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ORIGINAL RESEARCH

Sex Differences in the Combined Ablation and Left Atrial Appendage Closure

Results From LAACablation Registry

Mu Chen, MD,* Jian Sun, MD,* Wei Li, MD, Peng-Pai Zhang, MD, Rui Zhang, MD, Bin-Feng Mo, MD, Mei Yang, MD, Qun-Shan Wang, MD, Yi-Gang Li, MD

ABSTRACT

BACKGROUND More than 40% of left atrial appendage closure (LAAC) procedures were combined with atrial fibrillation (AF) ablation in China.

OBJECTIVES This study aimed to assess the sex differences in the combined radiofrequency catheter ablation and LAAC procedures.

METHODS Data from the LAACablation (Left Atrial Appendage Closure in Combination With Catheter Ablation) registry, which enrolled AF patients who underwent the combined procedure between 2018 and 2021, were analyzed. Procedural complications, long-term outcomes, and quality of life (QoL) were compared between sexes.

RESULTS Of 931 patients, 402 (43.2%) were women. Compared with men, women were older (age 71.3 ± 7.4 years vs 68.7 ± 8.1 years; $P < 0.001$), presented more often with paroxysmal AF (52.5% vs 42.7%; $P < 0.003$), and had higher CHA_2DS_2-VASc scores (4.1 ± 1.5 vs 3.1 ± 1.5; $P < 0.001$), but received less often linear ablation and had shorter total procedural times and radiofrequency catheter ablation times. Women had similar rates of total and major procedural complications but presented with a higher incidence of minor complications than men (3.7% vs 1.3%; $P = 0.027$). Follow-up over 1,812 patient-years revealed similar adverse events between women and men, including all-cause death (HR: 0.89; 95% CI: 0.43-1.85; $P = 0.754$), thromboembolic events (HR: 1.17; 95% CI: 0.54-2.52; $P = 0.697$), major bleeding (HR: 0.96; 95% CI: 0.38-2.44; $P = 0.935$), and their composite (HR: 0.85; 95% CI: 0.56-1.28; $P = 0.434$). The recurrence rates of atrial tachyarrhythmia were also comparable between sexes presenting either paroxysmal or persistent AF. Women were seen with greater QoL impairment at baseline, but the sex gap narrowed at 1-year follow-up.

CONCLUSIONS In AF patients who underwent the combined procedure, women had similar procedural safety and long-term efficacy to men and presented greater QoL improvement. (Left Atrial Appendage Closure in Combination With Catheter Ablation [LAACablation]; NCT03788941) (JACC: Asia 2023;3:138–149) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF) has become a growing problem worldwide, especially in the aging society. Sex differences exist in almost all aspects of AF, including mechanism, epidemiology, management, and prognosis.[1] AF is more prevalent in men than women in most countries.[2] By contrast, the prevalence of AF is similar between sexes in China, or even higher in women than men in regions

From the Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, China. *Drs Chen and Sun contributed equally to this work.

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with more severe aging, such as Shanghai.[2,3] Meanwhile, women with AF are known to be associated with more prominent symptoms, poorer quality of life (QoL), and higher risks of stroke and mortality.[1] However, women were less likely to receive standardized treatment of stroke prevention and symptom control, especially for the interventional strategies including left atrial appendage (LAA) closure (LAAC) and radiofrequency catheter ablation (RFCA).[1-4] Both medical and socioeconomic factors contributed to the undertreatment in women with AF.[4,5]

In China, more than 40% of LAAC procedures were combined with AF ablation, which is known as the combined or "one-stop" procedure.[6] The 2 left atrial interventions, aiming to achieve stroke prophylaxis and rhythm control simultaneously, have been shown to be feasible and effective in previous small-scale studies.[7] However, the sex differences in the combined procedure have not been investigated yet. Here for the first time, we reported the sex differentiated outcomes of the combined procedure of RFCA and LAAC from a large, prospective cohort.

METHODS

STUDY POPULATION. A total of 931 AF patients who were enrolled in the LAACablation (Left Atrial Appendage Closure in Combination With Catheter Ablation) registry between 2018 and 2021 were screened. The LAACablation registry (NCT03788941) is a physician-initiated, non-company-sponsored, prospective observational study recruiting patients undergoing the combined RFCA and LAAC procedures in Shanghai Xinhua Hospital, one of the largest electrophysiological centers in China. The LAACablation registry was approved by the ethics board of Xinhua Hospital and complies with the Declaration of Helsinki. Written informed consent was provided by all participants.

COMBINED PROCEDURE OF CATHETER ABLATION AND LAAC. The information of medical history, demographic characteristics, and socioeconomic status were collected at baseline. Within 48 hours before the procedure, transesophageal echocardiography (TEE) was performed to exclude intracardiac thrombus.

AF patients underwent successive RFCA and LAAC. The procedure was conducted under conscious sedation with intravenous midazolam (0.02 mg/kg/h) and fentanyl (0.001 mg/kg). The CARTO (Biosense Webster) or ENSITE (St. Jude Medical) navigation system was used for the guidance of AF ablation by the irrigated catheter with contact force. Pulmonary vein isolation (PVI) was routinely performed. Additional ablation, including left atrial roof, anterior septal, posterior and inferior lines, mitral isthmus, and cavotricuspid isthmus lines, complex fractionated electrograms modification, and ablation of ganglionated plexi and extrapulmonary vein triggers, as well as vein of Marshall ethanol infusion, were performed at the operators' discretion. Intracardiac cardioversion up to 15 J was conducted if AF was persistent at the end of the ablation phase. LAAC with the WATCHMAN device (Boston Scientific) was subsequently performed. Because patients were under light sedation, the LAAC device implantation was guided only by fluoroscopy without intraprocedural TEE. Such a TEE-free procedure was commonly performed in China, which achieved comparable procedural success and outcomes with those with TEE guidance.[6,8]

POSTPROCEDURE MANAGEMENT AND FOLLOW-UP. Patients were generally followed every 3 months. For the initial 3 months, oral anticoagulant agents were prescribed if there were no contraindications. TEE was performed at 3 months to detect any peridevice leaks (PDLs) and device-related thrombi (DRT). If there was no or minimal PDL (≤5 mm) or DRT, anticoagulant agents were switched to dual antiplatelet agents (aspirin 100 mg + clopidogrel 75 mg) until 6 months. Otherwise, anticoagulant agents were prescribed until the repeated TEE. In patients with low TEE compliance, cardiac computed tomography served as the alternative modality. After 6 months, an indefinite single antiplatelet agent was recommended. In addition, electrocardiogram and/or Holter monitoring were advised at every follow-up visit to detect recurrence of atrial tachyarrhythmias. In patients with recurrent atrial tachyarrhythmia, redo ablation might be considered in patients refractory to antiarrhythmic drugs after the 3-month blanking period. The approach for the redo ablation was similar to the index procedure, except with greater care when manipulating the catheters around the LAAC device.

EVENTS DEFINITION. Major procedural complications were defined as cardiac tamponade, device embolism, thromboembolism (stroke, transient ischemic attack [TIA], and systemic embolism [SE]), major bleeding, and death within 7 days. Minor procedural complications included pericardial effusion not requiring pericardiocentesis, transient air

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AFEQT = Atrial Fibrillation Effect on Quality-of-Life questionnaire

DRT = device-related thrombus

LAA = left atrial appendage

LAAC = left atrial appendage closure

PDL = peridevice leak

PVI = pulmonary vein isolation

QoL = quality of life

RFCA = radiofrequency catheter ablation

SE = systemic embolism

TEE = transesophageal echocardiography

TIA = transient ischemic attack

TABLE 1 Clinical Characteristics by Sex

	Women (n = 402)	Men (n = 529)	*P* Value
Age, y	71.3 ± 7.4	68.7 ± 8.1	<0.001
<65	69 (17.2)	145 (27.4)	<0.001
≥65–<75	188 (46.8)	258 (48.8)	0.544
≥75	145 (36.1)	126 (23.8)	<0.001
Height, cm	159 ± 5	171 ± 6	<0.001
Weight, kg	64.0 ± 9.7	74.6 ± 11.3	<0.001
BMI, kg/m^2	25.1 ± 3.5	25.3 ± 3.4	0.433
AF types			
Paroxysmal	211 (52.5)	226 (42.7)	0.003
Persistent/long-standing persistent	191 (47.5)	303 (57.3)	0.003
CHA_2DS_2-VASc score	4.1 ± 1.5	3.1 ± 1.5	<0.001
HAS-BLED score	2.3 ± 1.0	2.4 ± 1.0	0.140
Hypertension	308 (76.6)	398 (75.2)	0.626
Diabetes mellitus	97 (24.1)	137 (25.9)	0.538
Myocardial infarction	10 (2.5)	15 (2.8)	0.745
Cardiac revascularization	42 (10.4)	56 (10.6)	0.946
Congestive heart failure	66 (16.4)	92 (17.4)	0.695
Hypertrophic cardiomyopathy	14 (3.5)	26 (4.9)	0.286
Obstructive sleep apnea	7 (1.7)	28 (5.3)	0.005
Chronic obstructive pulmonary disease	9 (2.2)	33 (6.2)	0.004
History of strokes/TIAs/SE	131 (32.6)	248 (46.9)	<0.001
History of LAA thrombus	23 (5.7)	16 (3.0)	0.041
History of major bleeding	26 (6.5)	38 (7.2)	0.669
History of malignant tumor	28 (6.9)	53 (10.0)	0.102
History of chemotherapy	24 (6.0)	46 (8.7)	0.118
Pacemaker implantation	16 (4.0)	17 (3.2)	0.531
Current smoker	45 (11.2)	235 (44.4)	<0.001
Echocardiographic parameters			
LVEF, %	62.9 ± 5.5	61.5 ± 7.2	0.001
Left atrial diameter, mm	41.8 ± 5.6	43.3 ± 5.9	<0.001
LVEDD, mm	47.9 ± 4.2	50.9 ± 5.0	<0.001
LVESD, mm	31.3 ± 3.8	33.8 ± 5.2	<0.001
Estimated PASP, mm Hg	33.2 ± 9.2	31.3 ± 7.5	0.003
NT-proBNP, pg/mL	631 (215-1,472)	593 (210-1,078)	0.066
Troponin I, ng/mL	0.010 (0.004-0.020)	0.009 (0.004-0.018)	0.164
Antithrombotic therapy before admission			
Anticoagulant agents	240 (59.7)	402 (76.0)	<0.001
Warfarin	64 (15.9)	73 (13.8)	0.366
Dabigatran	67 (16.6)	128 (24.2)	0.005
Factor Xa inhibitor	109 (27.1)	201 (38.0)	<0.001
Antiplatelet agent	68 (16.9)	84 (15.9)	0.424
None	97 (24.1)	43 (8.1)	<0.001
Drug therapy before admission			
Rate control antiarrhythmic agents only	221 (55.0)	251 (47.4)	0.023
Rhythm control antiarrhythmic agents only	113 (28.1)	191 (36.1)	0.010
Rate and rhythm antiarrhythmic agents	68 (16.9)	87 (16.4)	0.849
ACE inhibitor/ARB/ARNi	196 (48.8)	252 (47.6)	0.735
Diuretic agents	114 (28.4)	135 (25.5)	0.333
Statin	168 (41.8)	258 (48.8)	0.034

Values are mean ± SD, n (%), or median (IQR).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARNi = angiotensin receptor-neprilysin inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; LAA = left atrial appendage; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; SE = systemic embolism; TIA = transient ischemic attack.

embolism, and femoral access complications. Endpoints of the long-term follow-ups included all-cause death, thromboembolic events (strokes, TIAs, and SE), and major bleeding. In addition, recurrence of arrhythmias was evaluated and reported independently of other outcomes. The recurrence of atrial tachyarrhythmias was defined as AF, atrial flutter, or atrial tachycardia lasting more than 30 seconds after the 90-day blanking period.

QUALITY OF LIFE ASSESSMENT. At baseline and at the 1-year follow-up visit, patients were required to complete a 20-item questionnaire based on the Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT) measure.[9] The 20-item AFEQT survey evaluated 4 domains regarding the QoL assessment and the perception of treatment, that is, symptoms, daily activities, treatment-related concerns, and treatment satisfaction. The first 3 domains constituted the global score. The scores of each individual domain and the global score ranged between 0 and 100, with 100 representing the best health status and 0 being the worst health status possible. A validated culturally and linguistically translated version of the AFEQT for China was used.

STATISTICS. Continuous variables are presented as mean ± SD, or median [25th-75th percentile], and categorical variables as counts and percentages, unless specifically stated otherwise. Student's *t*-tests, Mann-Whitney *U* tests, Pearson chi-square, and Fisher exact tests were used for comparisons between sexes as appropriate. Unadjusted and adjusted multivariable logistic regression was used to obtain ORs with a 95% CI for women vs men for total, major, and minor procedural complications. Cumulative event probabilities were estimated using the Kaplan-Meier method and the log-rank test to calculate the *P* value. Observed rates of thromboembolic events and major bleeding were compared with predicted thromboembolism and bleeding rates derived from historical cohorts according to CHA_2DS_2-VASc and HAS-BLED scores.[10] A 2-sided *P* value <0.05 was considered statistically significant. Statistics were performed using SPSS 23.0 (IBM).

RESULTS

BASELINE CHARACTERISTICS. Among 931 AF patients who enrolled in the LAACablation registry, there were 402 women (43.1%) and 529 men (56.8%). The demographic characteristics are shown in Table 1. Women were older (age 71.3 ± 7.4 years vs 68.7 ± 8.1 years; $P < 0.001$) and presented a higher proportion in age group ≥75 years than men (36.1% vs 23.8%;

$P < 0.001$). Compared with men, women were more likely to present paroxysmal AF (52.5% vs 42.7%; $P = 0.003$), higher CHA_2DS_2-VASc scores (4.1 ± 1.5 vs 3.1 ± 1.5; $P < 0.001$), but similar HAS-BLED scores (2.3 ± 1.0 vs 2.4 ± 1.0; $P = 0.140$). AF-related comorbidities were comparable between sexes, except the history of stroke/TIA/SE, obstructive sleep apnea, and chronic obstructive pulmonary disease were higher in men (46.9% vs 32.6%; $P < 0.001$; 5.3% vs 1.7; $P = 0.005$; and 6.2% vs 2.2%; $P = 0.004$, respectively). Echocardiography revealed a higher incidence of previous LAA thrombus (5.7% vs 3.0%; $P = 0.041$) and slightly higher left ventricular ejection fraction (62.9% ± 5.5% vs 61.5% ± 7.2%; $P = 0.001$), but smaller atrial and ventricular sizes in women than men. The medication use prior to the admission was also significantly different between sexes, that men were more often on oral anticoagulant agents (76.0% vs 59.7%; $P < 0.001$) and rhythm control antiarrhythmic agents (36.1% vs 28.1%; $P = 0.010$), but less often on no-antithrombotic regimen (8.1% vs 24.1%; $P < 0.001$) and rate control drugs (47.4% vs 55.0%; $P = 0.023$).

The socioeconomic status showed differences between sexes (Table 2). Compared with men, women were more likely to be in a marriage (82.6% vs 76.2%; $P = 0.018$). At the time of enrollment, women were less often employed (2.7% vs 12.3%; $P < 0.001$) and more often retired (93.8% vs 81.9%; $P < 0.001$). Women had lower education levels, because fewer women received higher education (6.5% vs 13.6%; $P < 0.001$). The proportions of the government-issued universal health insurance were comparable between sexes (94.2% vs 94.8%; $P = 0.679$), but men were more often insured by private or additional commercial insurance than women (8.7% vs 4.7%; $P = 0.019$). There were more nonlocals seeking for the procedure in men than women (15.3% vs 8.1%; $P < 0.001$).

TABLE 2 Socioeconomic Characteristics by Sex

	Women (n = 402)	Men (n = 529)	*P* Value
Marital status			
Married	332 (82.6)	403 (76.2)	0.018
Divorced/separated	29 (7.2)	59 (11.2)	0.042
Single/widowed	41 (10.2)	67 (12.7)	0.244
Employment status			
Working full-time or part-time	11 (2.7)	65 (12.3)	<0.001
Retired	377 (93.8)	433 (81.9)	<0.001
Unknown and unemployed	14 (3.5)	31 (5.8)	0.094
Education level			
High school or less than high school	373 (92.8)	446 (84.3)	<0.001
Some college or college	26 (6.5)	72 (13.6)	<0.001
Some graduate school or graduate school	3 (0.7)	11 (2.1)	0.111
Type of health insurance			
Government[a]	379 (94.2)	502 (94.8)	0.679
Private or additional private	19 (4.7)	46 (8.7)	0.019
None	5 (1.3)	9 (1.7)	0.787
Residency			
Shanghai resident	370 (92.0)	448 (84.7)	<0.001
Nonlocal	32 (8.0)	81 (15.3)	<0.001

Values are n (%). [a]Including the Urban Residents' Basic Medical Insurance (URBMI), the Urban-Employ Based Medical Insurance (UEBMI), and the New Rural Cooperative Medical Scheme (NRCMS).

PROCEDURAL CHARACTERISTICS. For the ablation phase, all patients underwent PVI. Additional ablation other than PVI were more often performed in men than women (61.4% vs 52.5%; $P = 0.006$). However, the proportions for specific ablation lines were comparable between sexes, despite the nonsignificant trend toward men receiving more often left atrial roof, mitral, and cavotricuspid ablation (29.3% vs 23.8; $P = 0.065$; 27.6% vs 22.1%; $P = 0.057$; 38.8% vs 32.8%; $P = 0.062$; respectively). The rates of intraprocedural sinus rhythm restoration were similar between sexes (99.6% vs 99.8%; $P > 0.999$). For the subsequent LAAC phase, the LAA morphology, as well as the size selection for WATCHMAN devices, was also comparable between women and men. Compared with women, men had longer procedural times (178 [151-186] minutes vs 148 [138-172] minutes; $P < 0.001$), which was attributed to longer procedural times during the RFCA phase (156 [120-164] minutes vs 127 [118-143] minutes; $P < 0.001$). The procedural times during the LAAC phase were comparable between sexes (25 [20-30] minutes vs 24 [20-29] minutes; $P = 0.156$).

There was a nonsignificant trend toward higher procedural complications in women over men (6.0% vs 3.4%; $P = 0.062$). This was attributed to higher minor complications, including pericardial effusion not requiring pericardiocentesis, transient air embolism, and femoral complications, in women than men (3.7% vs 1.3%; $P = 0.027$). The major complications were similar between sexes (2.2% vs 2.1%; $P = 0.868$) (Table 3). The unadjusted and adjusted rates of procedural complications are further shown in Supplemental Figure 1. After multivariable adjustment, women had statistically comparable odds with men of total (OR: 1.63: 95% CI: 0.85-3.12: $P = 0.143$), major (OR: 1.04; 95% CI: 0.41-2.62; $P = 0.937$), and minor (OR: 2.45; 95% CI: 0.96-6.26; $P = 0.062$) procedural events.

POSTPROCEDURAL IMAGING EVALUATION. At 3 months after the procedure, women were less likely to receive

TABLE 3 Procedural Characteristics and Follow-Up Parameters by Sex

	Women (n = 402)	Men (n = 529)	*P* Value
Ablation phase			
PVI (total)	402 (100)	529 (100)	>0.999
PVI only	191 (47.5)	204 (38.6)	0.006
LA roof line	96 (23.8)	155 (29.3)	0.065
LA posterior and/or inferior lines	51 (12.7)	87 (16.4)	0.114
Posterior wall isolation	21 (5.2)	36 (6.8)	0.338
Anterior septal line	45 (11.2)	71 (13.2)	0.308
Mitral isthmus line	89 (22.1)	146 (27.6)	0.057
CS and GCV musculature ablation	31 (7.7)	52 (9.8)	0.261
VOM ethanol infusion	22 (5.5)	36 (6.0)	0.405
LAA isolation	8 (2.0)	20 (3.8)	0.125
Cavotricuspid line	132 (32.8)	205 (38.8)	0.062
Superior vena cava isolation	29 (7.2)	51 (9.6)	0.191
CFAE ablation	75 (18.6)	116 (21.9)	0.214
Ganglionated plexi ablation	3 (0.7)	7 (1.3)	0.528
Intracardiac cardioversion	97 (24.1)	151 (28.5)	0.131
Intraprocedural sinus rhythm restoration	401 (99.8)	527 (99.6)	>0.999
LAAC phase			
LAA morphology types			
Chicken wing	64 (15.9)	102 (19.2)	0.184
Windsock	27 (6.7)	26 (4.9)	0.240
Cauliflower	303 (75.4)	382 (72.2)	0.278
Cactus	8 (2.0)	19 (3.6)	0.171
LAA ostium, mm	22.4 ± 3.4	22.9 ± 3.7	0.057
Device size for WATCHMAN, mm			
21	35 (8.7)	44 (8.3)	0.833
24	94 (23.4)	101 (19.1)	0.111
27	117 (29.1)	151 (28.5)	0.852
30	87 (21.6)	115 (21.7)	0.971
33	69 (17.2)	118 (22.3)	0.052
Procedural characteristics			
Total procedural time, min	148 (138-172)	178 (151-186)	<0.001
Procedural time of RFCA phase, min	127 (118-143)	156 (120-164)	<0.001
Procedural time of LAAC phase, min	24 (20-29)	25 (20-30)	0.156
Heparin dosage, unit	7,994 ± 1,167	9,282 ± 1,367	<0.001
Average ACT level, s	286 (275-295)	288 (275-297)	0.096
Procedural complications, total	24 (6.0)	18 (3.4)	0.062
Major complications	9 (2.2)	11 (2.1)	0.868
Cardiac tamponade	6 (1.5)	5 (0.9)	0.545
Cardiac tamponade during RFCA phase	1 (0.3)	1 (0.2)	>0.999
Cardiac tamponade during LAAC phase	5 (1.2)	4 (0.7)	0.511
Stroke/TIA/SE	2 (0.5)	2 (0.4)	>0.999
Device embolism	0 (0)	1 (0.2)	>0.999
Major bleeding	1 (0.2)	3 (0.6)	0.462
Death	0 (0)	0 (0)	>0.999
Minor complications	15 (3.7)	7 (1.3)	0.027
Pericardial effusions	4 (1.0)	2 (0.4)	0.412
Pericardial effusions during RFCA phase	1 (0.3)	0 (0)	0.432
Pericardial effusions during LAAC phase	3 (0.7)	2 (0.4)	0.657
Transient air embolism	2 (0.5)	1 (0.2)	0.582
Transient air embolism during RFCA phase	0 (0)	0 (0)	>0.999
Transient air embolism during LAAC phase	2 (0.5)	1 (0.2)	0.582
Femoral complications	9 (2.2)	4 (0.8)	0.087

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TEE evaluation than men (61.2% vs 69.9%; $P = 0.005$), but might show a nonsignificant preference to receive cardiac computed tomography evaluation, the less invasive imaging modality (37.5% vs 31.6%; $P = 0.056$). The results of the postprocedural imaging evaluation, including the rates of DRT, PDL, satisfactory sealing, and LAA contrast filling, were uniformly similar between sexes (Table 4).

EVENTS FOLLOW-UP. During follow-up over 1,812 patient-years (median [25th-75th percentile]: 22.9 [11.6-33.8] months), a total of 74 events (34 in women and 40 in men) were observed, including 29 deaths (12 in women and 17 in men), 27 stroke/TIA/SE events (14 in women and 13 in men), and 18 major bleeding events (8 in women and 10 in men). At the end of follow-up, the cumulative event rates of death, thromboembolic events, and major bleedings were 8.56% (6.71% for women and 9.98% for men), 7.02% (8.26% for women and 5.82% for men), and 5.47% (2.66% for women and 8.03% for men), respectively. The annual event rates of death, thromboembolic events, and major bleedings were 1.59% (1.46% for women and 1.73% for men), 1.48% (1.70% for women and 1.32% for men), and 0.99% (0.97% for women and 1.01% for men), respectively. As shown in Figure 1, women had comparable rates of adverse events to men, including all-cause death (HR: 0.89; 95% CI: 0.43-1.85; $P = 0.754$), thromboembolic events (HR: 1.17; 95% CI: 0.54-2.52; $P = 0.697$), major bleeding (HR: 0.96; 95% CI: 0.38-2.44; $P = 0.935$). and the composite of death, thromboembolic events, major bleeding, and procedural complications (HR: 0.85; 95% CI: 0.56-1.28; $P = 0.434$). Additional subgroup analyses showed the rates of adverse events were also comparable between sexes in patients undergoing the procedure for primary stroke/TIA/SE prevention (Supplemental Figure 2) and for secondary stroke/TIA/SE prevention (Supplemental Figure 3). Compared with the rates predicted by the CHA_2DS_2-VASc score, the observed annual rates of thromboembolic events in the current cohort showed 79% and 76% relative risk reduction in women and men, respectively. Similarly, compared with the rates predicted by the HAS-BLED score, the observed rates of major bleeding showed 77% and 76% relative risk reduction in women and men, respectively (Figure 2). After the 3-month blanking period, the recurrences of atrial tachyarrhythmias were also comparable between women and men, for either paroxysmal AF (HR: 1.42; 95% CI: 0.91-2.22; $P = 0.123$) or persistent AF (HR: 1.30; 95% CI: 0.95-1.77; $P = 0.096$) (Figure 3).

QoL ASSESSMENT. A total of 244 women (60.6%) and 308 men (58.2%) completed AFEQT questionnaires, both at baseline and at 1-year follow-up (Figure 4). At baseline, women had lower AFEQT global scores than men (69.4 [65.7-72.2] vs 75.9 [74.1-78.7]; $P < 0.001$), as well as all 4 individual domain scores (symptom 75.0 [66.7-79.2] vs 79.2 [70.8-83.3]; $P < 0.001$; daily activities 70.8 [66.7-75.0] vs 77.1 [75.0-79.2]; $P < 0.001$); treatment concern 63.9 [55.6-72.2] vs 75.0 [69.4-77.8]; $P < 0.001$; treatment satisfaction 58.3 [52.1-66.7] vs 66.7 [58.3-75.0]; $P < 0.001$). At 1-year follow-up, the AFEQT global scores remained lower in women than men (89.5 [88.0-91.0] vs 90.7 [88.0-92.6]; $P < 0.001$), as well as the domains of symptom (87.5 [83.3-95.8] vs 91.7 [83.3-95.8]; $P = 0.020$) and daily activities (89.6 [85.9-91.7] vs 91.7 [87.5-93.8]; $P < 0.001$). However, the scores of treatment concern and treatment satisfaction in women became comparable between sexes (89.0 [86.1-94.0] vs 91.7 [88.9-94.4]; $P = 0.095$ and 91.7 [83.3-91.7] vs 91.7 [83.3-91.7]; $P = 0.168$, respectively). Consequently, the sex gap in QoL was prominently narrowed, as the improvement of AFEQT global score was significantly larger in women than men (20.4 [16.7-24.1] vs 14.8 [12.0-18.3]; $P < 0.001$).

DISCUSSION

This study reported sex-specific outcomes in a prospective cohort of 931 AF hospitalizations for the combined procedure of RFCA and LAAC. Women comprised approximately 43% of patients. Despite various disparities existed in demographic and socioeconomic chrematistics, women and men had comparably high procedural safety and low long-term adverse event rates, including death, thromboembolic events, major bleeding, and AF recurrence. The combined procedure significantly improved QoL of AF patients in both sexes, whereas the extent of improvement appeared greater in women than men (Central Illustration). Therefore, sex should not be used as a basis when making the decision of whether to perform the combined procedure of RFCA and LAAC in patients with AF.

In general, women were less vulnerable to AF development than men.[2] However, with population aging, the gap of AF prevalence between sexes might be narrowed due to higher life expectancy in women.[2,3] In specific regions, such as Shanghai where the current study was conducted, the prevalence of AF was even higher in women.[3] Compared with men, women with AF were exposed to significantly greater risks to all-cause and cardiovascular death.[11] Women also reported worse symptoms and QoL, suggesting more severe AF-related functional impairment.[1] However, women were less likely to receive invasive procedures of AF, including the 2 components of the combined procedure. Women were more prone to adopting rate control rather than rhythm control strategies (including RFCA), and such treatment preferences were uniformly observed in the United States, Europe, and China.[3,11,12] Similarly, women were less likely to receive LAAC, as observed in the EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the Watchman Left Atrial Appendage Closure Technology; 40.1% women) registry,[13] the U.S. National Inpatient Sample database (39.9% women),[14] Shanghai medical insurance database (43.0% women),[3] and the national registries in China (42.4% women).[6] The sex proportion of a current single-center registry (43.2%) was similar with that in the abovementioned multicenter studies in both the United States and China, suggesting a certain real-world representativeness of the current cohort.

TABLE 3 Continued

	Women (n = 402)	Men (n = 529)	*P* Value
Duration of hospitalization, d	8 (6-10)	7 (6-9)	0.073
Follow-up parameters			
12-lead surface ECG performed per patient	5.9 ± 2.9	5.7 ± 3.3	0.353
Holter monitoring performed per patient	4.6 ± 1.8	4.7 ± 1.7	0.464
Redo ablation	35 (8.7)	45 (8.5)	0.907

Values are n (%), mean ± SD, or median (IQR).

ACT = activated clotting time; CFAE = complex fractionated atrial electrogram; CTI = cavotricuspid isthmus; CS = coronary sinus; ECG = electrocardiogram; GCV = great cardiac vein; LA = left atrial; LAAC = left atrial appendage closure; PVI = pulmonary vein isolation; PW = posterior wall; SVC = superior vena cava; VOM = vein of Marshall; other abbreviations as in Table 1.

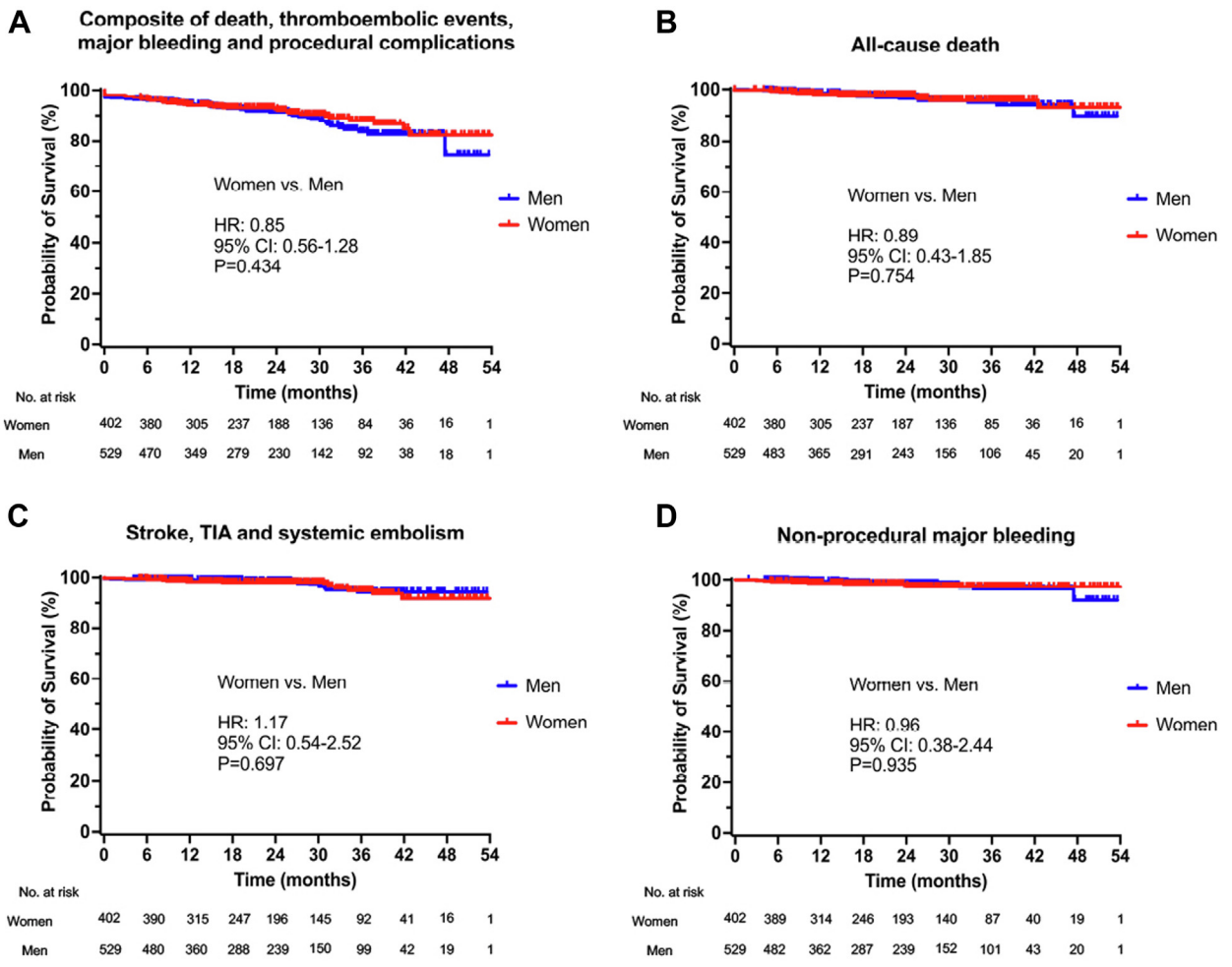
TABLE 4 Postprocedural Imaging Evaluation by Sex

Postprocedural Imaging[a]	Women (n = 402)	Men (n = 529)	*P* Value
TEE evaluation, n	246 (61.2)	370 (69.9)	0.005
DRT	4 (1.6)	6 (1.6)	>0.999
No PDL[b]	182 (74.0)	292 (78.9)	0.154
PDL ≤5 mm	64 (26.0)	76 (14.3)	0.112
PDL >5 mm	0 (0)	2 (0.5)	0.248
Satisfactory seal	246 (100)	368 (99.5)	0.519
Cardiac CT evaluation, n	151 (37.5)	167 (31.6)	0.056
LAA, no contrast filling[c]	79 (52.3)	91 (54.5)	0.698
LAA, contrast filling	72 (47.7)	76 (45.5)	0.698
Contrast filling with visible PDL	61 (40.4)	62 (37.1)	0.550
Contrast filling without PDL	11 (7.3)	14 (8.4)	0.716

Values are n (%). [a]102 patients underwent both evaluations. [b]Also known as complete seal. [c]Suggesting a complete endothelialization.

CT = computed tomography; DRT = device-related thrombus; LAA = left atrial appendage; PDL = peridevice leak; TEE = transesophageal echocardiography.

FIGURE 1 Time-to-Event Curves by Sex

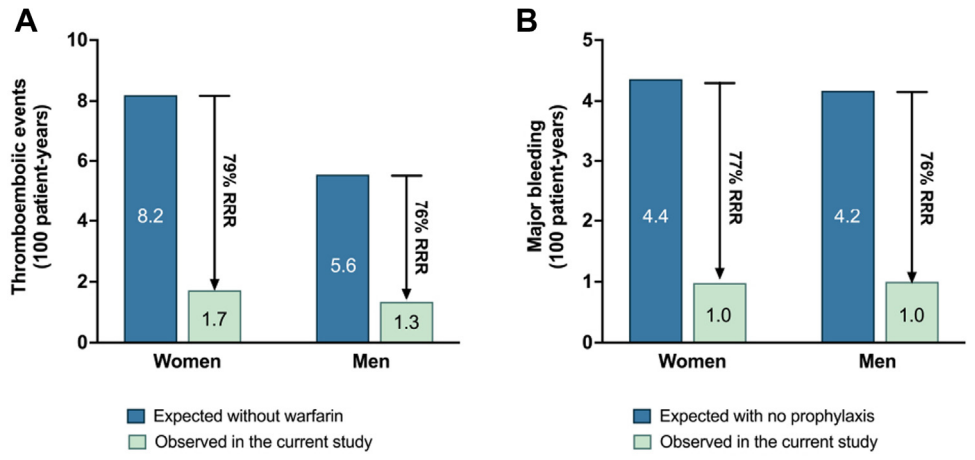


(A) Cumulative incidence of the composite of death, thromboembolic events, major bleeding, and major procedural complications. **(B)** Cumulative incidence of all-cause death. **(C)** Cumulative incidence of thromboembolic events (non-procedure-related strokes, transient ischemic attacks [TIA], and systemic embolism). **(D)** Cumulative incidence of major bleeding. **Tick marks** indicate censored data. The comparison was made between sexes.

The reasons for the sex-differentiated treatment preference of RFCA and LAAC might be comprehensive. The prevalence of AF in the population raises the possibility of potential referral bias, because women were 3 times less often to be referred to a specialized arrhythmia clinic than men.[15] Procedural safety and efficacy might be another concern. Previous studies reported higher rates of AF recurrence and procedural complications following RFCA or LAAC in women,[4,14,16] whereas such phenomenon was not observed by others.[17,18] Nevertheless, the decision-making of AF management was comprehensive, and socioeconomic status might also contribute.[19]

Knowledge gaps regarding the sex-specific outcomes existed when considering performing these 2 left atrial interventions simultaneously. Investigating the sex differences of the combined RFCA and LAAC is of high clinical importance because more than 40% of LAAC procedures were combined with RFCA in China.[6] Despite the general safety and feasibility having been validated,[20] the increased intracardiac maneuver and prolonged procedure time might raise concern of procedural safety and patients' tolerance especially in women. In the current study, highly individualized ablation strategies, including multiple liner ablation, substrate modification, vein of Marshall ethanol infusion, and non-pulmonary vein

FIGURE 2 **Relative Risk Reduction Comparing With the Expected Rates**

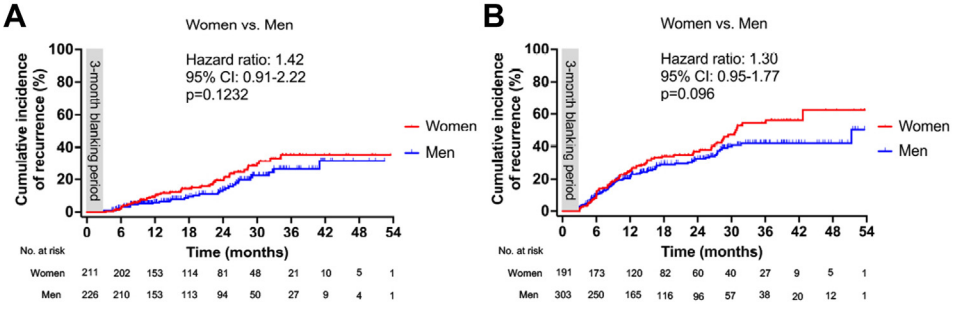


(A) Thromboembolic events (strokes, transient ischemic attacks, and systemic embolism) rate per 100 patient-years in the cohort of the combined procedure compared with expected rates when taking warfarin according to CHA_2DS_2-VASc score. **(B)** Major bleeding rates per 100 patient-years in the cohort of the combined procedure compared with expected rates according to HAS-BLED score. RRR = relative risk reduction.

foci elimination, were adopted considering a high proportion of persistent AF. Such a complex intracardiac catheter manipulation, in addition to subsequent LAAC device implantation, still achieved equally low procedural complications in both women and men. However, the minor procedural complications were higher in women, which was largely driven by vascular complications. This was in line with previous studies reporting higher hematomas and pseudoaneurysms in women when performing RFCA alone.[1]

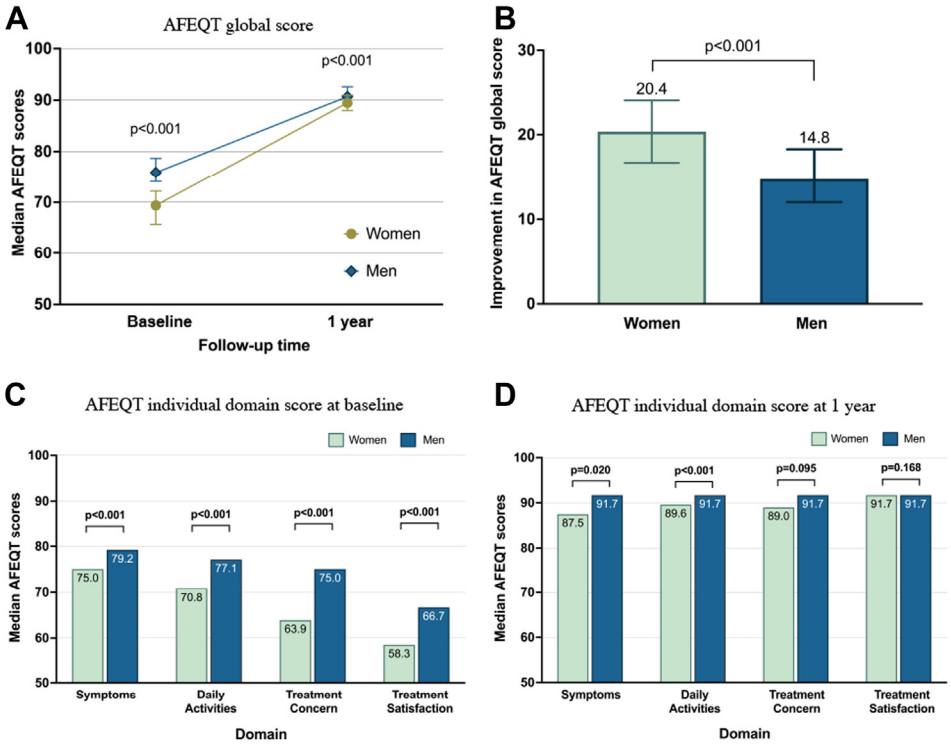
The event rates of the combined procedure during the long-term follow-up were comparable or even lower than the previous studies of LAAC alone, suggesting combining RFCA might bring extra benefit or at least do no harm to the patients undergoing LAAC.[21,22] The long-term outcomes, as well as the imaging evaluation, were also comparable between

FIGURE 3 **Recurrence of Atrial Tachyarrhythmias by Sex**



Recurrence of atrial tachyarrhythmia over time after the combined procedure for paroxysmal AF **(A)** and persistent atrial fibrillation **(B)**. Shown are Kaplan-Meier estimates of the recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting at least 30 seconds. A 90-day blanking period was adopted. **Tick marks** indicate censored data. The comparison was made between sexes.

FIGURE 4 Results of AFEQT Questionnaires by Sex

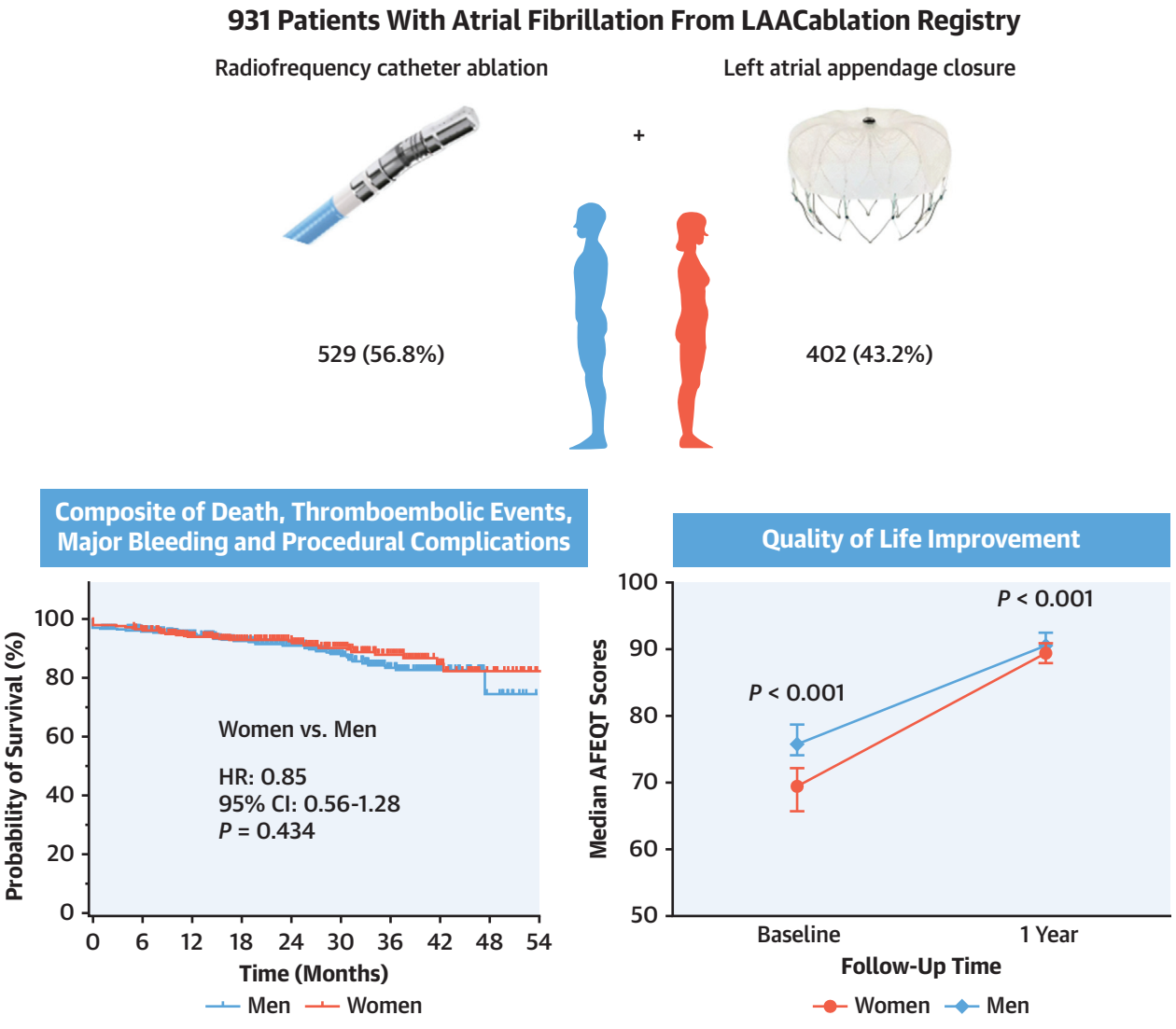


(A) Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT) global score at baseline and 1-year follow-up. The AFEQT global score includes symptoms, daily activities, treatment concern domains only. **Dots and error bars** represent median and 25th and 75th percentiles. **(B)** The improvement of AFEQT global score between baseline and 1-year follow-up. **Dots and error bars** represent median and 25th and 75th percentiles. **(C)** AFEQT individual domain score at baseline. **(D)** AFEQT individual domain score at 1-year follow-up. The *P* values indicate differences between sexes.

sexes. When compared with predicted risks by CHA_2DS_2-VASc and HAS-BLED scores, women might even achieve slightly greater relative risk reduction in thromboembolic events and major bleeding due to their higher baseline risks. This might be explained by more advanced left atrial remodeling and LAA contractile dysfunction in women than men, which yielded the higher risks of LAA thrombus formation and subsequent cardiogenic stroke in women.[23] Consequently, the "local" therapy of LAA might lead to the accentuated benefit in stroke risk reduction in women. Previous largescale cohorts of patients undergoing RFCA alone reported a higher AF recurrence in women than men.[24-26] In this cohort of combined procedure, trends toward women having higher AF recurrence for both paroxysmal and persistent AF were also noticed despite statistical significance was not achieved yet. Taken together, combining LAAC with RFCA might potentially be of greater benefit in women for reducing residual strokes, which was supported by meta-analysis showing higher stroke risk after RFCA in women than men.[26]

RFCA markedly improves the QoL of AF patients by reducing the arrhythmia recurrence and burden, autonomic neuromodulation, and reversing arrhythmia-induced or -aggravated heart failure.[27] The impact of LAAC on QoL, on the other hand, might be indirect but still positive. Compared with subjects who taking long-term warfarin, patients who underwent LAAC had improved QoL, which was attributed to the freedom from the frequent blood tests, the concerns regarding dietary issues and bleeding hazard, and the restriction of daily activities.[28] The current study indicated that the combined procedure of RFCA and LAAC could largely improve the QoL in both sexes. Consistent with previous studies, women with AF presented with greater QoL impairment at baseline, which may be attributed to the sex-specific physical and emotional functioning.[29] Despite the QoL remaining lower in women after the procedure,

CENTRAL ILLUSTRATION **Sex Differences in Atrial Fibrillation Patients Who Underwent Combined Radiofrequency Catheter Ablation and Left Atrial Appendage Closure**



Chen M, et al. JACC: Asia. 2023;3(1):138–149.

A total of 931 atrial fibrillation patients were enrolled in the LAACablation registry and underwent the combined procedure of radiofrequency catheter ablation and left atrial appendage closure, including 529 men (56.8%) and 402 women (43.2%). Follow-up over 1,812 patient-years revealed that women had similar composite adverse events to men, including procedural complications, all-cause death, thromboembolic events, and major bleeding. Women were seen with greater quality of life impairment at baseline, but the sex gap narrowed at 1-year follow-up. AFEQT = Atrial Fibrillation Effect on Quality-of-Life questionnaire.

the extent of improvement was larger in women than men. Consequently, the sex gap of QoL was markedly narrowed especially in the treatment-related subdomains, that is, treatment concern and treatment satisfaction. Considering similar outcomes between sexes in the hard endpoint such as mortality, thromboembolic events, and major bleeding, larger QoL improvement might serve as an increasingly important metric supporting the performing of the combined RFCA and LAAC in women.

In addition, socioeconomic status also influenced the decision-making, safety, and efficacy of AF treatment.[14,19] Previous studies reported that AF patients with higher levels of education and incomes were more frequently treated with RFCA or LAAC.[14,19] As for the current cohort, the higher proportion of

male participants might also be correlated with higher educational and economic levels in men. Despite being covered by the government-issued universal health insurance, the copay part of the combined procedure was still considerable. Nevertheless, despite higher payment in a lump sum, combining LAAC may be more cost-effective in patients who were planned for RFCA compared with long-term oral anticoagulation.[30]

STUDY LIMITATIONS. Despite a large sample size and prospective evaluation, the generalizability of the study results might be limited due to the nature of the current cohort, that is, single-center, nonrandomized, and all Chinese participants. The ablation approach was highly individualized without unified procedural flow, which might have lead to bias in procedural characteristics analyses. However, the proportions of patients undergoing specific ablation lines or substrate modification were comparable between sexes, which could partially reduce the impact. The Watchman device was the only LAAC device included. Whether sex disparities existed when RFCA combined with other LAAC devices, especially the devices with dual-seal mechanisms, remains unclear.

CONCLUSIONS

This study represents a comprehensive appraisal of sex-related differences and outcomes following the combined procedure of RFCA and LAAC. In AF patients who underwent the combined procedure of RFCA and LAAC, women had similar procedural safety and long-term efficacy with men. QoL improvement was prominent in both sexes after the procedure, which was greater in women. Therefore, there is no need to use sex as a basis on decision-making for the combined procedure of RFCA and LAAC for AF patients.

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ADDRESS FOR CORRESPONDENCE: Dr Yi-Gang Li, Department of Cardiology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, 1665 Kongjiang Road, Shanghai 200092, China. E-mail: liyigang@xinhuamed.com.cn.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Compared with men, women with AF had comparable procedural safety and long-term efficacy, and even greater QoL improvement when receiving the combined procedure of RFCA and LAAC. The results of this study support performing the combined RFCA and LAAC in both sexes.

TRANSLATIONAL OUTLOOK: Efforts should be made to minimize the impact of non-medical factors leading to the sex bias in decision making of the combined procedure of RFCA and LAAC.

REFERENCES

1. Volgman AS, Benjamin EJ, Curtis AB, et al. Women and atrial fibrillation. *J Cardiovasc Electrophysiol*. 2021;32:2793–2807.

2. Rahman F, Kwan GF, Benjamin EJ. Global epidemiology of atrial fibrillation. *Nat Rev Cardiol*. 2014;11:639–654.

3. Chen M, Li C, Liao P, et al. Epidemiology, management, and outcomes of atrial fibrillation among 30 million citizens in Shanghai, China from 2015 to 2020: a medical insurance database study. *Lancet Reg Health West Pac*. 2022;23:100470.

4. Darden D, Duong T, Du C, et al. Sex differences in procedural outcomes among patients undergoing left atrial appendage occlusion: insights from the NCDR LAAO registry. *JAMA Cardiol*. 2021;6:1275–1284.

5. Bhave PD, Lu X, Girotra S, Kamel H, Vaughan Sarrazin MS. Race- and sex-related differences in care for patients newly diagnosed with atrial fibrillation. *Heart Rhythm*. 2015;12:1406–1412.

6. Su F, Gao C, Liu J, et al. Periprocedural outcomes associated with use of a left atrial appendage occlusion device in China. *JAMA Netw Open*. 2022;5:e2214594.

7. Wintgens L, Romanov A, Phillips K, et al. Combined atrial fibrillation ablation and left atrial appendage closure: long-term follow-up from a large multicentre registry. *Europace*. 2018;20:1783–1789.

8. Chen M, Sun J, Wang QS, et al. Long-term outcome of combined catheter ablation and left atrial appendage closure in atrial fibrillation patients. *Int J Cardiol*. 2022;368:41–48. https://doi.org/10.1016/j.ijcard.2022.08.007

9. Spertus J, Dorian P, Bubien R, et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:15–25.

10. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510.

11. Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 2016;532:h7013.

12. Rienstra M, Van Veldhuisen DJ, Hagens VE, et al. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *J Am Coll Cardiol*. 2005;46:1298–1306.

13. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J*. 2016;37:2465–2474.

14. Sanjoy SS, Choi YH, Sparrow RT, et al. Sex differences in outcomes following left atrial appendage closure. *Mayo Clin Proc*. 2021;96:1845–1860.

15. Roten L, Rimoldi SF, Schwick N, et al. Gender differences in patients referred for atrial fibrillation management to a tertiary center. *Pacing Clin Electrophysiol*. 2009;32:622–626.

16. Patel D, Mohanty P, Di Biase L, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm*. 2010;7:167–172.

17. Forleo GB, Tondo C, De Luca L, et al. Gender-related differences in catheter ablation of atrial fibrillation. *Europace*. 2007;9:613–620.

18. Russo AM, Zeitler EP, Giczewska A, et al. Association between sex and treatment outcomes of atrial fibrillation ablation versus drug therapy: results from the CABANA trial. *Circulation*. 2021;143:661–672.

19. Olsen F, Uleberg B, Jacobsen BK, et al. Socioeconomic and geographic differences in ablation of atrial fibrillation in Norway—a national cohort study. *BMC Public Health*. 2022;22:303.

20. Li F, Sun JY, Wu LD, Hao JF, Wang RX. The long-term efficacy and safety of combining ablation and left atrial appendage closure: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol*. 2021;32:3068–3081.

21. Price MJ, Slotwiner D, Du C, et al. Clinical outcomes at 1 year following transcatheter left atrial appendage occlusion in the United States. *J Am Coll Cardiol Intv*. 2022;15:741–750.

22. Briosa EGA, Pope MTB, Monteiro C, et al. Long-term outcomes and periprocedural safety and efficacy of percutaneous left atrial appendage closure in a United Kingdom tertiary center: an 11-year experience. *Heart Rhythm*. 2021;18:1724–1732.

23. Yu HT, Lee JS, Kim TH, et al. Advanced left atrial remodeling and appendage contractile dysfunction in women than in men among the patients with atrial fibrillation: potential mechanism for stroke. *J Am Heart Assoc*. 2016;5(7):e003361. https://doi.org/10.1161/JAHA.116.003361

24. Tanaka N, Inoue K, Kobori A, et al. Sex differences in atrial fibrillation ablation outcomes: insights from a large-scale multicentre registry. *Europace*. 2020;22:1345–1357.

25. Wong GR, Nalliah CJ, Lee G, et al. Sex-related differences in atrial remodeling in patients with atrial fibrillation: relationship to ablation outcomes. *Circ Arrhythm Electrophysiol*. 2022;15:e009925.

26. Cheng X, Hu Q, Gao L, Liu J, Qin S, Zhang D. Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Europace*. 2019;21:1509–1518.

27. Mark DB, Anstrom KJ, Sheng S, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321:1275–1285.

28. Alli O, Doshi S, Kar S, et al. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2013;61:1790–1798.

29. Stromnes LA, Ree H, Gjesdal K, Ariansen I. Sex differences in quality of life in patients with atrial fibrillation: a systematic review. *J Am Heart Assoc*. 2019;8:e010992.

30. Kawakami H, Nolan MT, Phillips K, Scuffham PA, Marwick TH. Cost-effectiveness of combined catheter ablation and left atrial appendage closure for symptomatic atrial fibrillation in patients with high stroke and bleeding risk. *Am Heart J*. 2021;231:110–120.

KEY WORDS **atrial fibrillation, catheter ablation, left atrial appendage closure, quality of life, sex differences, stroke**

APPENDIX **For supplemental figures, please see the online version of this paper.**