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Study protocols.

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Early rhythm control vs. rate control in atrial fibrillation: A systematic review and meta-analysis

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Objective: It has long been debated whether rhythm control vs. rate control strategies have differing effects on mortality and morbidity for atrial fibrillation (AF). Recently, several randomized controlled studies (RCTs) and observational trials described that an early rhythm management method was linked to a lower likelihood of negative clinical outcomes in individuals with AF. We wanted to see if an early rhythm management method may help patients with AF.

Methods: We performed a systematic search to retrieve studies assessing the outcomes of early rhythm control vs. rate control in AF by using PubMed, Web of Science, Cochrane Library, and Embase published between 01/01/2000 and 15/04/2022.

Results: Finally, two RCTs, one retrospective analysis of RCTs, and four observational studies were identified. Compared with rate control, early rhythm control has been linked to lower all-cause mortality. [risk ratio (RR), 0.76; 95% CI 0.69–0.83; $P < 0.00001$; $I^2 = 77\%$]. The early rhythm control group was also associated with a lower risk of cardiovascular mortality (RR, 0.68; 95% CI 0.63–0.74; $P < 0.00001$; $I^2 = 33$), stroke (RR, 0.77; 95% CI 0.67–0.87; $P < 0.001$; $I^2 = 64$), and heart failure hospitalization (RR, 0.74; 95% CI 0.59–0.93; $P = 0.0009$; $I^2 = 93\%$). We found no significant difference in nights spent in hospital per year, acute coronary syndrome, major bleeding, and cardiac arrest/ventricular arrhythmia between the groups.

Conclusion: In this meta-analysis, early rhythm therapy was linked to a lower risk of all-cause mortality, cardiovascular mortality, stroke, and heart failure hospitalization compared with the rate control group.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42022333592.

KEYWORDS

atrial fibrillation, early rhythm control, rate control, meta-analysis, cardiovascular outcome

1. Introduction

Atrial fibrillation (AF) is a kind of cardiovascular disease that affects millions of people throughout the world and is associated with an increased risk of mortality and morbidity, with a fivefold increased risk of stroke (1–3). The current two essential aims of AF clinical care are (1) thromboembolism prophylaxis with anticoagulation and (2) maintenance of an appropriate heart rate or sinus rhythm by medications or interventional procedures (4). Rate

control is part of AF management and can adequately improve related symptoms. Rhythm control refers to the use of antiarrhythmic drugs, cardioversion, and AF ablation to try to restore and maintain sinus rhythm. It has been argued for a long time whether rhythm vs. rate control strategies have differing effects on mortality and morbidity for AF. The choice of rhythm or rate control in current guidelines relies on several randomized controlled studies (RCTs) (5–7). No significant difference in all-cause mortality, cardiovascular mortality, and other related morbidities was found between rhythm control and rate control in the meta-analyses of the above studies included (8, 9). However, the treatment of AF has changed dramatically since the above RCTs were published. Several studies have recently shown that the incidence of adverse cardiovascular outcomes was reduced by early rhythm control compared with rate control (10–17). To determine whether early rhythm control is better than rate control in patients with AF, we performed a systematic review and meta-analysis.

2. Materials and methods

The meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Literature search

From 1 January 2000, to 15 April 2022, a systematic search for RCTs and observational studies was undertaken using PubMed, EMBASE, Web of Science, and Cochrane Library databases, with no language restrictions. A manual search was conducted that included all of the relevant references following the computerized search. The following were among the most important search topics and terms: (1) atrial fibrillation, (2) rate control, and (3) rhythm control. Detailed search strategies are summarized in the **Supplementary material**. The PRISMA statement was followed when performing this meta-analysis. The review protocol has been registered in PROSPERO (registration number: CRD42022333592).

2.2. Selection and data abstraction

The following criteria were used to choose articles: (1) observational studies or RCTs that included patients with AF based on early rhythm control vs. rate control; (2) based on "Early Treatment of Atrial Fibrillation for Stroke Prevention Trial" (EAST-AFNET 4) study, patients were enrolled within 1 year after the first diagnosis of AF (early AF); (10) (3) the studies' follow-up time was at least 1 year; and (4) the goal of the study was to examine the effect and prognosis of AF treated with early rhythm vs. rate control. All studies were restricted to those including human subjects who were at least 18 years old. Reviews, case studies, conference papers, comments, and animal trials were all omitted from the study. Two reviewers separately evaluated article titles and abstracts to exclude papers that were not relevant. Disagreements were addressed by consensus and, if needed, the consulting of a third reviewer. The risk of bias was assessed using the Cochrane collaboration tool for RCTs and using the Newcastle-Ottawa scale for non-randomized clinical studies. The following information was gathered from eligible studies: (1) design of the research; (2) primary/secondary outcome; (3) mean follow-up time and baseline characteristics; and (4) anticoagulation therapy, rate, and rhythm protocols. The outcomes of the present analysis were as follows: all-cause mortality, cardiovascular mortality, ischemic stroke, heart failure (HF) hospitalization, nights spent in hospital per year, acute coronary syndrome, major bleeding, and cardiac arrest/ventricular arrhythmia.

2.3. Statistical analysis

Dichotomous variables were investigated using the Mantel-Haenszel method. The risk ratio (RR) and 95% confidence interval (CI) were determined. Continuous variables were described as the mean and standard deviation. To examine heterogeneity, the Cochran Q and I^2 statistics were utilized. We defined moderate or high heterogeneity as an I^2 of more than 50%. Given the expected between-study heterogeneity, a meta-analysis was conducted using a random effects model for all outcomes. If more than 10 studies were included, a funnel plot was used to measure publication bias. By removing one study at a time, we performed a series of sensitivity analyses to establish the contribution of each study to the pooled estimate. All P values were two-tailed. R programming language (version 4.1.2, R Foundation) was used to perform sensitivity analyses. Review Manager Version 5.3 software (The Nordic Cochrane Centre) was used to conduct an overall effect analysis and subgroup analysis.

3. Results

As shown in **Figure 1**, a total of 11,359 studies were found in the database. 5,557 duplicate records were excluded. A total of 5,543 records were excluded based on title/abstract, animal studies, irrelevant study design, and inapplicable study. We read the full text of 181 studies carefully. Finally, seven studies were included: two RCTs, one retrospective analysis of RCT, and four observational studies. The sample size ranged from 273 to 301,064. The mean follow-up times ranged from 1 to 5 years. **Table 1** and **Supplementary Table** provided the features of our included studies. **Table 2** summarizes the quality appraisal for the studies that were included.

3.1. Mortality

Seven studies reported all-cause mortality (10–15, 17, 18). Mortality was as high as 50% in Ionescu-Ittu et al.'s study during a mean follow-up of 3 years. When we included this study, the heterogeneity of our analysis was 97%. Therefore, we excluded this study from the analysis to better interpret our results and reduce heterogeneity. Finally, the pooled analysis showed lower all-cause mortality in the early rhythm group than in the rate control group (RR 0.76; 95% CI 0.69–0.83; $P < 0.00001$; $I^2 = 77\%$; **Figure 2A**). Analysis of pre-defined subgroups based on the study design also showed significantly lower mortality with RCT (RR, 0.86; 95% CI 0.75–1.00; $P = 0.04$) or observational studies (RR, 0.73; 95% CI, 0.65–0.81; $P < 0.00001$; **Figure 2A**). When the data were pooled based on the time it took for patients to enroll (before 2009 vs. after 2009), similar results were found (**Supplementary Figure 1**). Three

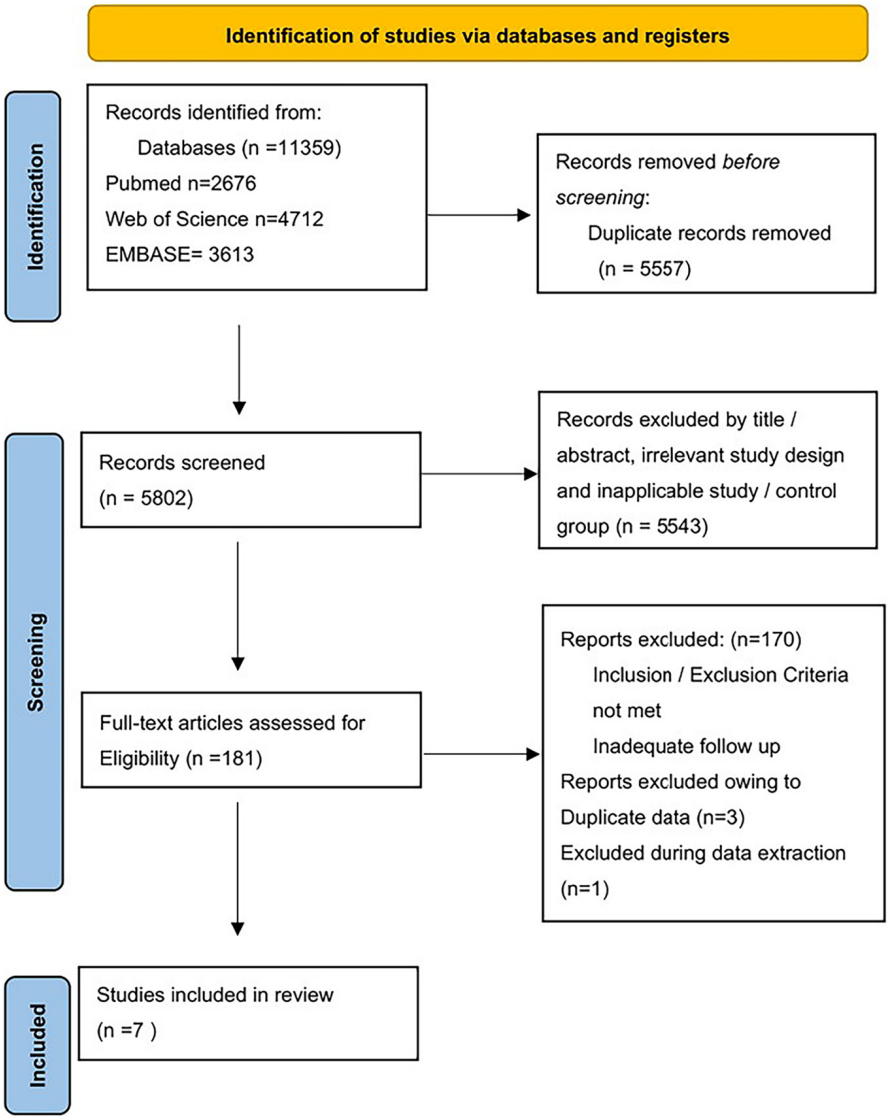

FIGURE 1
Summary of electronic search and included/excluded studies.

clinical studies reported cardiovascular mortality (10, 11, 14). The incidence of cardiovascular mortality was low in early rhythm control compared to rate control (RR, 0.68; 95% CI 0.63–0.74; $P < 0.00001$; **Figure 2B**) without statistically significant heterogeneity ($I^2 = 33\%$).

3.2. Morbidity

Six studies assessed ischemic stroke (10, 11, 13–15, 17). Early rhythm control was linked to a lower risk of stroke in the patients (RR, 0.77; 95% CI 0.67–0.87; $P < 0.0010$; $I^2 = 64\%$; **Figure 3**). We also performed subgroup analyses based on the time of patient enrollment, and study design and found no change in the above findings (**Supplementary Figure 2**). Only four studies included HF hospitalization (10–12, 14). Patients with early rhythm were associated with a reduced relative risk of HF hospitalization. However, there was obvious heterogeneity (RR, 0.74; 95% CI, 0.59–0.93; $P = 0.0009$; $I^2 = 93\%$; **Figure 4**).

Regarding nights spent in the hospital per year, acute coronary syndrome, major bleeding, and cardiac arrest/ventricular arrhythmia, early rhythm control and rate control showed no significant differences. The results were summarized in **Table 3** and **Supplementary Figure 3**.

Two studies reported adverse events related to treatment in early rhythm control vs. rate control. We did not include pooled analysis because of the limited number of studies. We found that syncope, cardiac tamponade, atrioventricular block, and pacemaker implantation were higher in the early rhythm group than rate control group, but none were statistically significant.

3.3. Sensitivity analyses

We conducted a sensitivity analysis by eliminating one study at a time to determine how each one affected the outcomes. The sensitivity analysis findings are summarized in

TABLE 1 Main study characteristics.

Trials	EAST-AFNET4 (2020)	AFFIRM substudy (2021)	Kim et al. (11)	Pope et al. (17)	RAFAS trial (2022)	Proietti et al. (12)	Chao et al. (14)
Study design	RCT	RCT substudy	Retrospective	Retrospective	RCT	Retrospective	Retrospective
Early rhythm vs. rate							
No. of patients	1,395 vs. 1,394	1,269 vs. 1,657	9,246 vs. 7,077	6,595 vs. 37,606	178 vs. 95	2,056 vs. 1,722	62,649 vs. 238,415
Type of AF (%)							
First episode	38.0 vs. 37.3	NR	NR	54.8 vs. 50.6	No	22.8 vs. 32.8	NR
Paroxysmal	36 vs. 35.4	NR	NR	25.5 vs. 32.5	52.8 vs. 50.5	38.8 vs. 43.1	NR
Persistent	26 vs. 27.3	NR	NR	19.7 vs. 16.7	47.2 vs. 49.5	38.5 vs. 24.2	NR
Mean age (SD) or median (IQR)	70.2 ± 8.4 vs. 70.4 ± 8.2	69 (61–75) vs. 72 (64–78)	69 (61–75) vs. 72 (64–78)	69 (61–75) vs. 72 (64–78)	67.0 (58.0–74.0) vs. 71.0 (63.0–78.0)	68.9 ± 8.9 vs. 70.1 ± 7. 8	69 (62–76) vs. 74 (66–79)
Men (%)	53.8 vs. 53.5	60.3 vs. 59.3	52.9 vs. 51.9	58.5 vs. 55	60.7 vs. 64.2	55.9 vs. 51.0	55.52 vs. 56.56
Hypertension (%)	88.3 vs. 87.5	72 vs. 70.5	84.3 vs. 64.1	75.2 vs. 76.5	65 vs. 74.5	70.1 vs. 65.4	64.01 vs. 67.08
Valvular disease (%)	43.8 vs. 46.1	NR	8.6 vs. 10.2	NR	NR	47.2 vs. 50.3	NR
HF (%)	28.4 vs. 28.8	NR	49 vs. 54.9	23.5 vs. 21.6	6.2 vs. 9.6	NR	24.79 vs. 22.79
CAD (%)	16.9 vs. 17.2	NR	NR	25.7 vs. 24.6	6.2 vs. 6.4	21.2 vs. 22.8	7.58 vs. 8.36
NOAC	91.2 vs. 81.7 (NOAC + VKA)	NR	26.7 vs. 22.5	36.9 vs. 26.5	89.3 vs. 89.5	42.8 vs. 43	3.56 vs. 4.67
VKA		84.4 vs. 94.1	79.1 vs. 83.1	33.9 vs. 38.7	4.5 vs. 4.3	43.6 vs. 39.9	11.7 vs. 13.35
years of follow-up	median 5.1 y	median 5.1 y	median 2.1 y	mean 2 y	mean1 y	mean 675.4 d	Estimated no less than 5 years

AF, atrial fibrillation; RCT, randomized controlled trials; NR, not report; HF, heart failure; CAD, Coronary artery disease; NOAC, non-vitamin K antagonist oral anticoagulant. VKA, vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack; IQR, interquartile range.

TABLE 2 (A) Quality assessment of cohort study by Newcastle-Ottawa scale.

References	Selection				Comparability	Outcome			Score
	1	2	3	4	1	1	2	3	
Kim et al. (11)	1	1	1	1	2	1	1	1	9
Pope et al. (17)	1	1	1	1	2	1	1	1	9
Proietti et al. (12)	1	1	1	1	1	1	1	1	8
Chao et al. (14)	1	1	1	1	2	1	1	1	9

Selection: 1. Representativeness of the exposed cohort; 2. Selection of the non-exposed cohort; 3. Ascertainment of exposure; 4. Demonstration that the outcome of interest was not present at start of the study. Comparability: 1 Comparability of cohorts based on the design or analysis. Outcome: 1 Assessment of outcome; 2. Was follow-up long enough for outcomes to occur? 3. Adequacy of follow-up of cohorts.

TABLE 2 (B) Quality assessment of randomized control trials by Cochrane collaboration's tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
EAST-AFNET 4 (2020)	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
AFFIRM substudy (2021)	Unclear risk of bias	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
RAFAS trial (2022)	Low risk of bias	Unclear risk of bias	High risk of bias	Unclear risk of bias	Low risk of bias	High risk of bias	Low risk of bias

Supplementary Figure 4. Overall, successive exclusion of each study had no meaningful effect on any of the clinical outcomes. Due to the limited number of included studies, we did not perform a publication bias assessment.

4. Discussion

This meta-analysis was performed to compare the benefits of early rhythm control vs. rate control in patients with AF. When

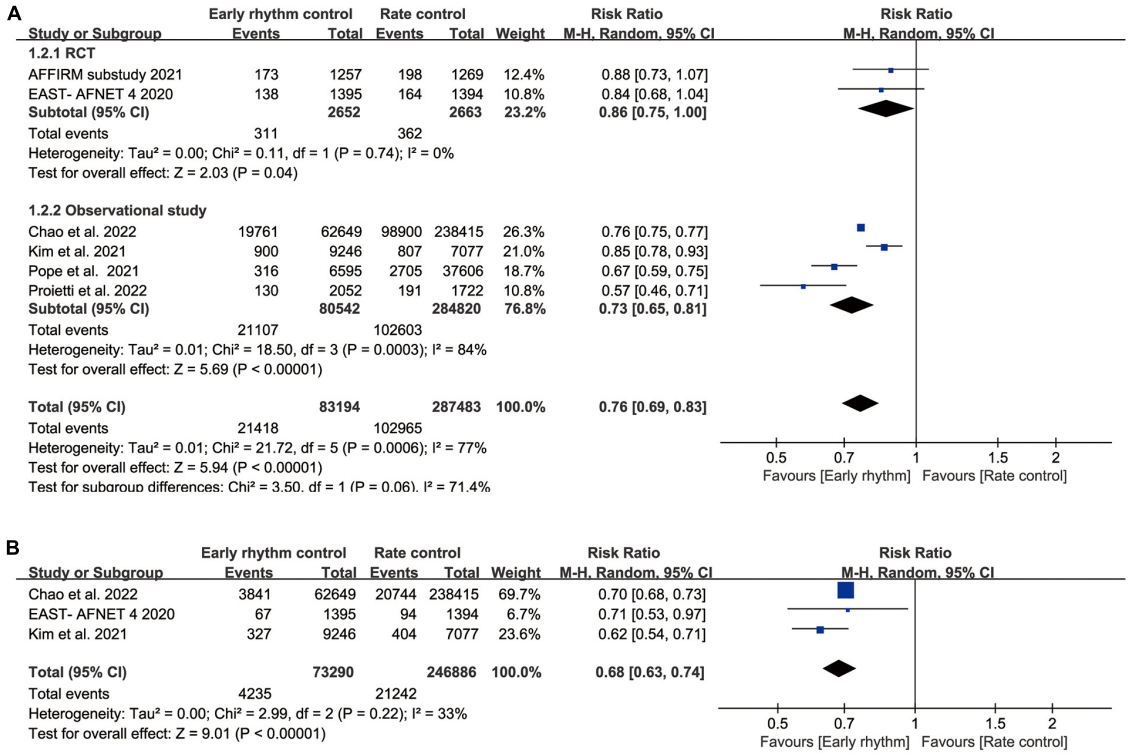

FIGURE 2
(A) Forest plot showing all-cause mortality between early rhythm group and rate group. **(B)** Forest plot showing cardiovascular mortality between early rhythm group and rate group.

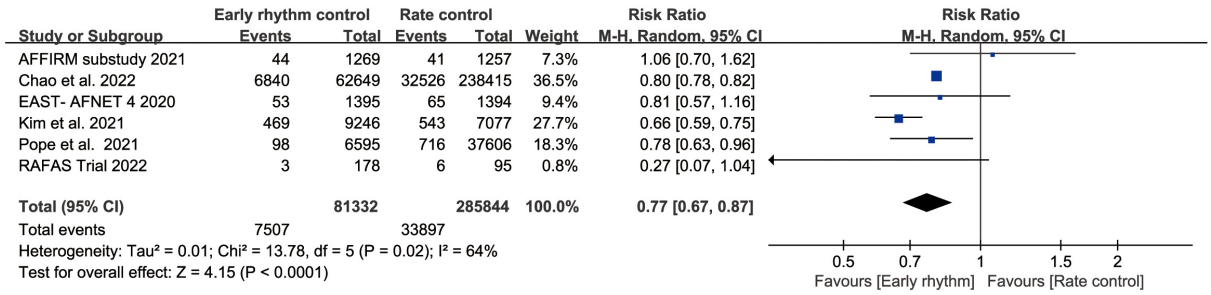

FIGURE 3
Forest plot showing risk of stroke between early rhythm group and rate group.

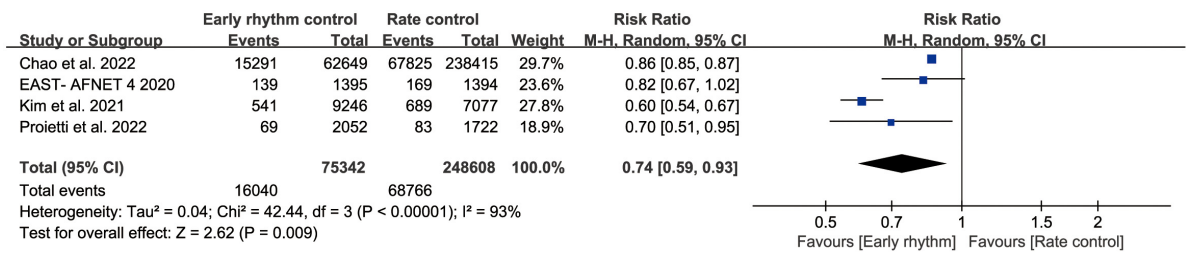

FIGURE 4
Forest plot showing risk of heart failure hospitalization between early rhythm group and rate group.

compared to rate control, early rhythm control appears to be related to lower all-cause mortality, cardiovascular mortality, stroke, and HF hospitalization. Nevertheless, there was no difference between the two groups for acute coronary syndrome, major bleeding, nights spent in the hospital per year, and cardiac arrest/ventricular arrhythmia. To the best of our knowledge, our systematic review

TABLE 3 Outcome of patients who underwent early rhythm control or rate control for atrial fibrillation.

Outcome endpoints	No. of studies	Participants	*P*-value	Effect estimate (95% CI)	I^2
All-cause mortality	7	370950	<0.01	0.76 (0.69, 0.83)	77%
Cardiovascular mortality	3	320176	<0.01	0.68 (0.63, 0.74)	33%
Stroke	6	367176	<0.01	0.77 (0.67, 0.87)	64%
Heart failure hospitalization	4	323950	<0.01	0.74 (0.59, 0.93)	93%
Nights spent in hospital per year	4	25412	0.63	−0.03 (−0.17, 0.10)	95%
Acute coronary syndrome	4	322702	0.44	0.96 (0.87, 1.06)	11%
cardiac arrest/ventricular arrhythmia	3	21638	0.21	1.18 (0.91, 1.52)	0%
Major bleeding	3	65219	0.60	0.95 (0.78, 1.16)	36%

meta-analysis is the first to report on early rhythm control in patients with AF.

4.1. Interpretation of results

Our study concluded that early rhythm control may benefit patients compared with rate control. AF is usually thought to be a progressive disorder, in which arrhythmia begins as paroxysmal form and progresses from persistent to "permanent" AF with electrical and structural remodeling of the atrium (19). AF produces mechanisms for self-perpetuation after it has been established ("AF begets AF') (20). Structural, electrical, and autonomic remodeling are all affected by arrhythmia and it can exacerbate pre-existing issues, making the patient more susceptible to recurring and chronic AF (21, 22). In addition, the Framingham Heart Study demonstrated that in the first year after AF is identified, the risk of cardiovascular problems increased (2). Amiodarone, the most effective medicine now available for long-term sinus rhythm maintenance, has anti-remodeling effects (23). In patients with AF, catheter ablation is superior to medical therapy for the maintenance and restoration of sinus rhythm (4, 24). Previous research has suggested that catheter ablation can prevent left atrial remodeling (25, 26). A shorter period between the first AF diagnosis and the ablation therapy has also been demonstrated to improve the chances of ablation success (27). Therefore, maintaining sinus rhythm as early in the natural history as feasible would appear to be a rational method to avoid AF development. However, since 2002, rhythm control has been proven to be unlikely to reduce all-cause and cardiovascular mortality in the general population compared to rate control in RCTs (5, 6, 28). This seemingly conflicting outcome might be explained. The poor rate of sinus rhythm restoration and maintenance in most of these experiments is a key issue. Only 39% of patients in the rhythm-control arm of the RACE experiment were in sinus rhythm at the end of the study (28). Patients in the late phases of the illness process were also included in these studies. Patients with chronic AF were enrolled in the STAF, PIAF, and RACE studies (28–30). Likewise, a substudy of the AFFIRM study demonstrated no difference in all-cause mortality, and ischemic stroke when comparing early rhythm control with rate control in patients with AF. Of all the studies we included, this was the only study that early rhythm control showed no benefit compared with rate control. The proportion of anticoagulants used in the early rhythm group was lower than that in the rate group (84.4 vs. 94.1%). We think that this was a key factor leading to the above results. The AFFIRM study recruited patients with dilated left atrium (65%). Even with the use of antiarrhythmic medicines, it is difficult to reverse structural abnormalities and sustain sinus rhythm once AF has structural changes. In addition, over the last 20 years, AF ablation is an important role in the treatment of AF. The AFFIRM study included patients who were not treated with catheter ablation.

4.2. Clinical implications

These findings imply that early rhythm control is superior to rate control. Therefore, patients with AF should receive rhythm control immediately. However, guidelines currently recommend rhythm control therapy to improve symptoms and quality of life in symptomatic patients with AF (IA) (4). In fact, many newly diagnosed AF patients may be asymptomatic (31). A new AF diagnosis is linked to a high risk of stroke (7%), heart failure (14%), and death (49%) (32). Early rhythm management has been proven to have a lower risk of death and stroke in some studies. Nevertheless, there is no recommendation in the current guidelines early rhythm management to reduce severe adverse cardiovascular events such as stroke and mortality. Although early rhythm therapy has some associated side effects, long-term antiarrhythmic drugs-related significant adverse events, and mortality are usually linked to chronic AF and structural heart disease (33). Catheter ablation, an effective strategy for rhythm control, showed no significant increase in adverse events compared with the standard care group (34). Therefore, future guidelines may support the early rhythm control management of AF based on the long-term effects in reduced all-cause mortality, cardiovascular mortality, stroke, and HF hospitalization. Furthermore, patient selection and interaction between patient and operator should not be overlooked.

5. Limitations

First, due to the nature of observational studies, biases cannot be eliminated. Differences in techniques, demographics, and backgrounds inevitably convey unidentified confounders. Despite the random effects method employed in quantitative analysis, heterogeneity of clinical features and interventions among trials is a significant limitation. Second, several studies included patients between 1996 and 2020, causing changes in therapy over time.

The difference between the samples included in our study was large, ranging from 273 to 301,064. Therefore, we conducted a sensitivity analysis by eliminating one study at a time to determine how each one affected the outcomes. We did not find a meaningful effect on any of the clinical outcomes. Third, the lack of patient-level data made an extensive evaluation of baseline features regarding clinical outcomes impossible. However, all of the studies' baseline parameters were well-matched in both groups. Fourth, the studies we included had different definitions of early intervention, but we performed a series of sensitivity analyses and found no significant difference. Finally, most of the studies we included were real-world studies, and only one large-scale prospective RCT in our meta-analysis. In our subgroup analysis, a retrospective analysis of an RCT was also classified as a randomized controlled study.

6. Conclusion

This is the first meta-analysis to conclude that early rhythm control may be more beneficial than rate control in patients with AF. Our study demonstrated that early rhythm control can reduce all-cause mortality, cardiovascular mortality, stroke, and HF hospitalization. However, early rhythm control was not associated with acute coronary syndrome, major bleeding, nights spent in the hospital per year, and cardiac arrest/ventricular arrhythmia. We hope that more research will be done in the future to confirm our findings.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

SH and RJ conceived the review. SH drafted and wrote the manuscript. RJ, ZC, SZ, RG, and YB revised and edited all the version of the manuscript. During the revision of the manuscript, MX made great contributions to us, including the correction of the manuscript, statistical analysis, language polishing and literature retrieval. KC revised the sections. All authors contributed to manuscript revision and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.978637/full#supplementary-material

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Chronic vagus nerve stimulation in patients with heart failure: challenge or failed translation?

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Autonomic imbalance between the sympathetic and parasympathetic nervous systems contributes to the progression of chronic heart failure (HF). Preclinical studies have demonstrated that various neuromodulation strategies may exert beneficial cardioprotective effects in preclinical models of HF. Based on these encouraging experimental data, vagus nerve stimulation (VNS) has been assessed in patients with HF with a reduced ejection fraction. Nevertheless, the main trials conducted thus far have yielded conflicting findings, questioning the clinical efficacy of VNS in this context. This review will therefore focus on the role of the autonomic nervous system in HF pathophysiology and VNS therapy, highlighting the potential reasons behind the discrepancy between preclinical and clinical studies.

KEYWORDS

vagus nerve stimulation, heart failure, anti-inflammatory, tragus nerve stimulation, translation

1. Introduction

Heart failure (HF) represents a major public health problem associated with high morbidity, mortality and health care-related costs (1). It has been estimated that greater than 26 million patients suffer from HF worldwide. HF poses a substantial economic burden on patients and society. Expenditures associated with HF are thought to exceed $30 billion per year, and this value is expected to double in 2030 (2, 3). Despite important advances in medical and device-based therapies, hospitalizations and readmissions in patients living with HF continue to increase, particularly in patients aged ≥65 years (4, 5).

It is widely accepted that HF is characterized by an autonomic imbalance with a sustained increase in sympathetic drive and by withdrawal of parasympathetic activity (6). Decreased vagal tone is related to increased mortality in patients with HF (7). Given the evidence suggesting that increased vagal activity could reduce the risk of heart-related mortality, there is increasing interest in vagus nerve stimulation (VNS), which targets autonomic imbalance (6, 7). The use of VNS is supported by a strong rationale, consistent experimental data and encouraging preliminary clinical findings. However, a recent INOVATE-HF trial failed to demonstrate successful translation from animals to clinical studies (8). Therefore, whether device-based modulation of the VNS is a viable therapeutic strategy for patients with HF remains an important question. In this review, we will discuss the reasons for the potential reasons.

2. Autonomic dysfunction and heart failure

It has been considered for decades that HF is characterized by autonomic imbalance and hormonal hyperactivity. Autonomic dysfunction has been regarded as a manifestation of the clinical syndrome of HF, presumably as a consequence of hemodynamic changes associated with alterations in cardiac function (9, 10). Autonomic dysfunction is characterized by sympathetic hyperactivity and vagal withdrawn, whereas the hormonal response involves the activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic activation (11). The sympathetic nervous system innervates the adrenal glands and modulates the production of neurohormonal responses. Although the precise mechanisms involved in sympathovagal imbalance in HF patients remain to be clarified, consistent evidence suggests a key role played by the abnormal function of various reflex systems, including baroreflex, chemoreflex, and ergoreflex, as well as of their central integration, which may directly affect autonomic function (12–14).

At the cardiac level, cardiac ganglionated plexi (GPs) exist in the fat pads around the heart and constitute the so called "intrinsic cardiac nervous system". GPs connect with the intrathoracic extracardiac ganglia (the sympathetic paravertebral ganglia). The nodose ganglia (the inferior ganglia of the vagus nerve) are extrathoracic and extracardiac while the dorsal root ganglia are intrathoracic and extracardiac. At each level, the system has the ability to modulate cardiac activity with efferent feedback loops. GPs coordinate the sympathetic and parasympathetic inputs received from the rest of the cardiac ANS (15).

Sympathetic hyperactivity produces cardiac toxicity, which induces interstitial fibrosis, cardiac apoptosis, and inflammation (16). On the other hand, as cardiac output becomes less efficiently induced by HF, a reduction in renal reperfusion increases the secretion of renin and activates the RAAS (17, 18). Activation of the RAAS may damage the myocardium. The potential mechanisms include the induction of chronic energy starvation, ventricular fibrosis, oxidative stress, and proinflammatory activity (19). Both overactivated sympathetic output and overproduction of RAAS aggravate the development of HF. Therefore, the effects of inhibition of sympathetic output and RAAS are potentially beneficial. Despite the pivotal role of drugs as a landmark therapy in HF patients, the residual risk for these patients remains high. Therefore, the role of other devices in modulating autonomic function should not be overlooked. Neuromodulation methods, including baroreflex activation therapy, left stellate ganglion block and renal sympathetic denervation, have been demonstrated to benefit chronic heart failure in experimental studies (20, 21).

Vagal withdrawal is also a critical element in the pathophysiology of chronic HF. Lower vagal activity is associated with unfavorable long-term prognostic implications for patients with HF (22, 23). Over the past several decades, great interest has emerged in modulating vagal activity as a therapeutic target for the treatment of HF. It has long been recognized that electrical VNS can prevent sudden cardiac death in conscious dogs and improve survival in rats with chronic HF (24, 25). Numerous potential sites of abnormal vagal control are noted, including the central nervous system, preganglionic fibers, postganglionic fibers and intracellular signaling pathways. Electrical stimulation of postganglionic fibers resulted in larger responses in the HF group compared to controls (26, 27). The potential benefit from enhanced vagal activity may involve the improvement of left ventricular dysfunction and structural remodeling.

3. Potential mechanisms of VNS in heart failure

Multiple mechanisms responsible for the protective effects of VNS on failing hearts have been observed (28). It has been accepted that VNS directly leads to improved parasympathetic tone and reflexes. VNS not only ameliorates autonomic dysfunction but also results in greater nitric oxide expression, improvement of RAAS and modulation of inflammatory cytokines (29–31). Moreover, recent studies have demonstrated that VNS can reduce apoptosis, inhibit oxidative stress, promote cardiac electrical stability and suppress stellate ganglion nerve activity (29). This finding indicated that vagal nerve stimulation might improve the outlook of patients with congestive heart failure (30).

3.1. VNS potentially inhibits sympathetic nervous activity

VNS could improve autonomic imbalance in failing hearts. The stimulation electrode is implanted in the mid-cervical portion of the vagal nerve and delivers a biphasic current that continuously cycles between on and off periods. Vagal afferent activation generated by VNS projects to the medulla located in the brainstem (31). The medulla contains cell bodies of the sympathetic and parasympathetic nervous systems. The nucleus tractus solitarius (NTS) of the medulla receives vagal afferent input and integrates the information. Neural connections from the NTS activate sympathetic neurons located in the rostral ventrolateral medulla (RVM) and inhibit parasympathetic neurons located in the dorsal vagal nucleus (DVN) and nucleus ambiguous (NA). VNS not only appears to increase the vagal tone to the heart but also may decrease sympathetic activity to some extent (32, 33).

The cervical vagal nerve contains both afferent and efferent fibers. Vagal fibers include A-, B- and C-fibers (34). Different electrical parameters activate different fibers. The cardiac response to cervical VNS presents a dynamic interaction between afferent mediated decreases in central parasympathetic drive and suppressive effects evoked by direct stimulation of parasympathetic efferent axons to the heart. The neural fulcrum is defined as the functional balance between afferent and efferent

fibre activation. At low intensities and higher frequency VNS, HR increased during the VNS active phase owing to afferent modulation of parasympathetic central drive. As intensity increased further, HR was reduced during the active phase of VNS (35).

3.2. VNS modulates nitric oxide synthase expression

Nitric oxide (NO) plays a critical role in normal physiological functions and pathophysiological development in the heart. There are 3 distinct isoforms of nitric oxide synthase (NOS): neural NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) (36, 37). NO produced from eNOS contributes to regulating cell growth and apoptosis. Cardiomyocytes constitutively express eNOS, which enhances myocardial relaxation and modulates coronary perfusion (38). Endothelial NOS importantly regulated the development of HF. Both inflammatory cells and cardiac myocytes can express iNOS. A study has shown that iNOS overexpression in cardiomyocytes is related to ventricular fibrosis, left ventricular hypertrophy, chamber dilation and a cardiomyopathic phenotype (39). In dogs with heart failure induced by coronary microembolization, iNOS is obviously overexpressed, but eNOS is significantly downregulated (40). However, VNS in long-term therapy significantly improves the expression of eNOS and iNOS (40). nNOS is potentially upregulated in rats as well as in human failing hearts. A study demonstrated that preferential suppression of nNOS results in increased cardiac sensitivity to beta-adrenergic stimulation (41). nNOS was significantly overexpressed in the left ventricular myocardium after heart failure. However, VNS improved the abnormal expression of nNOS in the myocardium. Based on the above finding, HF could induce abnormal expression of three NOS isoforms. However, long-term VNS significantly tends to normalize the expression of NOS in the failing heart (40). nNOS can increase the release of Ach in parasympathetic neurons, while it could reduce the release of NE in sympathetic neurons. Interestingly, nNOS also may reverse impaired vagal and exaggerated sympathetic drive in the spontaneously hypertensive rat (42).

3.3. VNS suppresses activation of the renin-angiotensin system

As cardiac output becomes less efficient, a reduction in renal reperfusion increases the secretion of renin and activates the renin-angiotensin system (RAAS). Renin is a circulating aspartic proteinase that converts angiotensinogen to angiotensinogen I. Subsequently, angiotensinogen I is rapidly cleaved by angiotensin-converting enzyme to generate angiotensinogen II (Ang II). The effects of Ang II include vasoconstriction, ventricular remodeling, fibrosis, endothelin generation and sympathetic nervous action. Ang II contributes to enhancing sympathetic outflow in HF via central and peripheral effects. Mounting evidence demonstrates that AngII contributes to the increased SNA in CHF by acting in different brain regions, including the PVN, RVLM and area postrema. Ang II facilitates sympathetic neurotransmission at adrenergic nerve endings (18, 43). VNS inhibited RAAS activation. Vagal afferents from the cardiopulmonary region are reported to exert a tonic restraint on the release of renin. Vagal blockade significantly increased plasma renin activity in heart failure dogs (44, 45). VNS treatment decreased plasma Ang II levels in dog models. Therefore, inhibition of the renin-angiotensin system by VNS represents an additional therapeutic pathway (46).

3.4. VNS exerts an anti-inflammatory response

The vagal nerve facilitates the interactions of the neuroimmune system. It is now clear that VNS treats various inflammatory disorders of the organism. VNS contributes to controlling the inflammatory response by the cholinergic anti-inflammatory pathway through a vago-vagal reflex (47). Cholinergic receptors include muscarinic ACh (mACh) and nicotinic (nACh) receptors. mACh receptors are conventionally divided into five subtypes from M1 to M5 (48). However, the M2 and M3 receptor subtypes of the myocardium are important for cardiovascular diseases (49). nACh receptors have been identified in many cells. It is well known that α7nACh receptors of macrophages are involved in the cardioprotection conferred by VNS (50). ACh released from vagal terminals binds to the α7nACh receptors on macrophages and inhibits the production of inflammatory cytokines, including high-mobility group box 1 (HMGB1), TNF-α and interleukin-6 (IL-6) (51). Another anti-inflammatory pathway is the vagal-splenic pathway, which is a nonneuronal cholinergic pathway (52). In this pathway, VNS activates the splenic nerve, a sympathetic nerve issued from the celiac ganglion (53). Norepinephrine is released from the splenic nerve and binds to β2 receptors of T-lymphocytes of the spleen, resulting in the release of Ach. Ach binds to α7nAChR of macrophages to inhibit the release of TNF-α (54, 55).

4. Preclinical studies

Preclinical studies suggested that chronic VNS could exert protective effects on the heart in animal models of heart failure (see **Table 1**). In 2004, an experimental study reported by Li et al. showed that chronic VNS resulted in significant improvement in cardiac function and decreased mortality in a rat model of CHF after large myocardial infarction (25). Zhang et al. investigated the effect of chronic VNS in a canine rapid ventricular pacing model of heart failure. Chronic VNS significantly improved left ventricular (LV) ejection fraction and reduced LV end-diastolic and end-systolic volumes (46). VNS markedly attenuated the increased levels of plasma catecholamine, angiotensin II and C-reactive protein. Sabbah and colleagues established a canine model of HF produced by multiple sequential coronary microembolizations (56).

TABLE 1 Characteristics of the preclinical studies, clinical experiences and clinical trials in the treatment of HF by VNS.

Authors	Study design	Subjects	VNS number	Diagnosis	Assessment	Intervention	Time of Intervention	Main outcomes	Summary
Li et al. (25)	Controlled experimental study	Rats	11	HF induced by myocardial infarction	Cardiac remodeling and long-term survival	Right-sided VNS	6 weeks	VNS improved the long-term survival and cardiac remodeling.	VNS is a feasible method in rats study.
Zhang et al. (46)	Control experimental study	Dogs	8	HF induced by high-rate pacing	High-rate pacing/HF development	Right-sided VNS	8 weeks	VNS prevented HF development, improved autonomic control and reduced inflammatory effects.	VNS is a feasible and effective method in canine study.
Hamann et al. (57)	Controlled experimental study	Dogs	7	HF induced by microembolizations induced	LV structure and function	Right-sided VNS	6 months	VNS improved LV structure and function, and biomarkers.	VNS is a feasible and effective method in canine study.
Schwartz et al. (59)	Single central, pilot study	Humans	8	HF	Feasibility, safety and efficacy of chronic VS in HF patients.	Right-sided VNS	6 months	Improvements in NYHA class, quality of life, LV structure.	VNS is a feasible and effective method in patients with HF.
De Ferrari et al. (60)	Multiple-centre, open-label, two-staged study	Humans	32	HF	Feasibility, safety and efficacy of chronic VS in HF patients.	Right-sided VNS	6 months	Improvements in NYHA class, quality of life, LVEF and LV volume. The improvements maintained for 1 year.	VNS in CHF patients is a safe, tolerable and effective method.
Premchand et al. (63)	Randomized and controlled trial	Humans	60	HF HF patients.	Safety and efficacy of left or right VNS in HF patients.	Left-sided or right-sided VNS	10 weeks	Improvements in HRV, 6 min walk distance and LVEF.	Both left- or right-sided VNS is feasible, tolerated, and effective.
Zannad et al. (66)	A Phase II, randomized clinical trial	Humans	96	HF	The primary endpoint with LVESD, and the second endpoint with exercise capacity, quality of life, 24-holter, and circulating biomarkers.	Right-sided VNS	6 months	No significance among echocardiographic parameters, but a significant improvement in quality of life.	It failed to demonstrate a significant effect on primary and secondary endpoint measures, but quality-of-life measures showed significant improvement.
Gold et al. (8)	A multinational, randomized trial	Humans	707	HF	Safety and efficacy of VNS among patients with HF	Right-sided VNS	18 months	Quality life and NYHA were improved, but LVESVI were not significant.	VNS does not reduce the rate of death or HF events in chronic HF patients.

CHF, chronic heart failure; HF, heart failure; HRV, heart rate variability; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESVI, left ventricular end-systolic volume index; NYHA, New York Heart Association; VNS, vagus nerve stimulation.

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After 3 months of chronic VNS therapy, LV end-systolic volume decreased, and LV ejection fraction increased. Several biomarkers of heart failure were positively attenuated by VNS.

Hamann et al. developed a canine model of HF induced by intracoronary microembolizations that has been used for chronic vagal nerve stimulation without causing heart rate reduction. They found that VNS treatment significantly increased LV ejection fraction, reduced left ventricular chamber dimension, and improved biomarkers of inflammatory cytokines and cellular apoptosis in heart failure (57). These preclinical studies indicated that VNS is an effective and feasible treatment for chronic heart failure. VNS could induce bradycardia in chronic HF. Therefore, β blockers may potentially cover the beneficial effects of VNS on chronic HF. Sugimachi et al. performed a study and found that VNS exerted additional beneficial effects on HF with the β blockers treatment. They found that VNS achieved beneficial effects on the failure heart independently of its anti-beta-adrenergic mechanism (58).

5. Clinical experiences

VNS was approved for the treatment of patients with drug-refractory epilepsy in 1997 and medically refractory depression in 2005. Based on the efficacy of preclinical studies and the safety of VNS management in patients, clinical studies of the treatment of VNS were started (see **Table 1**).

Schwartz et al. reported a single-center pilot study of 8 patients with severe HF who were implanted with the Cardiofit system. This first-in-man experience of chronic VNS in patients with HF demonstrated that VNS significantly reduced the NYHA classification, markedly improved the quality of life and decreased left ventricular end-systolic volume (59). This result suggested that VNS treatment was feasible and appeared safe and tolerable. Given the beneficial results, De Ferrari et al. subsequently expanded the study and enrolled 32 patients with symptomatic HF and reduced LV ejection from multiple centers. At the preliminary 6-month follow-up, VNS significantly improved LV ejection fraction, LV end-systolic volume and 6 min walk test results, and these effects were maintained to the 1-year follow-up (60). These encouraging results suggested that VNS has clinical merit in HF treatment.

6. Clinical trials

Currently, most neurostimulation devices provide stimulation in an open-loop manner; however, closed-loop neurostimulation devices (i.e., modulate therapy in response to physiological changes) may provide more effective and efficient therapy. Herein, we focused on clinical trials of implantable closed-loop vagus nerve stimulation for the treatment of chronic heart failure (61, 62). The positive results of CARDIOFIT^{TM} have led to further clinical trials, including ANTHEM-HF (Autonomic Neural Regulation Therapy of Enhance Myocardial Function in Heart Failure) (63–65), NECTAR-HF (Neural Cardiac Therapy for Heart Failure) (66, 67), and INOVATE-HF (Increase of Vagal Tone in Congestive Heart Failure) (34, 68) trials (see **Table 1**).

The ANTHEM-HF study was a prospective and open-label study enrolling 60 NYHA class II-III patients with an LV ejection fraction <40% and a QRS <130 ms (64). Patients followed for over 6 months were randomized to either left or right cervical VNS; no control group was included in this study. The stimulation protocol with an amplitude of 2.0 ± 0.6 mA at 10 Hz stimulation and with a duty cycle of 17.5% (14 s on and 66 s off) was used in the VNS system. LV ejection fraction significantly increased by 4.5% ($p < 0.05$), but no significant decrease in LV end-systolic volume was noted. Improvements in NYHA classification (77% of patients) and the Minnesota Living with Heart failure score were observed. Interestingly, no statistical significance was noted between left-sided and right-sided vagal stimulation. Owing to insufficient dosing of autonomic regulation therapy (ART) such as VNS, larger clinical studies need further to be studied. Recently, the ANTHEM-HFrEF study was designed to explore whether VNS using appropriate ART could improve morbidity and mortality as well as symptoms and function for patients with advanced HF. The ANTHEM-HFrEF study, with adaptive sample size selection, is an adaptive, open-label, randomized, controlled study (69).

The NECTAR-HF study was a prospective and double-blinded study enrolling 96 patients in NYHA class II-III, with an LV ejection fraction ≤35% and LV end-diastolic diameter >55 mm. All patients were implanted with a VNS device without the use of a right ventricular sensing lead and then randomly divided 2:1 into the active group and sham group for the first 6 months. For the second 6 months, all patients received VNS treatment. The stimulation parameters had an average amplitude of 1.42 ± 0.8 mA at 20 Hz and a duty cycle of 17% (10 s on and 50 s off). No significant change in the LV end-systolic dimension of the primary endpoint was noted. No significant differences in LV end-systolic and diastolic volume, LVEF or plasma biomarkers were noted as secondary endpoints, whereas significant improvements in NYHA functional class and quality of life were observed (67).

The INOVATE-HF study was a pivotal phase III multicenter study enrolling 707 patients with NYHA class III, LV ejection fraction <40% and LV end-diastolic diameter 50–80 mm. Patients were randomized 3:2 to either the VNS group or the sham implantation group. The primary endpoints of this study focused on complications at 90 days, all-cause mortality and HF hospitalizations at 12 months. This trial was stopped in the last year by the Steering Committee due to the results. There was no significant difference in primary efficacy between the VNS group and the control group. No significant difference in LV end-systolic volume index was observed between groups. However, significant improvements in NYHA classification, quality of life and 6 min walking distance were noted (8). VNS delivery was open-loop in ANTHEM-HF and NECTAR-HF, but VNS delivery was closed loop in INOVATE-HF. Open-loop delivery targeted at both central and peripheral nervous activity. Closed-loop delivery preferentially aimed at peripheral neural targets. It required a right ventricular intracardiac lead in order to synchronize VNS delivery to R-wave sensing.

7. Cervical VNS in patients with HF: A failed translation?

The results between preclinical studies and clinical trials are inconsistent. Moreover, the INOVATE-HF trial presented somewhat negative study results. Do the results mean that it fails to demonstrate a successful translation of VNS treatment? To better understand these results, there are some concerns that should not be ignored.

7.1. Dose issue

The dose–response curve is estimated to determine the proper dosage and achieve the greatest possible benefit in pharmacological trials. A dose-response curve should also be generated for VNS treatment. However, given the different parameters of combinations, the "dose" of electrical therapies is considerably more complex than that noted for pharmacological therapies. The cervical vagal nerve contains both afferent and efferent fibers composed of A-, B- and C-fibers (34). Given that the threshold for stimulation varies inversely with fiber diameter, VNS at low-intensity stimulus initially activates A-fibers and gradually recruits B-fibers with higher intensity. As the intensity continues to increase, C-fibers are recruited (35). Owing to intrinsic properties and larger diameters, afferent fibers are preferentially activated at low stimulation thresholds, which subsequently increases vagal activity and suppresses sympathetic activity via CNS modulation (70). Regarding the frequency of stimulation, low frequencies (5–10 Hz) activate vagal afferents, whereas high frequencies (10–30 Hz) activate both vagal afferents and efferents (29, 30, 47, 71). In order to the demonstrate the effect of chronic VNS on central–peripheral neural network interactions for integrated control of the heart, Ardell et al. firstly proposed "neural fulcrum". Based on frequency–amplitude–pulse width, the "neural fulcrum" is defined as the operating point, where a null heart rate response is reproducibly evoked during the on-phase of VNS. The fulcrum point stably maintains over the average 14 months of chronic VNS (72).

The stimulating lead and strength in NECTAR-HF and ANTHEM-HF studies were designed to stimulate afferent fibers, whereas lead and strength used in CardioFit and INOVATE-HF studies were designed to stimulate efferent fibers. In theory, afferent fiber stimulation would be more beneficial for decreasing sympathetic activity than efferent fiber stimulation. However, a large dose may damage vagal fibers. A stimulation frequency of 1–2 Hz was applied in the CardioFit system, and a stimulation current of 4.1 ± 1.2 mA was achieved at the end of titration. A stimulation frequency of 10 Hz was applied in ANTHEM-HF, and a current output of 2.0 ± 0.6 mA was achieved at the end of titration. NECTAR-HF used a frequency of 20 Hz and reached 1.2 ± 0.7 mA (see **Table 2**). The low intensity of stimulation applied in NECTAR-HF was related to B fibers. B fibers contributed to a lower heart rate and anti-remodeling effects. Although the low stimulation current in NECTAR was previously considered a cause for the negative findings, it was questioned by the neutral result of the INOVATE-HF study with a high stimulation amplitude (3.9 ± 0.7 mA). Therefore, other factors are responsible for the failure to achieve the different results of VNS in the HF long term (67, 73). Moreover, the duty cycle designed in the CardioFit study led to a reduced heart rate, whereas no reduction in heart rate was noted in the INOVATE-HF trial. Therefore, the results of chronic VNS in patients with HF are related to multiple factors, including stimulating parameters (current intensity, frequency, duty cycle), electrode design and stimulated-side selection. Research on the optimal dose of VNS needs further study. Despite the intended design, the stimulation in all 4 studies resulted in both afferent and efferent stimulation. Furthermore, the relative benefit of afferent vs. efferent stimulation (or both) has not been demonstrated clinically.

TABLE 2 Stimulation parameters of VNS in three clinical trials.

Parameters	ANTHEM-HF pilot study	NECTAR-HF	INOVATE-HF
Neural target	Central/peripheral	Central/ peripheral	Peripheral
Delivery site	Left- or right-sided VNS	Right-sided VNS	Right-sided VNS
Delivery intensity			
Amplitude (milliamperes)	2.0 ± 0.6	1.4 ± 0.8	3.9 ± 1.0
Frequency (Hz)	10	20	From 1 to 2
Duration (ms)	250	300	500
Duty cycle	17.5%	17%	25%
On-time/off time (s)	18/62	10/50	Variable
Electrode polarity	Caudal	Caudal	Cephalad
Model of delivery	Open loop/cyclic	Open loop/ intermittent	Closed loop/ intermittent

HF, heart failure; VNS, vagus nerve stimulation.

7.2. Patient selection

Optimal patient selection also holds the key to obtaining better outcomes for patients with HF. The benefit of patients with HF from VNS is likely to be associated with the extent of neuro-hormonal derangement. The patients with low levels of autonomic imbalance may not benefit from VNS therapy. VNS is known to relieve the inflammatory response. Patients with evidence of cardiac inflammation may benefit much more (74). Furthermore, patients with long-standing heart failure may be refractory to all therapies, including VNS treatment (75). Finally, lifestyle changes, such as exercise, can increase vagal activity and reduce mortality in patients with HF. Whether VNS combined with exercise will offer benefits remains an open question (76).

8. More research for possible improvement

Resting heart rate (HR) is a simple index reflecting the external autonomic regulation of the intrinsic heart rate at the sinus node level that is achieved with the combined activity of the

sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). In fact, heart rate has two components -the intrinsic and the extrinsic component. Intrinsic HR is the HR measured in the absence of sympathetic and parasympathetic inputs (achieved by denervation or pharmacologic blockade). In healthy human subjects, this is approximately 100 bpm and is age- and gender-dependent (77). Intrinsic HR depends on sinus node automaticity and on the ionic transportations through the cell membrane that continuously generate the action potential. Denervated transplanted hearts, which lack the SNS and PNS function, beat fast at 100 bpm and their frequency exclusively depends on intrinsic automaticity. It is the impact of PNS tone during rest that dominates SNS and sinus node automaticity and decreases this frequency to 50–60 bpm. The slope of action potential depolarization is determined from If channels. SNS and PNS increase or decrease the heart rate by changing this slope. The influences of the SNS and PNS on HR have been proposed to be defined by the following formula: $HR = m \times n \times HR0$; where m is the sympathetic influence (>1), n is the parasympathetic influence (<1), and HR0 is the intrinsic HR (78). Given the heart rate physiology analyzed above, it is rational to propose that the VNS effectiveness on the autonomic nervous system's status is reflected by the resting HR. In other words, VNS may be therapeutic and efficient if a critical decrease of the post-VNS baseline resting HR is achieved. In this case, SNS and PNS may reach a new (and therapeutic) balance. The ANTHEM-HF study reported an improvement in 24 h HR from 78 bpm to 70 bpm ($p = <0.0005$) after 12 months of VNS, while SDNN from HRV increased from 95 ms to 109 ms ($p = <0.01$). This information is not presented in the INOVATE-HF study, so it is not possible to determine the effectiveness of PNS stimulation that was applied in this study.

It is currently unknown what the most appropriate stimulation protocol would be. Indeed, all studies applied protocols with variances in amplitude, frequency of stimulation, and afferent—efferent vagus activity targeting (Schwartz, ANTHEM-HF, NECTAR-HF, INOVATE-HF). The effectiveness of the applied protocol may be estimated according to the above comment 1 from ΔHR while ΔHR = HR baseline—HR post VNS. Additionally, measuring the differences in plasma concentrations of catecholamines pre- and post-VNS (Δ Nor-Epinephrine and Δ Epinephrine) may also serve well as a useful biomarker of a therapeutic efficient new SNS-VNS status, especially if these catecholamines are found to decrease after VNS application. Before any VNS study's results be interpreted, it is necessary to clarify whether the applied VNS protocol was optimal and therapeutic. One simple way to quantify the response of the ANS to the applied VNS is by comparing the achieved differences in heart rate and catecholamines.

It is unclear whether the afferent or the efferent vagus nerve fibers targeting neurostimulation is cardio-protective. Afferent targeting VNS may be necessary for ANS central reset. Further research is required. Vagal function may include two distinct components: reflex vagal activity (79) and tonic vagal activity (80). The extent to which these activities are improved by VNS is unknown. Furthermore, it is unspecified which one contributes more to protection against mortality in HF patients. For example, reflex vagal activity may be protective during ischemia-induced arrhythmias, while tonic vagal activity may improve left ventricular properties, function, and dimensions. Heart Rate Turbulence may quantify reflex vagal function, while Deceleration Capacity of Heart Rate and RMSSD from HRV may quantify tonic vagal activity. Future VNS studies may include such Holter indices to investigate the improvement of tonic and reflex vagal activity after VNS. Therefore, more research need to be further studied to explore the really effectiveness of VNS in patients with heart failure.

9. Evolving strategy

The auricular branch of the vagus nerve (ABVN) on the outer ear is the only peripheral branch of the vagus nerve distributed on the skin (81). Transcutaneous VNS, a novel noninvasive neuromodulation (**Figure 1**), targets ABVN at the outer ear instead of resorting to VNS with surgery and impacts autonomic tone (82). We previously showed that low-level ta-VNS (LL-TS) suppressed AF by prolonging atrial effective refractory periods and reducing AF inducibility in a canine AF model induced by rapid atrial pacing (83). Po and his team demonstrated that LL-TS could effectively suppress atrial fibrillation and decrease inflammatory cytokines in patients with paroxysmal atrial fibrillation (84, 85). A recent clinical study by Jiang et al. demonstrated that LL-TS could reduce myocardial ischemia-reperfusion injury in patients with ST-segment elevation myocardial infarction (86). This result indicated that LL-TS begins to gradually result in clinical efficacy. More importantly, the results of LL-TS in the treatment of cardiovascular diseases

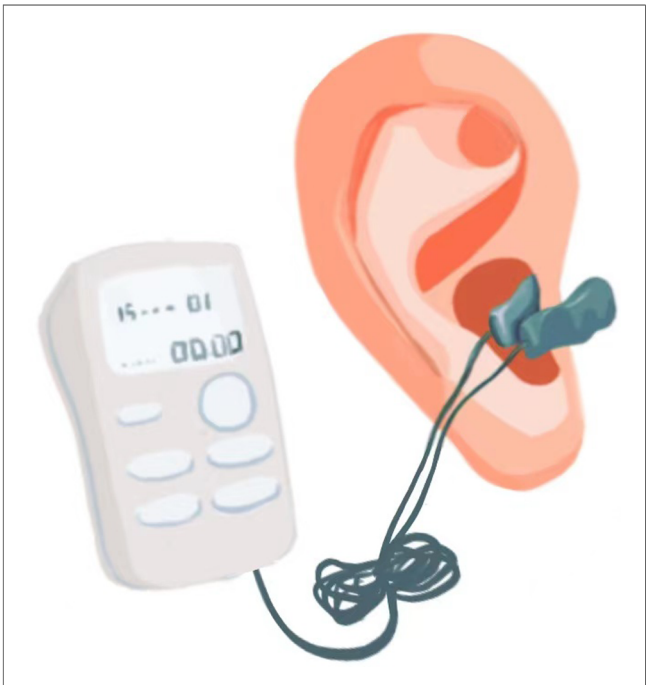

FIGURE 1
Tragus nerve stimulation at auricular branch of the vagus nerve.

are encouraging. Beyond the protective effects in atrial fibrillation and acute myocardial infarction, LL-TS has also been applied to research left ventricular remodeling. Wang et al. showed that chronic intermittent LL-TS could attenuate left ventricular remodeling in conscious dogs with healed myocardial infarction (87). In a preclinical model of postinfarction cardiomyopathy, tragus stimulation was associated with attenuation of ANS imbalance (plasma NE) and neurohormonal activation (NT-proBNP) as well as improvement in LV function. However, the translational effects of LL-TS in the treatment of heart failure still require further study. More recently, LL-TS has emerged as an intriguing option in patients with chronic HF. LL-TS resulted in a significant improvement in global longitudinal strain, inflammatory cytokines, and quality of life in patients with heart failure with preserved ejection fraction (88, 89). The ta-VNS opens an era in the treatment of HF (**Figure 2**).

The different translation results of VNS treatment on HF, another reason was that the patients were not able to tolerate higher-intensity stimulation in clinical trials. As a result, VNS could not achieve the effective stimulation. In order to reduce the adverse effects and increase the tolerance of VNS, recently, selective VNS was also considered as a promising strategy (90–93). Selective VNS targets specific fiber to cause functionally specific effects. Selective VNS not only can reduce side effects, but also increase efficacy to some extent. Several methods, including spatially selective, fiber-selective, anodal block, neural titration, kilohertz electrical stimulation block, stimulation pulse parameters setting, and electrode array geometries changes, have been applied in the field of selective VNS. The development of selective VNS techniques will likely benefit patients in future, however, selective VNS is also a small research area. More and more studies should be

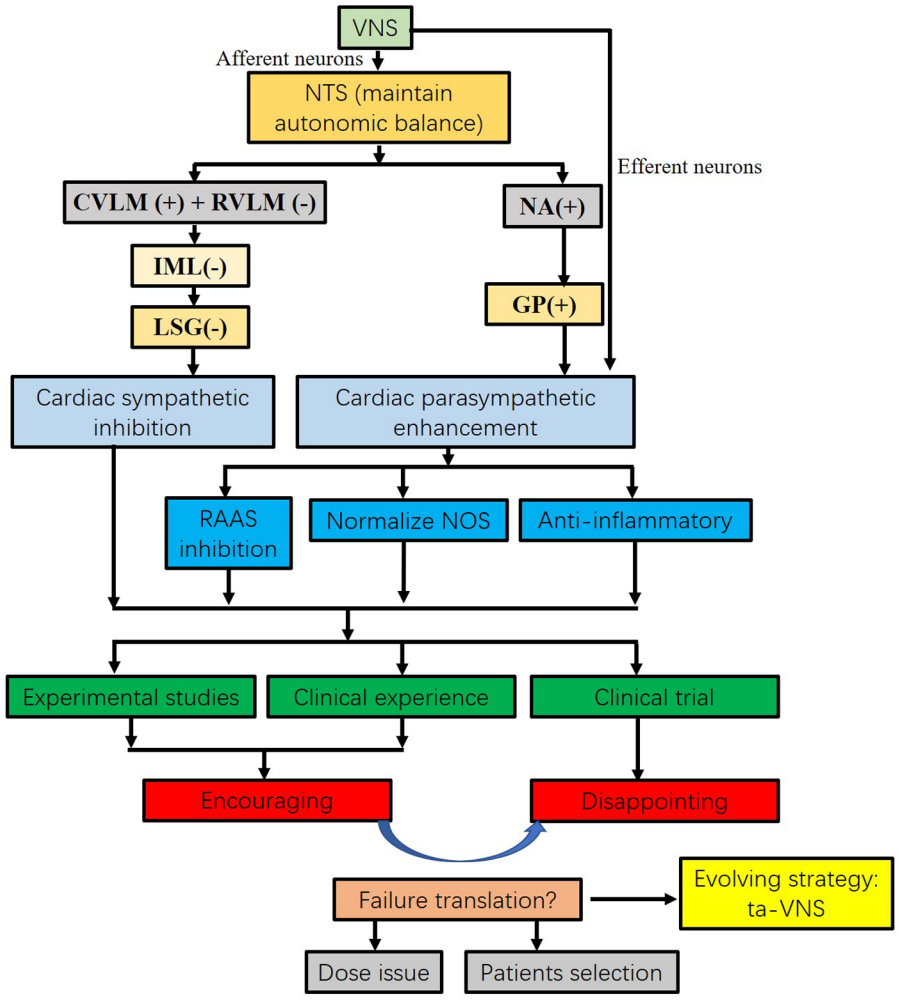

FIGURE 2
Flow chart of VNS on heart failure from concept to translation. VNS maintains autonomic balance. VNS significantly inhibits sympathetic nervous activity and enhances vagal tone. Increased vagal activity attenuates heart failure by RAAS inhibition, NOS normalization, and anti-inflammatory response. The results from the experimental studies and clinical experiences are encouraging. However, the results from recent clinical trials did not achieve the same benefit as experimental studies. Several reasons may contribute to the translation, including dose issues and patient selection. Instead of electrical VNS, tragus nerve stimulation is an evolving strategy. CVLM, caudal ventrolateral medulla; GP, ganglion plexus; IML, intermediolateral cell column; LSG, left stellate ganglion; Ta-VNS opens an era in the treatment of heart failure. NOS, nitric oxide synthase; NTS, nucleus of the solitary tract; RAAS, renin-angiotensin-aldosterone system; RVLM, rostroventrolateral medulla; ta-VNS, tragus nerve stimulation; VNS, vagus nerve stimulation.

performed its safety and efficacy in the treatment of cardiovascular diseases.

10. Conclusion

Experimental and clinical pilot studies of VNS yielded encouraging results in the treatment of HF. However, the results of large randomized clinical trials have been disappointing. The discrepancy between experimental and large clinical trials may be associated with optimal dosing of stimulation, appropriate patient selection, and study design. The clinical translation of VNS in the treatment of HF is a challenge. The era of vagus nerve stimulation for the treatment of heart failure is approaching; however, significant experimental and clinical research is still needed (69).

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

MC, and ZW participated in the study design and drafted the manuscript. MC, JL and ZW were responsible for writing the manuscript. SZ and QL contributes to the manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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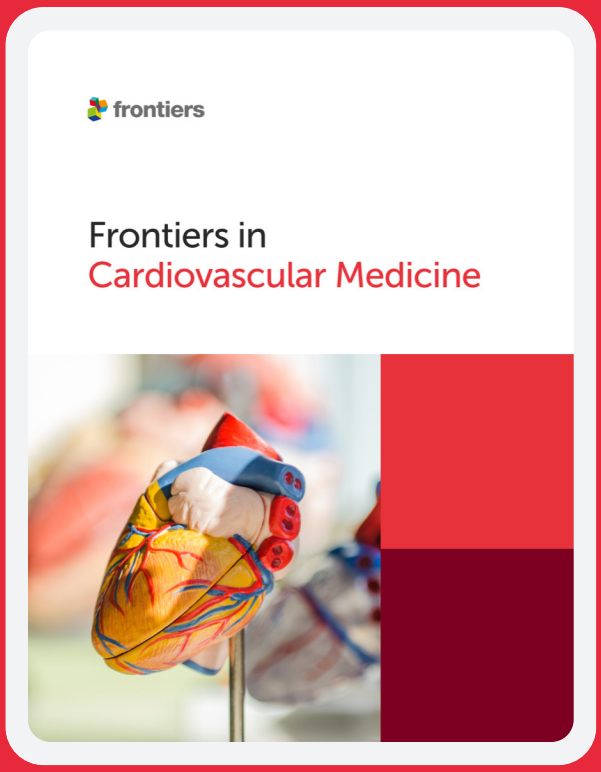

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