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Title: The long-term efficacy and safety of combining ablation and left atrial appendage closure: A systematic review and meta-analysis

Running Title: Combining ablation and left atrial appendage closure

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Abstract

Backgroud

Combined ablation and left atrial appendage closure (LAAC) is an intriguing alternative for atrial fibrillation (AF) patients with a high stroke risk. However, the long-term outcomes of this combined procedure remain elusive. This meta-analysis aimed to assess the long-term efficacy and safety of combined procedure.

Methods

PubMed, Embase, Cochrane Library, and Web of Science were systematically searched from the establishment of databases to 1 January 2021. Studies on the long-term (defined as a mean follow-up of approximately 12 months or longer) efficacy and safety outcomes of combined ablation and LAAC were included for meta-analysis.

Results

A total of 16 studies comprising 1,428 patients were included in the meta-analysis. The pooled long term freedom rate from atrial arrhythmia was 0.66 (95% confidence interval [CI], 0.59-0.71), long-term successful rate sealing of LAAC was 1.00 (95% CI, 1.00-1.00), and ischemic stroke/transient ischemic attack/systemic embolism during follow-up was 0.01 (95% CI, 0.00-0.02). Meanwhile, the rates of peri-procedural adverse events included phrenic nerve palsy, intracoronary air embolus, device embolization, peri-procedural death of 0.00 (95% CI, 0.00-0.00), procedure-related bleeding events of 0.03 (95% CI, 0.02-0.04), and pericardial effusion requiring or not requiring intervention of 0.00 (95% CI, 0.00-0.01). Moreover, the rates of long-term adverse events rate included device dislocation, intracranial bleeding, and pericardial effusion requiring or not requiring intervention, and all-cause mortality of 0.00

1(95% CI, 0.00-0.00), device embolization of 0.01 (95% CI, 0.00-0.01), and other bleeding 2events of 0.01 (95% CI, 0.00-0.03).

3**Conclusion**

4This meta-analysis suggests that the strategy of combined atrial ablation and LAAC is 5effective and safe during long-term follow-up.

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7**Keywords:** Atrial ablation; Left atrial appendage closure; Atrial fibrillation; Clinical 8outcomes; Meta-analysis

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23**1. Introduction**

Atrial fibrillation (AF) is the most common sustained atrial arrhythmia, leading to many severe complications [1], of which stroke is a fatal one in AF patients with an overall risk of 5% per year [2]. To date, AF ablation has been recommended treatment considering its effective rhythm control in drug-refractory, symptomatic AF patients [3]. However, accumulating studies revealed recurrence rate significantly increased over time in AF patients following ablation, and the long-term effect of AF ablation on preventing thromboembolic events remains elusive [3, 4]. Accordingly, a continuation of long-term oral anticoagulation following AF ablation treatment for AF is necessarily recommended to reduce the risk of ischemic stroke and systemic embolism, whereas it also significantly increases the risk of bleeding events [4-6].

Recently, left atrial appendage (LAA) has been demonstrated as a significant thrombus formation source in more than 90% of patients with non-valvular AF [7-9]. Meanwhile, multiple studies have showed left atrial appendage closure (LAAC) is an important alternative to prevent stroke for AF patients, especially for those intolerant to oral anticoagulation drugs [10, 11]. AF ablation and LAAC are both important left atrial intervention technologies, which enable combining the two interventions with being an available and practical approach [12]; moreover, AF ablation can provide rhythm control while LAAC can prevent stroke for patients with AF. Therefore, the procedure of combined ablation and LAAC is increasingly used in clinical practice for high stroke risk AF patients.

Preliminary studies have demonstrated that the procedure of combined ablation and LAAC could be performed successfully and safely, with a more than 95% success rate and a less than 5% peri-procedural adverse events [13, 14]. Additionally, several meta-analysis showed the combined procedure was a feasible and safe strategy for AF patients with high stroke risk

1[15, 16]. Despite the promising results, few studies provided reliable and comprehensive 2conclusion due to small sample size (e.g., less than ten patients) [17-19], lack of long-term follow-3up (e.g., less than 6 months) [20-22], and non-combined ablation and LAAC [23, 24]. In this study, we 4evaluated the long-term (defined as a mean follow-up of approximately 12 months or longer) 5efficacy and safety of combination of ablation and LAAC.

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72. Methods

82.1 Search strategy

9A systematic literature search was conducted by two independent reviewers (Feng Li and Jin-10Yu Sun) in online databases, including PubMed, Embase, Cochrane Library, and Web of 11Science from the establishment of databases up to 1 January 2021. Search keywords included 12“atrial fibrillation”, “left atrial appendage closure”, “left atrial appendage occlusion”, 13“cryoablation”, “catheter ablation”. Moreover, the reference list of retrieved eligible literature 14and review literature was hand-searched for potential publications not being identified 15previously.

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172.2 Study design

18The inclusion criteria in this review were as follows: (1) single- or multi-center clinical trials; 19(2) study subjects with non-valvular AF underwent a combined AF ablation and LAAC; (3) 20studies with a mean follow-up of approximately 12 months or longer; (4) studies on the 21efficacy outcomes, including long-term freedom rate from atrial arrhythmia, long-term 22successful sealing rate of LAAC (successful sealing of LAAC was defined as no flow or the 23presence of a remaining jet less than 5 mm by transesophageal echocardiography assessment),

and ischemic stroke/TIA (transient ischemic attack)/systemic embolism during follow-up; (5) studies on the safety outcomes, including peri-procedural adverse events: phrenic nerve palsy, intracoronary air embolus, device embolization, procedure-related bleeding events (e.g., groin hematoma, gastrointestinal bleeding, or hematuria), pericardial effusion requiring or not requiring intervention, and peri-procedural death; and long-term adverse events: device embolization, device dislocations, intracranial bleeding, other bleeding events (e.g., gastro-intestinal bleeding, pulmonary bleeding, hematoma, hematuria, or nose bleedings), pericardial effusion requiring or not requiring intervention, and all-cause mortality; (6) studies with full texts published in English in peer-reviewed journals. Importantly, for multiple publications of the same trial, we only included the study containing the most data. However, review articles, case reports, animal studies, letters, editorials, studies without original data, and studies with enrolling subjects not more than ten or with follow-up less than six months were excluded. Two independent reviewers (Feng Li and Jin-Yu Sun) searched and reviewed the titles, abstracts, and full texts to determine the eligibility. Any disagreements about eligibility were resolved with a third reviewer (Ru-Xing Wang).

2.3 Data extraction and quality assessment

For each eligible study, data were extracted by two independent researchers (Jin-Yu Sun and Li-Da Wu), and any potential disagreements were discussed together with the third researcher (Ru-Xing Wang). We first extracted the study characteristics, including first author, publication year, study design, number of patients, and follow-up duration. The demographic and clinical characteristics of patients and the procedure-related indexes were also recorded.

Moreover, information on the long-term efficacy and safety outcomes were documented.

The risk of bias of each eligible study was assessed by two researchers (Jin-Yu Sun and Li-Da Wu) independently using the Newcastle-Ottawa Quality Assessment Scale (NOS) [25]. Any disagreements were resolved by discussion or by consulting a third researcher (Ru-Xing Wang).

2.4 Statistical analysis

The Stata (version 12.0) was used for all statistical analyses. Categorical variables were presented as frequencies or percentages, and continuous variables were presented as means ± standard deviations (SD). Pooled results were presented as the incidence rate of the events (ratio of the number of events to patient number) and 95% confidence interval (CI). I^2 was used to quantify the proportion of variance due to between-study heterogeneity [26], and I^2 values of 0%, <25%, 25%-49%, and >50% denoted no, low, moderate, and high heterogeneity, respectively. If I^2 value is more than 50%, we consider the between-study heterogeneity is significant, and a random effect model would be adopted. Otherwise, a fixed effect model was used. When significant heterogeneity was presented, a sensitivity analysis was performed to inspect the effect of a single study on the overall risk estimate by sequentially omitting one study at a time. Additionally, potential publication bias was assessed via Begg's and Egger's test. $P < 0.05$ was considered statistically significant.

Also, subgroup analyses were conducted to explore the sources of heterogeneity. According to previously reported factors and the characteristics of included studies, the

subgroup factors included the number of the center, age, gender, AF ablation history, the proportion of paroxysmal atrial fibrillation (PAF), the proportion of Watchman-device, procedure strategy, and ablation strategy. If the number of the center was more than 1, it was assigned to the multi-center subgroup; otherwise, it was assigned to the single-center subgroup. Based on the cut-off value of 70 years of mean age and 70% of male, the included studies were divided into two subgroups, respectively. If the study contained the patients who underwent the redo procedure for AF ablation, it was assigned to the AF ablation history (+) subgroup; otherwise, it was assigned to the AF ablation history (-) subgroup. According to the cut-off value of 50%, the proportion of PAF and the proportion of Watchman-device were divided into two subgroups, respectively. If ablation was performed before LAAC, it was assigned to the First ablation Then LAAC subgroup; otherwise, it was assigned to the First LAAC Then ablation subgroup. Moreover, if pulmonary vein isolation (PVI) was performed only, it was assigned to the PVI subgroup; otherwise, it was assigned to the PVI+ subgroup.

3. Results

3.1 Study selection and characteristics

A total of 426 articles were identified in the initial search. After duplicate articles removal and title/abstract screening, 41 articles were eligible for full-text reviews. After the assessment of the 41 full-text studies, we excluded 25 articles (6 review articles, 1 case report, 3 meta-analysis, and 15 not relevant articles). The flowchart of the study selection process was shown in **Figure. 1**. In total, 16 studies were included [13, 27-41], and one of the studies was divided into two arms for meta-analysis according to the procedural strategies (First LAAC then RFA or

First FRA then LAAC) [35], leading to a total of 17 study items for analysis. The baseline characteristics of patients were presented in **Table 1**, and the procedure indexes of combined ablation and LAAC were presented in **Table 2**.

3.2 Quality assessment

Overall study quality was moderate and the quality assessment was presented in **Table 3**. All studies generally had representative study populations, i.e., patients with symptomatic drug-resistant non-valvular AF and the mean CHA_2DS_2-VASc score more than 2 or the relative/absolute contraindications for long-term oral anticoagulant therapy. All studies had internally representative control groups and secure records, and the interest outcomes were not present at the start of the study. Assessment of outcomes (e.g., long-term freedom from atrial arrhythmia, long-term successful sealing of LAAC, or ischemic stroke/TIA/systemic embolism during follow-up) was satisfactory except for one study [29] without the freedom from atrial arrhythmia. The mean follow-up of all studies was approximately 12 months or longer, but 6 studies explicitly stated that patients' follow-up rate was 95% or lower. No study was excluded from quantitative analysis because of the risk of bias.

3.3 Pooled long-term efficacy of combined AF ablation and LAAC

3.3.1 Long-term freedom rate from atrial arrhythmia

A total of 15 included studies (16 study items and 1,122 patients) reported the incidence of long-term freedom from atrial arrhythmia [13, 27, 28, 30-41]. The long term freedom rate from atrial arrhythmia was assessed by random effect model, and pooled analysis showed an overall mean rate of long term freedom from atrial arrhythmia was 0.66 (95% CI, 0.59-0.71; P=0.00;

I^2=73.90%; **Figure. 2**).

Sensitivity analysis showed that no substantial change was detected in the overall combined proportion, which ranged from 0.64 (95% CI, 0.58-0.70) to 0.67 (95% CI, 0.63-0.72), suggesting that no single study dominated the combined proportion and heterogeneity. Begg's test showed no publication bias (*P*=0.26), while Egger's test showed the opposite result (*P*=0.00). Furthermore, subgroup analysis was performed, and the results were presented in **Table. 4**.

3.3.2 Long-term successful sealing rate of LAAC

All studies (17 study items and 1,302 patients) reported the incidence of long-term successful sealing of LAAC, which was analyzed by a fixed effect model. The results showed the pooled long-term successful rate sealing of LAAC was 1.00 (95% CI, 1.00-1.00; *P*=0.66; I^2=0.00%; **Figure. 3**)

3.3.3 Ischemic stroke/TIA/systemic embolism during follow-up

The pooled ischemic stroke/TIA/systemic embolism during follow-up was analyzed in all studies by a fixed effect model, and the pooled result was 0.01 (95% CI, 0.00-0.02; *P*=0.12; I^2=30.29%; **Figure. 4**), suggesting that patients had a lower thromboembolism rate following the procedure of combined ablation and LAAC.

3.4 Pooled safety outcomes

3.4.1 Peri-procedural adverse events

All peri-procedural adverse events were analyzed by a fixed effect model. The results showed the pooled phrenic nerve palsy was 0.00 (95% CI, 0.00-0.00; *P*=0.77; I^2=0.00%), intracoronary air embolus was 0.00 (95% CI, 0.00-0.00; *P*=0.99; I^2=0.00%), device

embolization was 0.00 (95% CI, 0.00-0.00; P=0.99; I^2=0.00%), pericardial effusion (required drainage) was 0.00 (95% CI, 0.00-0.01; P=0.18; I^2=23.67%), pericardial effusion (not required drainage) was 0.00 (95% CI, 0.00-0.01; P=0.03; I^2=43.44%), procedure-related bleeding events were 0.03 (95% CI, 0.02-0.04; P=0.59; I^2=0.00%), and peri-procedural death was 0.00 (95% CI, 0.00-0.00; P=1.00; I^2=0.00%).

3.4.2 Long-term adverse events

All included studies reported the long-term adverse events. One of the long-term adverse events, other bleeding events, was analyzed by random effect model, and the remaining was analyzed by a fixed effect model. The pooled results showed device embolization was 0.01 (95% CI, 0.00-0.01; P=1.00; I^2=0.00%), device dislocation was 0.00 (95% CI, 0.00-0.00; P=1.00; I^2=0.00%), intracranial bleeding was 0.00 (95% CI, 0.00-0.00; P=1.00; I^2=0.00%), pericardial effusion (required drainage) was 0.00 (95% CI, 0.00-0.00; P=1.00; I^2=0.00%), pericardial effusion (not required drainage) was 0.00 (95% CI, 0.00-0.00; P=1.00; I^2=0.00%), all-cause mortality was 0.00 (95% CI, 0.00-0.00; P=0.95; I^2=0.00%).

In the case of other bleeding events, the pooled data showed an overall mean incidence of 0.01 (95% CI, 0.00-0.03; P=0.00; I^2=57.14%; **Figure. 5**). Sensitivity analysis showed that no significant change was detected in the overall combined proportion, which ranged from 0.01 (95% CI, 0.00-0.03) to 0.02 (95% CI, 0.00-0.03), suggesting that no single study dominated the combined proportion and heterogeneity. Additionally, Begg's test and Egger's test showed no publication bias (P=0.11 and P=0.27, respectively). In addition, subgroup analysis results were presented in **Table. 5**, indicating subgroup factors were not the source of heterogeneity. Therefore, the results were considered to be robust.

4. Discussion

We comprehensively evaluated 1,428 patients from 16 published original articles (including 417 study items). To the best of our knowledge, this study is the first meta-analysis to assess the long-term efficacy and safety of combined ablation and LAAC. Our results suggest that this combined procedure is both effective and safe for long follow-up. Due to the lack of randomized controlled trials, all included studies were retrospective and observational studies.

The epidemiological investigation has shown more than 30 million people worldwide are affected by AF, which attributes to the nearly five-fold risk of stroke and two-fold risk of death. Recently, the guideline for the management of AF patients has suggested AF care requires a multifaceted approach, including stroke prevention, symptom control, and management of other comorbidities and risk factors [42]. Radiofrequency ablation or cryoballoon ablation has been proven as an effective strategy for rhythm control in patients with symptomatic and drug-refractory AF. However, to date, no randomized controlled trials have shown a decrease in the risk of thromboembolic events or ischemic stroke following AF ablation [43], and it was even reported that the risk of stroke remained high post-ablation [44]. Moreover, Kornej *et al*. [45] revealed The CHA_2DS_2-VASc risk score was significantly associated with the risk of thromboembolic events post-ablation, underlining the necessity of on-going stroke protection with high-risk patients. Therefore, long-term oral anticoagulation for high stroke risk patients was widely recommended following AF ablation. Whereas the challenge was reported, oral anticoagulation seemed to be significantly related to an increased risk of bleeding events, including fatal hemorrhage, e.g., intracranial bleeding. LAAC was

designed to mechanically occlude the orifice of LAA, where is considered as the origin of more than 90% thrombi. Accumulating studies revealed LAAC was effective and safe for AF patients who were not suitable for lifelong antithrombotic treatment with high stroke risk. PREVAIL trial and EWOLUTION trial also showed the implant success rates were as high as, respectively, 95.1% and 98.1%, and the adverse event rates were as low as, respectively, 4.2% and 2.7% [46, 47]. Although LAAC is currently recognized as a feasible approach to antithrombotic therapy for AF patients, it still faces several challenges, including failing to rhythm control, failure to prevent the thrombi outside the LAA, and prone to device-related thrombosis [48].

Due to sharing similar procedural characteristics and technical requirements, the combination of ablation and LAAC has been demonstrated as an available and practical approach for AF treatment. Moreover, combination of rhythm control based on AF ablation and stroke prevention based on LAAC enables this procedure strategy to be a valuable and promising alternative, especially for AF patients related with high stroke risk or/and intolerant to oral anticoagulant therapy. Recently, multiple clinical studies have reported the results of combined ablation and LAAC. A total of 349 non-valvular AF patients who underwent the combined procedure were analyzed in a prospective and non-randomized multi-center study reported by Wintgens *et al*. [28], and the results showed the success of the LAAC was as high as 98.9%, an annualized stroke rate sharply decreased to 0.9% (compared to an expected stroke rate of 3.2%), and the adverse events were rather low (only including 1.5% pericardial effusion, 0.3% minor stroke, and no death), suggesting the combined procedure was feasible, effective and safe. Instead, more than half of the patients had AF recurrence. Similar results

also were presented in another international, multi-center registries study [29]. In addition, a study from China showed an excellent result, including a 76.2% long-term freedom rate from atrial arrhythmia, 100% successful sealing of LAAC, and no ischemic stroke/TIA/systemic embolism during follow-up [30]. However, the definitive conclusions of related studies should be drawn with caution given several important limitations, including small sample size [17-19], short follow-up duration [20, 21], and non-combined procedure [23, 24].

In our meta-analysis, we pooled the efficacy and safety outcomes of combined ablation and LAAC. In the case of efficacy outcomes, the results showed the combined procedure had a high rate of 1.00 in long-term successful sealing of LAAC, similar to recent meta-analysis results with a successful sealing rate of 0.98 [16]. The pooled rate of ischemic stroke/TIA/systemic embolism during follow-up was as low as 0.01. Meanwhile, of the 1,428 patients enrolled, 691 were free from atrial arrhythmia during follow-up, and the pooled long-term freedom rate from atrial arrhythmia was 0.66. To summarize these results, it revealed combination of ablation and LAAC was rather feasible and effective with a long-term follow-up.

Also, in the assessment of peri-procedural adverse events, we recognized that the pooled rates were as low as 0.00 in terms of phrenic nerve palsy, intracoronary air embolus, device embolization, procedure-related bleeding events, pericardial effusion requiring intervention, and peri-procedural death. Moreover, the pooled rate of pericardial effusion not requiring intervention was only 0.03. Similarly, the pooled rates of device dislocation, intracranial bleeding, pericardial effusion requiring or not requiring intervention, and all-cause mortality were 0.00 during long-term follow-up. And the pooled rates of device embolization and other

bleeding events were as low as 0.01. The results of the long-term adverse events were likely to previous studies [15, 16], indicating this combined procedure had a good performance on safety.

Furthermore, due to the existence of significant heterogeneity, sensitivity analysis, publication bias analysis, and subgroup analysis were performed on the long-term freedom from atrial arrhythmia and other bleeding events of long-term adverse events. In the assessment of long-term freedom from atrial arrhythmia, we found no single study dominated the combined proportion and heterogeneity. Instead, Begg's test and Egger's test showed the opposite results, suggesting a potential publication bias may exist. Moreover, subgroup analysis revealed age, the proportion of males and the procedure strategy can partly explain the heterogeneity of long-term freedom from atrial arrhythmia between the included studies, but the subgroup difference did not yet reach the level of statistical significance (P=0.11, P=0.09 and P=0.15, respectively). As we know, age and gender played important roles in the occurrence and recurrence of atrial arrhythmia [49, 50]. However, in our meta-analysis, age and gender did not seem to have an influence on the long-term freedom from atrial arrhythmia, considering to be related to small sample size, reporting bias and confounding factors. In addition, only one study reported the procedure strategy (First ablation or First LAAC) in combined ablation and LAAC, and the results showed the rates of freedom from atrial arrhythmia were comparable between the First ablation group and First LAAC group with a mean follow-up of 11.2 months (75.0% vs 70.0%, log-rank P=0.311), which was consistent with our subgroup analysis[35]. Then, in the case with other bleeding events of long-term adverse events, sensitivity analysis and, publication bias analysis indicated this result was

robust, and subgroup analysis showed these subgroup factors were not involved in the formation of heterogeneity between enrolled studies. In summary, this meta-analysis demonstrated that combined ablation and LAAC had the long-term efficacy and safety for high stroke risk patients with AF.

5. Limitation

Several limitations of our meta-analysis should be acknowledged. Although all enrolled studies showed long-term results, they all were observational studies. Without a comparative arm, it is still a challenge to objectively ascertain the efficacy and safety of this combined procedure; thus, prospective, multi-center, randomized comparative studies are urgently needed to further draw a credible conclusion. Moreover, some outcomes in the eligible studies were not provided separately, leading to a failure to do more in-depth research. Additionally, Egger's test showed the result of P=0.00, suggesting the presence of a potential publication bias in studies on the long-term freedom rate from atrial arrhythmia. Except for four studies with sample size of more than 100 subjects, the remaining studies had relatively smaller sample sizes, which may have an effect on the stability of the outcome indicators, reduce the test efficiency, and cause possible bias to the research results.

6. Conclusion

Our results demonstrate that the combined ablation and LAAC is effective and safe for AF patients with long-term follow-up. However, more prospective, randomized controlled trials in large cohorts are required to further confirm these outcomes.

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Figure legends

Figure. 1 Flow chart of study selection

Figure. 2 Forest plot of the pooled long-term freedom rate from atrial arrhythmia

Figure. 3 Forest plot of the pooled long-term successful rate sealing of LAAC. LAAC: left atrial appendage closure

Figure. 4 Forest plot of the pooled ischemic stroke/TIA/systemic embolism during follow-up. TIA: transient ischemic attack

Figure. 5 Forest plot of other bleeding events of long-term adverse events