



# Mid-term outcomes of concomitant left atrial appendage closure and catheter ablation for non-valvular atrial fibrillation: a multicenter registry

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## Abstract

To investigate the safety and midterm outcome of concomitant left atrial appendage (LAA) closure and catheter ablation (CA) as a one-stage hybrid procedure for non-valvular atrial fibrillation (AF) in a multicenter registry. A total of 50 consecutive patients with symptomatic drug-resistant non-valvular AF with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  and contraindications for antithrombotic therapy were included in the prospectively established LAA closure registry, and underwent concomitant LAA closure (48 for WATCHMAN and 2 for ACP) and CA procedure (40 for radiofrequency and 10 for cryoballoon CA). Two cardiac tamponades, one peripheral vascular complications and one mild air embolism were observed during perioperative period. After mean follow-up of  $20.2 \pm 11.5$  months, 18 (36%) patients presented with atrial arrhythmia relapse and 45 (91.8%) patients presented with complete sealing; furthermore, there were two transient ischemic attacks and one ischemic stroke under an off-oral anticoagulant situation, respectively. Concomitant CA and LAA closure as a one-stage hybrid procedure might be feasible and potentially decrease costs in patients with symptomatic non-valvular AF with high stroke risk and contraindication to antithrombotic treatment, and as safe as LAA closure procedure only during the perioperative period. However, it was necessary to further validate the mid-term safety.

**Keywords** Atrial fibrillation · Left atrial appendage closure · Catheter ablation · Concomitant

## Abbreviations

AF	Atrial fibrillation	LVEF	Left ventricular ejection fraction
CA	Catheter ablation	ACP	Amplatzer cardiac plug
LAA	Left atrial appendage	PV	Pulmonary vein
OAC	Oral anticoagulant	ECV	Electric cardioversion
TEE	Transesophageal echocardiography	AADs	Antiarrhythmic drugs
		TIA	Transient ischemic attack
		AA	Atrial arrhythmia

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## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practices and represents an independent and important risk factor for thromboembolic events.

According to international guidelines, anticoagulation treatment needs to be prescribed to patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 1$  to prevent embolic events [1]. Although catheter ablation (CA) is helpful to relieve symptoms, it cannot completely eliminate the risk of stroke in AF patients. Studies identified the left atrial appendage (LAA) as the source of thrombus formation in at least 90% of patients with non-valvular AF [2–6]. Concomitant LAA closure and CA as a one-stage hybrid procedure could relieve the symptoms of AF and simultaneously reduce the risk of stroke. We report on the mid-term outcome of this approach in a prospective multicenter registry.

## Methods

### Patient population

Patients from five different tertiary hospitals with symptomatic drug resistant non-valvular AF, a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  and relative/absolute contraindications for long-term oral anticoagulant (OAC) therapy were included in a prospectively established LAA closure multicenter registry (ChiCTR-PPR-15007044). The CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores were calculated for stroke and bleeding risk evaluations, respectively. Written informed consent was obtained from each participant. The study protocol was approved by the local ethics committee. Left atrial (LA) and LAA thrombus were ruled out via transesophageal echocardiography (TEE) or cardiac computed tomography prior to the procedure, along with a transthoracic echocardiogram for the assessment of left ventricular ejection fraction (LVEF), LA dimensions, and valvular function. Exclusion criteria were the occurrence of LA thrombus, contraindication to general anesthesia and conscious sedation, and an enlarged LA ( $\geq 55$  mm).

### CA procedure

All procedures were performed under general anesthesia and conscious sedation. Briefly, a decapolar catheter was introduced into the coronary sinus via the left femoral vein, and a quadripolar catheter was placed at the right ventricular apex, if necessary. Transseptal puncture (single for cryoballoon, double for radiofrequency CA) was used to insert a 28-mm cryoballoon (Arctic Front  $\pm$  Advance, Medtronic,

MN, USA) through a transseptal steerable sheath (Flex-Cath, Medtronic) into the LA, or a circular mapping catheter (LASSO SAS, Biosense Webster, CA, USA) and contact-force sensing irrigated-tip catheter (Thermocool SMART-TOUCH, Biosense Webster) through an SL1 long sheath (St. Jude Medical, MN, USA). Boluses of unfractionated heparin were administered after the transseptal puncture to achieve an activated clotting time of 250–300 s. Pulmonary vein (PV) isolation was performed in all patients. Power-controlled radiofrequency energy was delivered with power of 30–35 W and flow velocity of 17 ml/min; Cryoenergy was applied with two times of 240 s per PV antra with first-generation cryoballoon and two times of 180 s with second-generation cryoballoon. An electric cardioversion (ECV) was performed in patients remaining AF rhythm after PVI. A PV revisit and supplement ablation if necessary were performed after LAA closure procedure. The procedural endpoint was durable PV isolation. At the end of the AF CA, patients received prophylactic antibiotic treatment with cefuroxime.

### LAA closure procedure

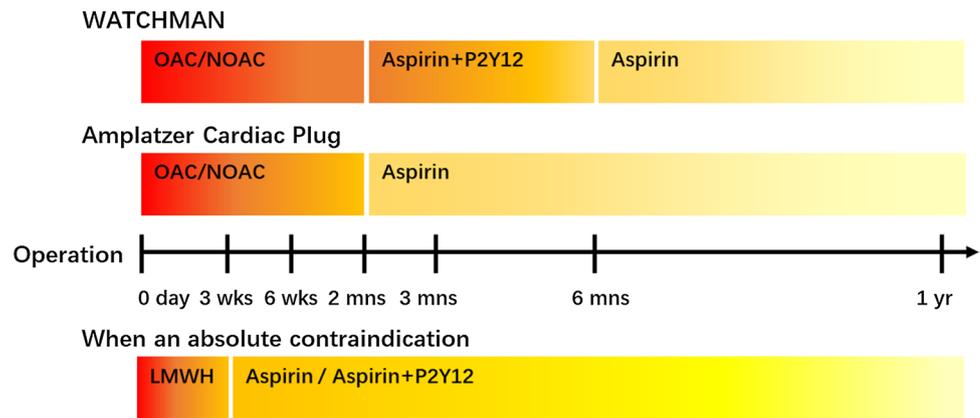
The transseptal long sheath previously used for AF CA was replaced by a 14 F access sheath for LAA closure and maneuvered towards the LAA ostium. Under the LAA angiography and TEE guidance, Watchman (Boston Scientific, MA, USA) or Amplatzer Cardiac Plug (St. Jude Medical) devices were implanted according to LAA size, morphology, and physician preference. Based on TEE measurements, a post-implantation compression of at least 10%, the absence of peri-device leakage ( $> 5$  mm) and no compression of adjacent structures (such as the mitral annulus, circumflex coronary artery, or pulmonary veins) were defined as available. A tug test was performed repeatedly prior to final device release.

### Post-procedural management and follow-up

The patients underwent continuous ECG telemetry in the coronary care unit for 24 h after the procedure. Patients were discharged at 48 h after an uncomplicated procedure. All patients underwent anticoagulation therapy (VKA or Novel OACs) for 2 months after the procedure, followed by dual antiplatelet therapy to the sixth month in patients with a WATCHMAN device and aspirin to the first year in patients with an ACP device. In patients with an absolute contraindication for OAC, low-molecular weight heparin was administered for at least 3 weeks, and followed by aspirin/dual antiplatelet therapy. Thereafter, all patients were treated with aspirin for life in cases without aspirin contraindication [7] (Fig. 1).

All patients underwent 7-day continuous Holter monitoring at 3, 6, and 12 months and every 6 months thereafter

**Fig. 1** Flowchart of the anticoagulation management in patients who underwent concomitant left atrial appendage closure and catheter ablation procedure



during follow-up visits. If 7-day Holter monitoring was not possible, patients underwent at least 48-h Holter monitoring. Any clinical events, such as atrial arrhythmias or stroke/transient ischemic attack (TIA), occurring during the follow-up period were carefully identified. Antiarrhythmic drugs (AADs) were discontinued if the 3-month follow-up visit confirmed the absence of atrial arrhythmia (AA). All patients underwent a TEE examination to rule out any thrombus and residual leakage at approximately 6 weeks' post-procedure. According to the current guidelines [1], CA success was defined as no AAs lasting more than 30 s after the 3-month blanking period.

### Statistical analysis

Continuous variables were expressed as the mean  $\pm$  standard deviation for normally distributed data; otherwise, they were expressed as the median (interquartile range). Categorical variables were expressed as percentages. For comparison of variables, the Wilcoxon's test, Chi-square test, and Student's *t* test were performed as appropriate. Survival plots were generated using Kaplan–Meier survival analysis. Comparisons between survival curves were performed using the log-rank test. A two-tailed *P* value  $< 0.05$  was considered to indicate statistical significance. All statistical analyzes were performed using IBM SPSS Statistics, version 19.0 (IBM Inc., NY, USA). Any episode of AAs lasting more than 30 s detected after the 3-month postprocedural period by electrocardiography, pacemaker interrogation, or 7-day, 48-h continuous Holter monitoring performed at 3, 6, 9, and 12 months was considered failure.

## Results

### Patient characteristics

A total of 50 consecutive patients (33 males, mean age of  $64.9 \pm 7.7$  years) were enrolled in the study. Prior to the

procedure, 27 (54%) patients presented with paroxysmal AF and 23 (46%) with persistent AF. Mean AF duration since diagnosis, LA dimension, and LVEF were  $4.6 \pm 6.3$  years,  $38.6 \pm 5.1$  mm, and  $63.9 \pm 9.0$ , respectively. Thirty-three patients (66%) underwent a one-stage procedure (combined CA and LAA closure) with secondary prevention for previous stroke and TIA. The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score and HAS-BLED score were  $3.7 \pm 1.4$  and  $2.5 \pm 0.9$ , respectively. Table 1 had shown the baseline characteristics of the patient population.

### Procedural data

Procedural data are shown in Tables 1 and 2. The mean procedure duration was  $185 \pm 25.1$  min, CA time and device implantation time were  $19.1 \pm 2.8$  min and  $38 \pm 13$  min, respectively. The mean whole fluoroscopic time was  $28.3 \pm 4.7$  min.

### CA procedure

Forty patients underwent radiofrequency CA with ThermoCool SmartTouch™. During cryoballoon CA, the first-generation Arctic Front™ and the second-generation Arctic Front Advance™ were used in five patients each. There were no significant differences between the two CA techniques regarding baseline characteristics and procedural data. Procedural duration and CA time were longer in persistent AF patients than in paroxysmal AF patients. CA endpoints were achieved in all patients: all PVs were isolated in all AF patients except one (first-generation cryoballoon CA requiring radiofrequency touch-up). A total of 23 patients (1 for paroxysmal, 22 for persistent AF) underwent ECV after PVI and restored sinus rhythm. One peripheral vascular complication and one mild air embolism (during atrial septum puncture) were observed. There were no more complications occurring during the pre-ablation period and CA procedure.

**Table 1** The baseline characteristics of the patient population

Variates	All/N=50	Paroxysmal AF N=27	Persistent AF N=23	P value
Female, <i>n</i> (%)	17 (34)	13 (48.1)	4 (17.4)	0.022*
Mean age, years	64.9±7.7	66.4±7.1	63.2±8.2	0.146
AF history				
Median (IQR), years	3 (1–6)	3 (0.8–6)	3 (2–8)	0.389
Mean ± SD, years	4.6±6.3	3.5±3.2	5.9±8.6	0.225
Minor bleeding, <i>n</i> (%)	29 (58)	15 (55.6)	14 (60.9)	0.778
Major bleeding, <i>n</i> (%)	2 (4)	0	2 (8.7)	N/A
Intolerance on OAC, <i>n</i> (%)	7 (14)	4 (14.8)	3 (13)	0.999
Labile INR on warfarin, <i>n</i> (%)	17 (34)	8 (29.6)	9 (39.1)	0.557
Congestive heart failure history, <i>n</i> (%)	5 (10)	2 (7.4)	3 (13)	0.651
Hypertension, <i>n</i> (%)	42 (84)	23 (85.2)	19 (82.6)	0.999
Diabetes, <i>n</i> (%)	11 (22)	6 (22.2)	5 (21.7)	0.967
Previous stroke/TIA, <i>n</i> (%)	33 (66)	19 (70.4)	14 (60.9)	0.480
Vascular disease, <i>n</i> (%)	12 (24)	8 (29.6)	4 (17.4)	0.313
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	3.7±1.4	4.0±1.5	3.4±1.3	0.124
HAS-BLED score	2.5±0.9	2.5±0.9	2.5±0.8	0.868
Antithrombotic therapy (pre-procedure)				
Warfarin, <i>n</i> (%)	29 (58)	18 (66.7)	11 (47.8)	0.252
Novel OAC, <i>n</i> (%)	1 (2)	1 (3.7)	0	N/A
Antiplatelet drugs, <i>n</i> (%)	6 (12)	1 (3.7)	5 (21.7)	0.082
Low molecular weight heparin, <i>n</i> (%)	4 (8)	3 (11.1)	1 (4.3)	0.614
None	10 (20)	4 (14.8)	6 (26.1)	0.178
Echocardiography				
LA dimension, mm	38.6±5.1	37.2±4.7	40.3±5.2	0.032*
RA dimension, mm	50.2±6.4	47.5±5.5	53.5±6.0	0.001*
LA/RA ratio, %	77.8±8.9	79.1±9.6	76.9±7.9	0.206
LVDd, mm	45.3±6.1	45.6±6.6	45±5.6	0.721
LVSD, mm	28.9±7.5	28.9±8.6	28.8±6.2	0.963
LVEF, %	63.9±9.0	64±9.6	63.8±8.4	0.935
LAA emptying velocity, mm/s	43.4±21.1	43.4±22.2	43.3±20.2	0.984
Cyro, <i>n</i> (%)	10 (20)	7 (25.9)	3 (13)	0.308
Procedure duration, min	185±25.1	177±18.5	194±28.9	0.020*
Ablation time, min	19.1±2.8	17.4±2.5	21.1±1.7	< 0.001*
LAA closure time, min	38±13	38.1±14.4	37.9±11.4	0.948
Fluoroscopic time, min	28.3±4.7	28.5±4.3	28.1±5.2	0.770

AF atrial fibrillation, IQR interquartile range, SD standard deviation, TIA transient ischemic attack, OAC oral anticoagulant, LA left atrial, RA right atrial, LVDd Left ventricular end diastolic dimension, LVSD left ventricular end systolic dimension, LVEF left ventricular ejection fraction, LAA left atrial appendage

## LAA closure procedure

The WATCHMAN was implanted in 48 (96%) patients and ACP in 2 (4%) patients (Fig. 2). A total of 32 partial retrievals were performed in 22 patients because of slight position adjustment, and three complete retrievals were performed in three patients because of a nonadjustable bad compression condition after deployment. Two device manipulation-related cardiac tamponades were observed, of which one required emergency surgical hemostasis and appendage resection (radiofrequency+WATCHMAN). The

other case was successfully resolved by pericardial drainage (radiofrequency+WATCHMAN). There were no other complications during the LAA closure procedure. Mean intensive/coronary care unit stay and post-procedural hospitalization were 1.4±1.7 days and 3.4±4.2 days, respectively.

## Follow-up

All patients were followed up for at least 6 months, and no patient was lost during follow-up. A total of 22 patients underwent 7-day continuous Holter monitoring. During

**Table 2** Procedural and outcome data of concomitant left atrial appendage closure and catheter ablation procedure

Variates	All/N=50
Device and size, <i>n</i> (%)	
ACP	2 (4)
28	1 (2)
30	1 (2)
WATCHMAN	48 (96)
21	1 (2)
24	14 (28)
27	15 (30)
30	12 (24)
33	6 (12)
Partial retrieval, <i>n</i>	32 times on 22 patients
Complete retrieval, <i>n</i>	3 times on 3 patients
Mean compression rate, %	17.6 ± 6.3
Periprocedural complications, <i>n</i> (%)	4 (8)
Cardiac tamponade	2 (4)
Air embolism	1 (2)
Device embolization	0
Death	0
Major bleeding	0
Ischemic stroke/TIA	0
Peripheral vascular complication	1 (2)
Care unit stays, days	1.4 ± 1.7
Post-procedural hospitalization, days	3.4 ± 4.2
TEE follow-up at 6 weeks, <i>n</i> (%)	49
Complete sealing	43 (87.8)
Minimal leakage (< 5 mm)	6 (12.2)
Device-related thrombus	0
TEE follow-up at 6 months, <i>n</i> (%)	49
Complete sealing	45 (91.8)
Minimal leakage (< 5 mm)	4 (8.2)
Device-related thrombus	0
AF recurrence during follow-up, <i>n</i> (%)	18 (36)
Adverse events during follow-up, <i>n</i> (%)	3 (6)
Death	0
TIA	2 (4)
Stroke	1 (2)
Bleeding	0
Heart failure	0

AF atrial fibrillation, TEE transesophageal echocardiography, TIA transient ischemic attack

the mean follow-up period of 20.2 ± 11.5 months (range, 6.2–41.2 months), 36% (*n* = 18, 8 detected via 7-day Holter and 10 detected via 48-h holter) of patients presented with AA relapse after the initial blanking period of 3 months. Antiarrhythmic drugs were effective to maintain sinus rhythm in eight recurrent patients (44.4%) and no additional procedure was performed. The AAs recurrence in

paroxysmal AF was significantly superior to that in persistent AF (25.9% vs. 47.8%, *P* = 0.043). The AAs recurrence was comparable between cryoballoon and radiofrequency CA (40% vs. 35%, *P* = 0.674), as shown in Fig. 3a, b.

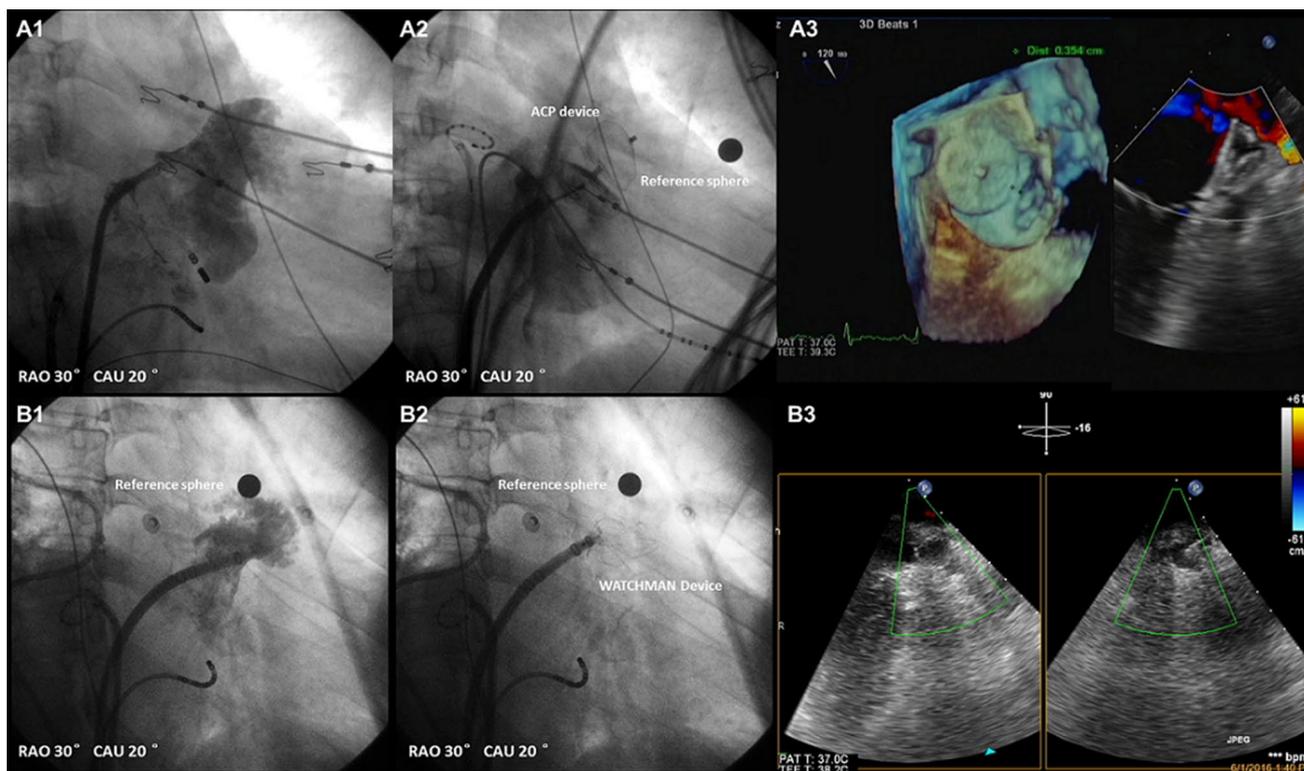
At the 6-week TEE examination, 43 patients (87.8%) presented with complete sealing. The remaining six patients (12.2%) showed minimal peri-device leakage (< 5 mm), and two of these patients showed complete sealing on TEE examination at 6 months. During the follow-up period, there were two TIAs and one ischemic stroke under an off-OAC situation at 11 months (TIA, enroll with persistent AF and CHA<sub>2</sub>DS<sub>2</sub>-VASc = 3, no AF recurrence), 19 months (TIA, enroll with persistent AF with CHA<sub>2</sub>DS<sub>2</sub>-VASc = 5, recurrence with persistent AF), and 8 months (ischemic stroke, enroll with persistent AF and CHA<sub>2</sub>DS<sub>2</sub>-VASc = 2, recurrence with paroxysmal AF), respectively. TEE did not detect any LA thrombus after stroke or TIAs but one patient (who suffered TIA) was found to have an approximately 2-mm peri-device leakage. These patients were treated with dabigatran 110 mg twice per day for secondary prevention.

## Discussions and limitations

In the present study, we investigated the effectiveness and safety of concomitant CA and LAA closure as a one-stage hybrid procedure in a population of patients with non-valvular AF, contraindication or resistance to OAC therapy, and a high risk of stroke via a prospective multi-center database. The findings of the study confirmed the feasibility of such an approach, perioperative complications were not increased by additional LAA closure procedure and it was an effective treatment in a selected population of AF patients.

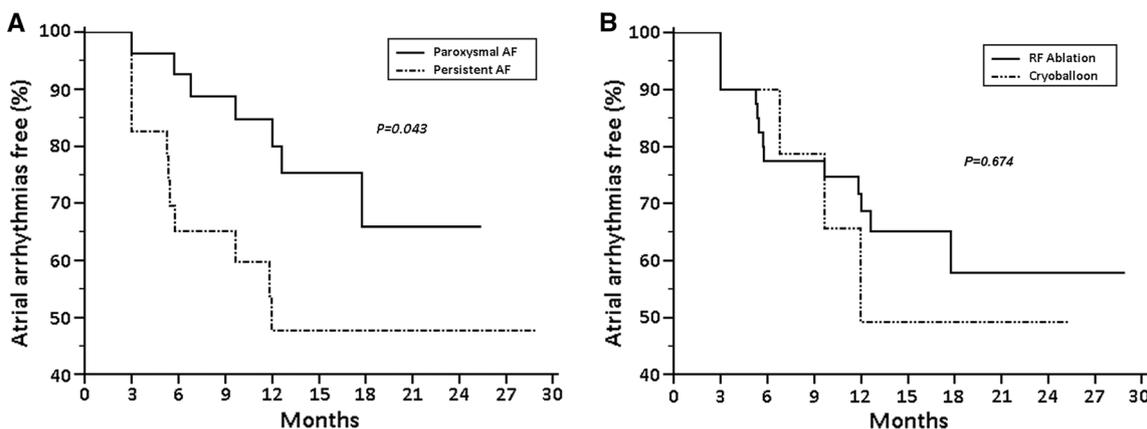
There were two concurrent therapeutic strategies in the management of AF: maintenance of sinus rhythm and thromboembolism prevention. CA was established as a primary rhythm-controlling therapy. Although the incidence of thromboembolism was low in patients who underwent successful AF CA, the current guidelines indicated that systemic anticoagulation therapy should not be discontinued in patients with a high risk of thromboembolism [1]. Considering the low success rate of CA in non-paroxysmal AF and the guideline recommendation of continuous anticoagulation therapy in high-stroke risk patients, the number of patients in which anticoagulation therapy was indicated was high.

Although OAC and novel OAC were effective for thromboembolic prophylaxis, they were associated with complications or poor tolerance. Approximately, 20% and 65% of patients discontinued novel OAC and OAC within 2 years, respectively [8, 9]. Therefore, nonpharmacological interventions in AF patients, such as the surgical or percutaneous exclusion of the LAA, had been explored in depth. The LAA, a cul-de-sac structure in the



**Fig. 2** Concomitant left atrial appendage closure and catheter ablation procedure with WATCHMAN and ACP device. **A1, B1** Left atrial appendage angiography; **A2, B2** fluoroscopic view (RAO 30°, CAU 20°)

during delivery of the ACP and WATCHMAN device; **A3** and **B3**: post-implantation compression and peri-device leakage were measured by TEE



**Fig. 3** Freedom from atrial arrhythmias rate after concomitant left atrial appendage closure and catheter ablation procedure. **a** Freedom from atrial arrhythmias in paroxysmal AF was significantly superior

to that in persistent AF. **b** Freedom from atrial arrhythmias was comparable between cryoballoon and radiofrequency CA

left atrium, was recognized as the source of thrombus in at least 90% of patients with non-valvular AF [2], which was the essential rationale for LAA closure. Previous randomized controlled trials [10–12] showed that LAA closure was not inferior to warfarin therapy for stroke prevention. However, LAA closure was not helpful for symptom

management. In our registry data, during the 22 months of follow-up, two patients presented with TIA and one with ischemic stroke under an off-OAC situation. The present results were slightly higher than others report from a single center, which might be attributed to slightly higher mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score (present result 3.7 ± 1.4;

Calvo et al. [13]  $3.1 \pm 1.1$ ; Romanov et al. [14]  $2.2 \pm 0.6$ ; Phillips et al. [15]  $2.6 \pm 1.0$ ).

For symptomatic AF patients with a high stroke risk and drug refractory AF, concomitant CA and LAA closure as a hybrid intervention shared certain technical factors and prevented stroke and relieved AF symptoms simultaneously. Few studies assessed the safety and feasibility of this type of hybrid procedure [13, 15–18]. Swaans et al. [17] first reported the clinical outcome of this one-stage strategy, showing only three minor perioperative complications with 97.3 min of median procedure time. At the 12-month follow-up, 70% of the patients were free from AAs. None of the patients had device-related thrombus and no thromboembolic events occurred other than the three patients with non-procedural bleeding events. Calvo et al. [13] and Fassini et al. [16] successively reported the feasibility of radiofrequency and cryoballoon CA in combination with Watchman or ACP device occlusion. Calvo et al. [13] reported three (8.6%) cases of perioperative complications with  $161 \pm 34$  min of mean procedure time, and Fassini et al. [16] reported one (3%) complication and  $165 \pm 34$  min. In both studies, there were no device embolization events or bleeding during the follow-up period. In the study by Calvo et al. [13], one patient died, one patient had a TIA, and one patient suffered an intracerebral hematoma associated with extremely high INR. In our registry data, there were 4 (8%) perioperative complications with  $185 \pm 25$  min of mean procedure time, and two of these cases were serious complications (cardiac tamponade) and took place during LAA closure procedure. The other two complications, arteriovenous fistula and transient air embolism, both came out from the same manipulation step of CA and LAA closure. It seemed that concomitant CA and LAA closure might be as safe as LAA closure procedure only. The present findings were similar to other data from cohort or randomized studies.

Pulmonary vein isolation was the cornerstone of nonpharmacological therapies for any subtype of AF [1]. However, the success rate of CA decreased in patients with advanced AF subtypes, despite the use of additional CA [19, 20]. Our registry data showed larger LA and RA dimensions and longer procedure and CA times in persistent AF than in paroxysmal AF. The recurrence of AAs was 36% at 22 months of follow-up. These data indicated that one third of the population could not maintain a sustained sinus rhythm and would benefit from LAA closure. The success rate of the procedure was comparable between radiofrequency energy and cryo-energy.

Recently, EWOLUTION trial [10] and Wintgens et al.'s registry [21] demonstrated a reduction in complete sealing rate (91.4% and 92.6%, respectively) during follow-up, which was similar with present research (91.8%). The acute and subacute edema should be the essential factor. However, the relationship between long-term

minimal leakage and thromboembolic event in AF patients remained to be validated via further trials. The lack of a consistent and suitable short-term and mid-term post-procedural anticoagulant/antiplatelet protocol was the main disadvantage of the hybrid procedure. Further studies were needed to determine the anticoagulant/antiplatelet protocol for this type of hybrid procedure. Concomitant CA and LAA closure as a one-stage hybrid procedure could be a comprehensive way to relieve AF symptoms and reduce the stroke risk simultaneously in a selected population of patients at high risk of stroke.

The present study was a prospective, multi-center registry with a mid-term follow-up; however, there were several limitations. The relatively small sample size and nonrandomized design limited the accurate determination of the effectiveness and safety of the one-stage hybrid procedure. Furthermore, the recurrence percentage of AAs might be underestimated during the follow-up period because of the lack of an implantable loop monitor and despite the use of long-term Holter recording in the present study.

## Conclusion

Concomitant CA and LAA closure as a one-stage hybrid procedure was feasible in patients with symptomatic non-valvular AF with a high stroke risk and contraindication to antithrombotic treatment, and as safe as LAA closure procedure only during the perioperative period. Although thromboembolic event rate of 3.6% per year was observed during mid-term follow-up, randomized clinical trials still were needed to determine the effectiveness of this strategy.

## Impact on daily practice

The present study was a prospective, multicenter registry for concomitant left atrial appendage and catheter ablation as one-stage hybrid procedure. Furthermore, the study investigated the feasibility and perioperative safety of this strategy, and reported the mid-term outcome of such an approach in southern China population.

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## Compliance with ethical standards

**Conflict of interest** Prof. Shu-lin Wu received research grants from Boston scientific and Biosense Webster. No financial disclosures for the other author.

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