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Effectiveness and safety of one-stop procedure versus ablation alone in patients with non-valvular atrial fibrillation: a meta-analysis

Yue Wang[1], Xu Zhang[2]

[1]*Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, China*
[2]*Medical College, China Three Gorges University, Yichang, Hubei, China*

Abstract: *Background: Catheter ablation (CA) and left atrial appendage closure (LAAC) are two effective treatments for atrial fibrillation. Furthermore, atrial fibrillation (AF) ablation combined with left atrial occlusion closure (LAAC) is a potential therapy option for AF in individuals who are at high risk of stroke or who are unable to take oral anticoagulants. This study intends to analyze and evaluate the difference in effectiveness and safety between one-stop operation, in which patients accept AF ablation and LAAC in one surgery, and ablation alone in patients with non-valvular AF through the method of meta-analysis. Methods: This study searches PubMed, Embase, Medline, the Cochrane Library, CNKI, VIP Database, and WANFANG Database for clinical studies of combined therapy and AF ablation in the prevention of AF, combining subject words with free words, and the retrieval time is from the establishment of each database to September 29, 2021. Results: The meta-analysis comprised five clinical studies with a total of 488 patients with AF who received AF ablation alone and 269 patients who received ablation and LAAC in one stop. Patients with paroxysmal AF, persistent AF, long-standing persistent AF, or all of these conditions were included in all of the investigations. At long-term follow-up, the rate of AF recurrence was not substantially different between the two groups (one-stop procedure 39.03 % vs. AF ablation 28.28 %, respectively; OR 1.34; 95% CI 0.95-1.87; P = 0.32). Furthermore, there was no statistically significant difference in terms of major complications and adverse events between the two groups (one-stop procedure 13.75 % vs. AF ablation 13.73 %, respectively; OR 0.73; 95% CI 0.44-1.18; P = 0.54). Conclusion: Using LAAC in addition to CA had no effect on the efficacy of AF ablation, and the combination method was performed without an increased risk of acute procedural complications or negative effects.*

Keywords: *left atrial appendage closure, ablation, one-stop procedure, meta-analysis, non-valvular atrial fibrillation*

1. Introduction

In clinic, AF is the most prevalent arrhythmia symptom. When AF occurs, it not only comprises cardiac function, but also increase the risk of atrial thrombosis. It is quite easy to get a stroke if the thrombosis goes off. Stroke usually develops quickly and has a dismal prognosis. As a result, the treatment guidelines for AF patients should primarily focus on preventing stroke complications and reducing AF recurrence.

Catheter ablation is a well-established treatment option for rhythm management, particularly in symptomatic patients with drug-resistant AF.[1] The cornerstone of AF ablation is still pulmonary vein isolation (PVI).[2] The cornerstone of AF ablation is still pulmonary vein isolation (PVI).[3] Despite this, the rate of AF recurrence remains high. Indeed, the LAA has been reported to be an important but underestimated site in the development of AF. [4,5] Left atrial appendage closure (LAAC) has been proven a safe and effective alternative to long-term anticoagulation for patients with increased risk of stroke and bleeding, reducing both ischemic and hemorrhagic events. [6] Thus, over a decade ago, combined procedure, which means patients accept CA and LAAC in one stop, became a feasible strategy in patients with symptomatic drug-refractory AF, high risk of stroke or contraindications to long-term Oriented Adaptive Cross Search (OACs).[8] The primary endpoint of this study is AF recurrence and adverse events in patients with non-valvular AF (NVAF). To the best of our knowledge, this is the first meta-analysis to compare effectiveness and safety between one-stop procedure and ablation alone in patients with NVAF.

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2. Methods

2.1. Data sources and searches

We systematically searched, with no language restriction, PubMed, Embase, Medline, the Cochrane Library, CNKI, VIP Database, and WANFANG Database, and the retrieval time is from the establishment of each database to September 29, 2021. We used permutations of the terms “atrial fibrillation”, “left atrial appendage”, “catheter ablation” and “left atrial appendage closure” to identify potential studies for inclusion. Hand searching with cross-references of retrieved publications, review articles and guidelines was also performed to ensure the inclusion of all relevant studies.

2.2. Selection criteria

Studies had to fulfil the following criteria to be included in the analysis: (i) the study was prospectively or retrospectively designed; (ii) study population was composed of patients undergoing radiofrequency ablation (RFA) , cryoablation, or left atrial appendage closure for non-valvular AF; (iii) study had LAAC+PVI group and PVI group; (iv) all efficacy and safety as an outcome; (v) follow-up duration was at least 12 months; and (vi) study provided enough data to calculate risk ratios (RRs).

2.3. Data extraction and quality assessment

Two authors (Wang Yue and Zhang Xu) searched the studies and extracted data independently. Data were extracted using standardized protocols and reporting forms. Disagreements were resolved by consensus. If data were not readily available in the written article, the respective principal investigator of the study was contacted to obtain pertinent information. Quality and reporting of included studies were assessed using NewcastleOttawa Scale. They were classified into one of the three categories: (i) high quality: 6–9 points; (ii) satisfactory quality: 3–5 points; and (iii) unsatisfactory quality: 0–2 points. No overlap of patients was present in the studies included in this meta-analysis.

2.4. Statistical analysis

We used RevMan 5.4.1 software to conduct meta-analysis on the collected data. The odds ratios and 95% CI was used for analyzing binary variable, and the mean difference and 95% confidence interval was applied for analyzing continuous variable. While four out of five clinical studies included in this meta-analysis were retrospective cohort and all of them were with small sample size, we calculated odds ratios and 95% confidence intervals for all studies. Heterogeneity among studies was examined with the I^2 test. When $I^2 \leq 50\%$, a fixed effect model was employed to analyze the extracted data. When $I^2 > 50\%$, a random effect model was used to analyze the extracted data. So, we used a fixed effect model for this study.

3. Results

3.1. Study selection

The search strategy led to the retrieval of 6930 citations from electronic database and manual searches as shown in Figure 1. We reviewed 11 citations for full-text articles; five full-text articles were included in final analysis. [7,9–12] Of the five included studies, one was a randomized prospective cohort study[7] and four were nonrandomized retrospective cohort studies.[9–12]

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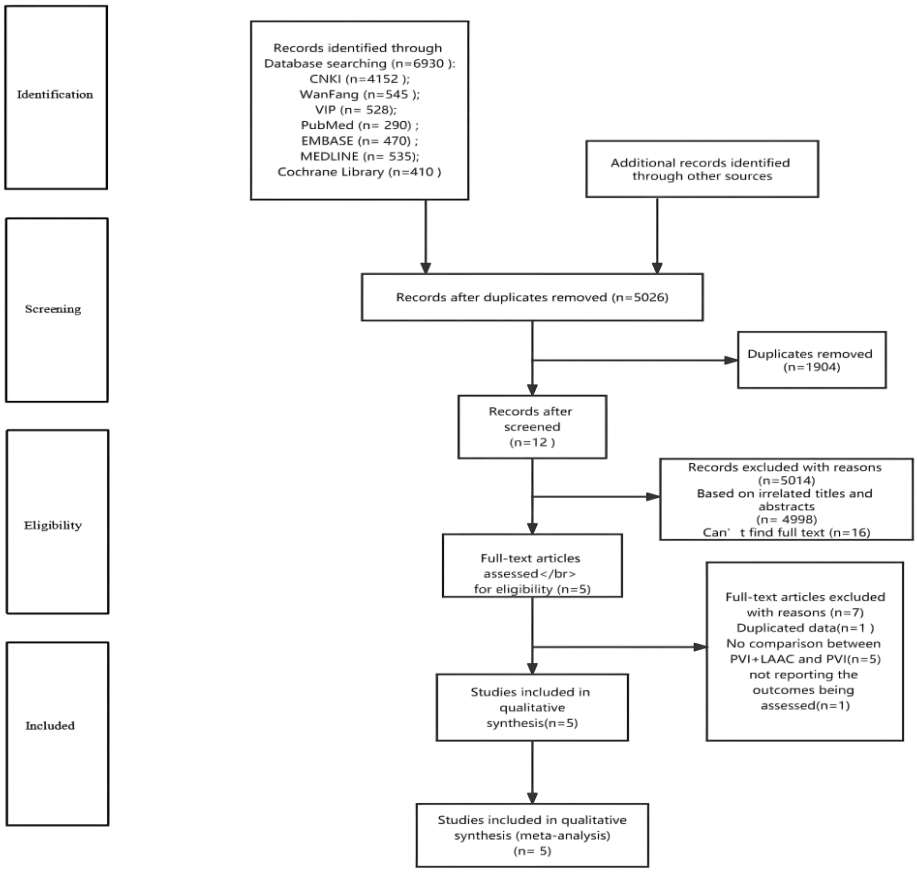

Figure 1: Flow chart of literature screening.

3.2. Quality assessment

All five studies were classified as high-quality based on NewcastleOttawa Assessment (Table1). All studies included in this meta-analysis had good methodological quality indicating 'low risk of bias.'In addition, due to the small number of articles included, no published bias test was performed.

Table 1: Results of quality assessment using the Newcastle-Ottawa Scale for cohort studies

Author	Selection				Comparability		Outcomes		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total scores
Alexander Romanov(2015)	★	★	★	★	★★	★	★	★	9
Bin-Feng Mo(2020)	★	★	★	★	★☆	★	★	★	8
Qingqing Yuan(2019)	★	★	★	★	★★	★	☆	★	8
Zhongyuan Ren(2020)	★	★	★	★	★☆	★	★	★	8
Shijie Zhu(2020)	★	☆	★	★	★★	★	☆	★	7

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3.3. Baseline characteristics

Five studies compared LAAC in addition to PVI compared to PVI alone. Non-pulmonary triggers, such as the posterior wall of the left atrium, the coronary sinus and the superior vena cava, were similarly ablated in both groups at the operators discretion. One study also involved patients who LAAC alone (LAAC-only group) to compare the procedural and long-term outcomes of combined procedures with isolated CA or LAAC.[9]

In the five included studies, 757 patients were enrolled. There was a total of 269 patients in the PVI + LAAC arm and 488 patients in the PVI alone arm. Baseline characteristics in three studies were comparable in both groups. Nonetheless, in two other studies baseline characteristics significantly differ in some aspects.[9,10] Bin-Feng Mo et al reported that the HAS-BLED score of the CA-only group was lower than that of the combined group (2.6 ± 0.9 vs. 3.3 ± 1.1, P < 0.001). [9] Besides, Zhongyuan Ren et al showed that both the CHA2DS2-VASc score (3.8 ± 2.1 vs 2.8 ± 1.9, p < 0.0001) and HAS-BLED score (3.8 ± 2.1 vs 2.8 ± 1.9, p < 0.0001) were significantly higher in the combined procedure group than in the CBA only group, and the combined procedure group was elder (70 ± 7.6 yrs vs 66.3 ± 9.5 yrs, p = 0.01) , with larger LA diameter (45.6 ± 5.8 mm vs 40.4 ± 5.6 mm, p < 0.0001), higher prevalence of hyperlipidemia (14.3% vs 3.8%, p = 0.01), and previous stroke history (61.9% vs 23.7%, p < 0.0001). Also, routine medications also differed, with the higher rate in the combined procedure group, including antiplatelet agents (46.3% vs 27.1%, p = 0.01) and statins (31.7% vs 15.6%, p= 0.01). [10] Study and baseline patient characteristics in the individual studies are shown in Tables 2 and 3, respectively. Five studies all included patients with non-valvular AF. Follow-up time ranged from 3 months to 35 months.

For the four studies that used PVI,[7,10–12] two were performed using radiofrequency ablation,[7,11] one used cryoballoon ablation[10] and last one used both[12] . The remaining one did not mention about it, and just reported as CA.[9] Of the five studies that used LAAC, only WATCHMAN (Boston Scientific, MA, USA) devices were used in two studies by Bin-Feng Mo et al and Alexander Romanov et al, [7,9] while other three studies used variouices.[10–12]

Table 2: Baseline study characteristics

Study first author (y)	Type	Procedure	Comparator	Follow - up (mo)	Primary endpoint
Alexander Romanov(2015)	Prospective cohort	PVI+LAAC	PVI	24	AF recurrence
Bin-Feng Mo(2020)	Retrospective cohort	CA+LAAC	CA	24	AF recurrence and adverse events
Qingqing Yuan(2019)	Retrospective cohort	RFA+LAAC	RFA	12	adverse events
Zhongyuan Ren(2020)	Retrospective cohort	CA+LAAC	CA	21	AF recurrence
Shijie Zhu(2020)	Retrospective cohort	RFA/CA+LAAC	RFA/CA	11	AF recurrence and adverse events

LAAC, left atrial appendage closure; PVI, pulmonary vein isolation; AF, atrial fibrillation; RFA, radiofrequency ablation; CB, cryoballoon.

ISSN 2706-6819 Vol.4, Issue 7: 27-34, DOI: 10.25236/IJFM.2022.040705

Table 3: Baseline patient characteristics

Study first author	Number		Age (y)		Male		Mean LVEF		AF type		LA diameter/ Size	
	A	B	A	B	A	B	A	B	A	B	A	B
Alexander Romanov(2015)	45	44	60±5	60±6	28	26	62±5	61±4	PAF 24 PER 21	PAF 25 PER 19	49±6	48±7
Bin-Feng Mo(2020)	76	76	69.9±7.9	69.5±7.8	40	36	63.9±6.3	64.2±5.4	PAF 37 PER 39	PAF 38 PER 38	42.7±5.7	41.7±4.9
Qingqing Yuan(2019)	50	50	60±8.1	61±8.5	27	28	49±3.3	48±3.4	PAF 21 PER 29	PAF 23 PER 27	-	-
Zhongyuan Ren(2020)	42	262	70±7.6	66.3±9.5	26	142	60.9±4.2	62.1±8.1	PAF 42	PAF 262	-	-
Shijie Zhu(2020)	56	56	65.2±6.6	64.8±8.5	33	34	58.6±7.8	44.5±6.2	PAF 24 PER 10 LSP 22	PAF 30 PER 7 LSP 19	45.6±6.3	44.5±6.2

A =one-stop procedure.
B = ablation alone.
LVEF, left ventricular ejection fraction; AF, atrial fibrillation; LA, left atrium; PAF, paroxysmal atrial fibrillation; PER, persistent; LSP, long - standing persistent.

3.4. Arrhythmia recurrence

Five studies all reported data on AF recurrence after follow-up. Among them, four studies reported that there was no significant difference in the recurrence of AF between the combined group and the PVI-only group.[7,9,11,12] Only one study, which only used CBA for PVI, showed that with a mean follow-up time of 22 ±11 months in the CBA only group and 20 ±9 months in the combined procedure group, the recurrence of AF was significantly higher in the latter (15.3% vs 29.3%, p = 0.04). [10] However, through adjusting confounding parameters, the results of this study showed combining LAAC in CBA procedure could achieve AF rhythm control with comparable efficacy to CBA alone. The recurrence of AF was not significantly different between the two groups (one-stop procedure 39.03 % vs. AF ablation 28.28 %, respectively; OR 1.34; 95% CI 0.95-1.87; P = 0.32) (figure 2). Thus, all study proved LAAC in addition to AF ablation did not impact the effectiveness of PVI.

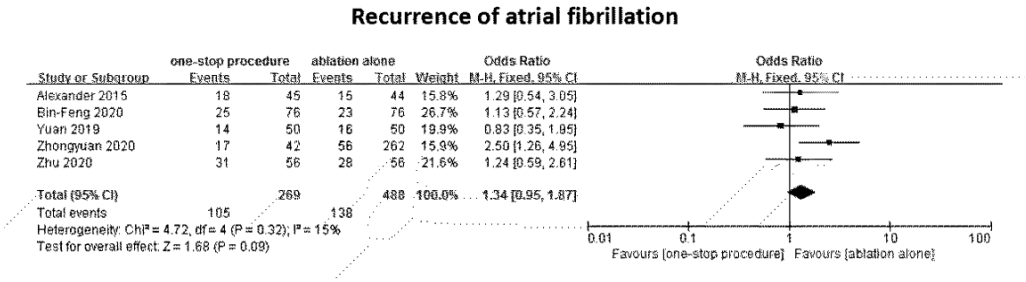

Figure 2: Forest plot of recurrence of AF comparing one-stop procedure Vs ablation alone. OR, odds ratio; CI, confidence interval

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3.5. Complications

Four studies reported data on specific complications, [7,9–11] while one just summarized in complications and thromboembolic events generally.[12] In four studies, three pericardial effusions, two groin hematomas, two complications of vascular access, one major bleeding event, two cardiovascular events and one arteriovenous fistula occurred in all combined groups compared to nineteen cardiovascular events, two deaths, two strokes, two myocardial infarctions, five pericardial effusions, one complication of vascular access, one major bleeding event, one cardiac tamponade and one groin hematoma in the PVI only group. These studies showed no significant difference was observed in the procedure-related complications between the two groups. Four studies reported data on both complications during the perioperative period and adverse events after follow-up. All reported adverse events are summarized in Table 4. Two studies reported there was no significant difference between two groups, while other two studies showed significant reduction was observed in the incidence of bleeding, stroke or TIA, and thromboembolic events in the combined group. Different results were presented. In general, there was no significant difference in the serious complications and adverse events between the two groups (one-stop procedure 13.75 % vs. AF ablation 13.73 %, respectively; OR 0.73; 95% CI 0.44-1.18; P = 0.54) (figure 3).

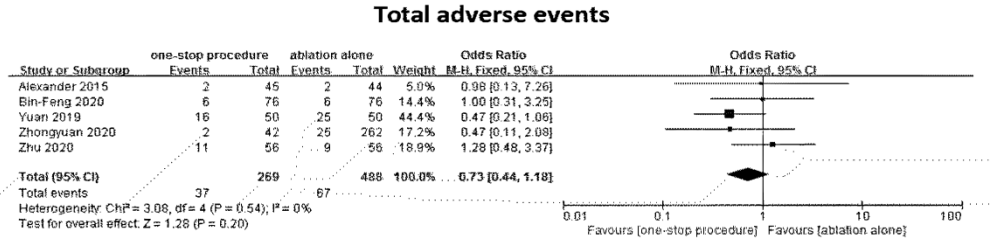

Figure 3: Forest plots of all reported adverse events in one-stop procedure vs ablation alone. OR, odds ratio; CI, confidence interval

Table 4: Adverse events

Study first author	Reported adverse events	
	one-stop procedure	ablation alone
Alexander Romanov(2015)	2(5%)groin hematoma	1(2%)cardiac tamponade 1(2%)groin hematoma
Bin-Feng Mo(2020)	1(1.3%)pericardial effusions 2(2.6%)complications of vascular access 1(1.3%)ishemic stroke events 2(2.6%)bleeding events	1(1.3%)pericardial effusions 1(1.3%)complications of vascular access 1(1.3%)ishemic stroke events 3(3.9%)bleeding events
Qingqing Yuan(2019)	Perioperative period:2(4%)pericardial effusions 8(16%)bleeding events 1(2%)arteriovenous fistula Follow-up period:2(4%)bleeding events 3(6%)systemic embolization	Perioperative period:4(8%)pericardial effusions 5(10%)bleeding events Follow-up period:9(18%)bleeding events 1(2%)systemic embolization 6(12%)TIA
Zhongyuan Ren(2020)	2(4.8%)cardiovascular events	2(0.7%)death 19(7.3%)cardiovascular events 2(0.7%)stroke 2(0.7%)myocardial infarction
Shijie Zhu(2020)	10(17.9%)perioperative complication 1(1.8%)thromboembolic events	7(12.5%)perioperative complication 2(3.6%)thromboembolic events

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4. Discussion

In this meta-analysis, we compared the effectiveness and safety between one-stop procedure and ablation alone in patients with non-valvular AF. We found that LAAC in addition to AF ablation did not impact the effectiveness of PVI. Surprisingly, a study reported by Alexander et al presented that while there was no significant difference in the long-term recurrence of AF between the combined group and the PVI-only group, and the one-stop group had a higher rate of AF recurrence during the blanking period, which they attributed to the fact that one-stop surgery is more complex in the heart cavity and induces a more inflammatory state in the heart.[7]

We also found no additional complications for LAAC as a result of the combination surgery. And there reports good periprocedural safety of the combined procedure. [9] Besides, four studies provided opposite data results on adverse events during follow-up. Two studies reported no significant difference between the two groups,[7,10] while two others showed a significant decrease in the incidence of bleeding, stroke or TIA and thromboembolism in the combined group. [9,11] Two multicenter studies also reported the efficacy of combination therapy in reducing stroke and bleeding compared to the risk calculated based on CHA2DS2-VASc and HAS-BLED scores.[13,14] However, this remains unclear and needs more further investigation.

Interestingly, two of the five articles mentioned a common problem with one-stop procedure, pulmonary vein ridge edema after ablation, which may lead to underestimation of the true LAA diameter and interfere the implantation of LAAC devices that require overlaying LAA opening, so that the rate of device displacement and the incidence of significant residual flow may increase after the subsiding of edema. [9,10] One study recommended that larger device sizes or measuring LAA diameter by preoperative CT could reduce this risk.[9] Another suggested plugging a LAAC device such as WATCHMAN as a first choice when considering LAAC immediately after cryoablation.[10]

The above mentioned findings indicates that the underestimation of the true LAA diameter may be the key reason for improving the efficacy and safety of combined surgery. Thus, long-term explanations and clinical consequences are warranted to provide stronger evidences. Moreover, previous studies mostly analysed the comparison between oral anticoagulants and LAAC in patients with non-valvular AF, while we discuss effectiveness and safety between one-stop procedure and ablation alone which could stimulate new inspiration of AF treatment.

There are several potential limitations to our meta-analysis. First, although our analysis found combined group was effective and safe, we did not observe combined group could improve AF-free or reduce periprocedural complications or other benefits for non-valvular AF. Besides, of the five included studies, one was a randomized prospective cohort study and four were nonrandomized retrospective cohort studies. The numbers of studies and patients included in each of the studies are small, and baseline characteristics varied from study to study. Two studies baseline characteristics significantly differ in some aspects, so a selection bias may exist. In addition, intraprocedural differences related to operators experience may have occurred between studies and centers. Finally, our study only compared PVI+LAAC with PVI, in the future we can add left atrial appendage isolation (LAAI) to comparison. Of the note, results will require validation in additional and larger trials.

5. Conclusions

One-stop procedure is an effective and safe way for non-valvular AF. LAAC in addition to PVI did not impact the effectiveness of AF ablation and combined procedure did not bring additional complications to LAAC. Large, multicenter randomized studies are needed to confirm the benefit of follow-up adverse events. Future research is required to elucidate the comparison between PVI+LAAC and PVI+LAAI.

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ISSN 2706-6819 Vol.4, Issue 7: 27-34, DOI: 10.25236/IJFM.2022.040705

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