

Efficacy and Safety of Catheter Ablation Combined with Left Atrial Appendage Closure in the Treatment of Atrial Fibrillation: A Systematic Review and Meta-Analysis

ABSTRACT

Background: Catheter ablation combined with left atrial appendage closure is effective in treating atrial fibrillation. However, the effectiveness of this combined treatment compared with catheter ablation alone is still controversial.

Methods: We searched studies in databases, including The Cochrane Library, PubMed, EMBASE, and Web of Science, that compared catheter ablation combined with left atrial appendage closure and catheter ablation alone in the treatment of atrial fibrillation. These studies reported at least one of the following outcomes: the freedom from atrial arrhythmia rate, the procedure time, the fluoroscopy time, perioperative complications, thromboembolic events, and bleeding events during follow-up. The risk ratio and standard mean difference with 95% CI were analyzed by the random-effects model.

Results: Five studies involving 699 people were included in our meta-analysis. We found no significant difference in the freedom from atrial arrhythmia rate (risk ratio=0.93, 95% CI=0.83-1.04, $I^2=0\%$, $P=.21$) between the 2 groups. Catheter ablation combined with left atrial appendage closure showed significantly longer procedure and fluoroscopy times than catheter ablation alone (standard mean difference=1.26, 95% CI=0.85-1.67, $P < .00001$ and standard mean difference=1.19, 95% CI=0.53-1.85, $P=.0004$, respectively). With regard to safety outcomes, no significant differences were observed in perioperative complications (RR=1.62, 95% CI=0.99-2.63, $I^2=0\%$, $P=.05$), thromboembolic events (RR=0.67, 95% CI=0.15-3.11, $I^2=0\%$, $P=.61$), or bleeding events (RR=0.67, 95% CI=0.11-3.88, $P=.65$) between the 2 groups during follow-up.

Conclusion: The freedom from atrial arrhythmia rate and safety outcomes of catheter ablation combined with left atrial appendage closure are similar to those of catheter ablation alone. Catheter ablation combined with left atrial appendage closure appears to have longer procedure and fluoroscopy times than catheter ablation alone.

Keywords: Atrial fibrillation, catheter ablation, left atrial appendage closure, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia. Approximately, 33 million people worldwide are affected by AF, and its rate is gradually increasing.¹ Atrial fibrillation also leads to a huge economic burden.² Catheter ablation (CA), which is an important method for treating AF, can improve symptoms and quality of life.^{3,4} In the 2020 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of AF developed in collaboration with the European Association of Cardio-Thoracic Surgery, CA is also recommended as class I for patients with paroxysmal AF or persistent AF with or without major risk factors for AF recurrence after failure or intolerance of class I or III antiarrhythmic drug.⁵

However, there is still recurrence or thromboembolic events (TEs) in patients with AF after CA.⁶ Thromboembolic complications are the main cause of death and disability in AF.⁷ Although anticoagulant therapy reduces the incidence of thromboembolism,⁸ it also has its limitations. First, the proportion of anticoagulant

META-ANALYSIS

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therapy is insufficient.⁹ Second, many patients cannot adhere to long-term medication.¹⁰ Third, there may be drug interactions that affect the anticoagulant effect of anti-vitamin K anticoagulants. Additionally, the bleeding risk of anticoagulant therapy cannot be ignored.¹¹

The left atrial appendage (LAA) plays an important role in thrombosis in patients with AF. A recent study of 1420 patients with nonvalvular AF or flutter showed that all patients with atrial thrombus had thrombus in the LAA.¹² The combination of CA and LAA closure (LAAC) in the treatment of AF is expected to achieve rhythm control and reduce the risk of thrombus formation in the LAA. The recommendation of the current guideline in terms of anticoagulation is based on CHA₂DS₂-VASc score irrespective of AF ablation procedure outcome, and that patients who had concomitant LAAC can avoid taking long-term anticoagulation.⁵ A meta-analysis also showed the efficacy and safety of this combined strategy.¹³ However, whether the efficacy and safety of the CA combined with LAAC strategy is different from that of CA alone is still unknown. A recent study showed that the 1-year freedom from AF rate was lower with the combined strategy than that of CA alone.¹⁴ However, other studies reached different conclusions.^{15,16} Therefore, we aimed to conduct this systematic review and meta-analysis to evaluate the efficacy and safety of CA combined with LAAC and CA alone in the treatment of AF.

METHODS

Our systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist. The protocol for this meta-analysis is available in International prospective register of systematic reviews (PROSPERO) (CRD42021236262).

Literature Search

We searched The Cochrane Library, PubMed, EMBASE, and Web of Science for relevant literature up to January 16, 2021. We searched keywords, including atrial fibrillation, atrial fibrillat*, auricular fibrillat*, atrium fibrillat*, AF, ablat*, isolat*, "left atrial appendage," LAA, occlu*, and clos* without language restriction. The specific search strategy is shown in the supplementary material. Two researchers (A.W. and J.J.) conducted the literature search independently. Differences in opinions were determined by a third reviewer (Z.X.). Approval from the Institutional Review Board was not

required because this study was a systematic review and meta-analysis.

Study Selection

Inclusion criteria included the following: (1) randomized, controlled trials (RCTs) or observational studies; (2) CA combined with LAAC versus CA alone in the treatment of AF; and (3) at least one of the following outcomes was reported: efficacy outcomes included the freedom from atrial arrhythmia rate, procedure time, fluoroscopy time, and safety outcomes included perioperative complications, TEs, and bleeding events during follow-up. Exclusion criteria included the following: (1) a surgical operation; (2) studies including LAA isolation; and (3) conference abstract.

Data Extraction and Quality Assessment

Two reviewers independently extracted the following information from the studies that were selected for inclusion: authors, year of publication, country, sample size, age distribution, sex proportion, proportion of paroxysmal AF, left atrial diameter, congestive heart failure/hypertension/age 75 years or older/diabetes mellitus/stroke/vascular disease/age 65 2 74 years/sex category (female) (CHA₂DS₂-VASc) score, uncontrolled hypertension/abnormal renal and/or hepatic function/stroke/bleeding history or predisposition/labile INR/elderly/drugs or excessive alcohol drinking (HAS-BLED) score, occlusion device, mean follow-up times, and study design. Efficacy and safety outcomes as described above were recorded. When the article only mentioned the recurrence of AF, we classified it as a recurrence of atrial arrhythmia. If stroke, transient ischemic attack, peripheral embolism, and myocardial infarction were mentioned in the included studies, we classified them as TEs. If the article only mentioned severe bleeding events, we classified them as bleeding events. Any disagreements between the 2 reviewers were determined by a third reviewer. The quality of RCTs was evaluated by Cochrane Collaboration's risk of bias tools, and observational studies were evaluated by the Newcastle–Ottawa Scale.

Statistical Analysis

Data were analyzed by Review Manager (RevMan) (version 5.3 for Windows; Cochrane Collaboration, Oxford, UK). Risk ratios (RRs) with 95% CIs were used for dichotomous variables. We analyzed continuous data using the standard mean difference (SMD) with the corresponding 95% CI. Significant heterogeneity was determined by an *I*² greater than 50%.¹⁷ The random-effects model was chosen for analysis. *P* < .05 was considered to be statistically significant. Subgroup analysis was conducted depending on the type of AF, ablation energy, type of study, and patients with a high risk of stroke. We did not detect any publication bias owing to the small number of documents included in this meta-analysis.

RESULTS

Study Selection

We identified 1343 articles by the search strategy. The screening process is shown in Figure 1. After eliminating repetitive or irrelevant literature by reading the title and/or

HIGHLIGHTS

- This is the first meta-analysis to compare the efficacy and safety of catheter ablation (CA) combined with left atrial appendage closure (LAAC) and CA alone.
- The freedom from atrial arrhythmia rate and safety outcomes of CA combined with LAAC are similar to those of CA alone.
- Catheter ablation combined with LAAC appears to have longer procedure and fluoroscopy times than CA alone.

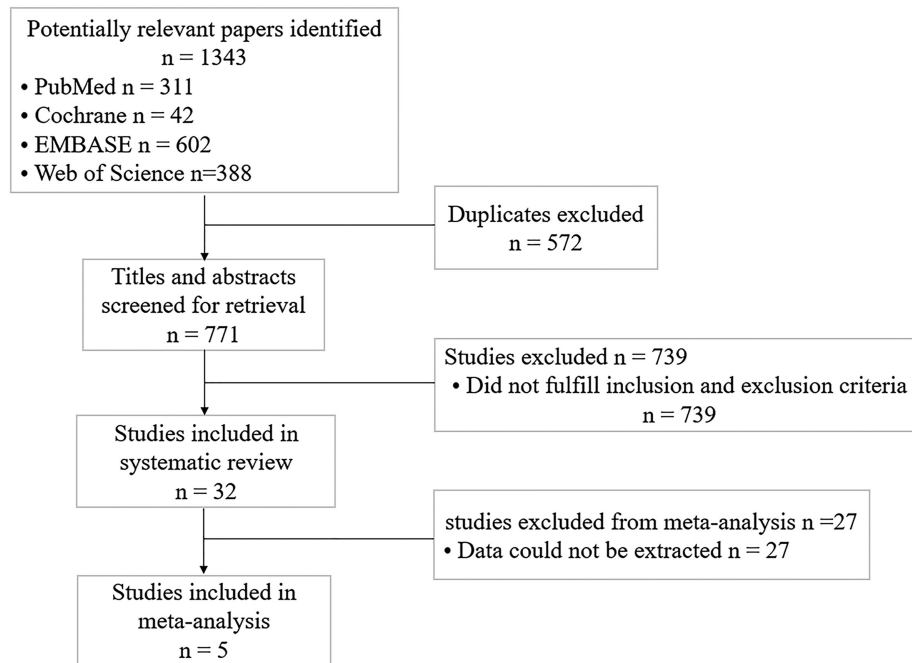


Figure 1. Flowchart of literature selection.

abstract, 32 articles were further screened. Finally, a total of 5 studies^{14-16,18,19} (1 RCT and 4 observational studies) that met the inclusion criteria were included in the meta-analysis.

Study Characteristics

Baseline characteristics of all included studies are shown in Table 1. A total of 699 patients were included in this meta-analysis, including 240 patients in the CA combined with LAAC group and 459 patients in the CA alone group. The mean time of follow-up ranged from 10.1 to 24 months. The research locations included China, Italy, and Russia. Two studies used radiofrequency energy,^{15,16} 2 used radiofrequency or cryotherapy,^{18,19} and 1 used cryoballoon ablation.¹⁴ With regard to the closure device, 2 studies only used the Watchman,^{15,16} 1 study used the Watchman and Amplatzer Cardiac Plug,¹⁸ and 1 study used the Watchman, LeFort, and Lachbes devices.¹⁴ Another study used 4 types of closure devices, including the Watchman, Lambre, Lagger, and Amplatzer Cardiac Plug.¹⁹ The average CHA₂DS₂-VASc score and HAS-BLED score ranged from 2.2 to 4.3 and 2.0 to 3.7, respectively. The risk of bias assessment of the RCT is shown in Figure 2. The observational studies were scored between 5 and 7 according to the Newcastle–Ottawa Scale score (Table 1).

Efficacy Outcomes

Our meta-analysis showed that for the main efficacy outcome, 163 (67.9%) patients in the CA combined with the LAAC group and 358 (78.0%) patients in CA alone group had freedom from atrial arrhythmia. There was no significant difference in the freedom from atrial arrhythmia rate between the 2 groups (RR=0.93, 95% CI=0.83-1.04, $I^2=0%$, $P=.21$, Figure 3A). Two^{15,18} of the included studies mentioned the procedure time. Patients in the CA combined with LAAC group showed a significantly longer procedure time than those in the

CA alone group (SMD=1.26, 95% CI=0.85-1.67, $P < .00001$, Figure 3B). Only one study mentioned the fluoroscopy time.¹⁸ Similar to the procedure time, the CA combined with LAAC group had a longer fluoroscopy time than the CA alone group (SMD=1.19, 95% CI=0.53-1.85, $P=.0004$, Figure 3C).

Safety Outcomes

With regard to safety outcomes, all included studies reported perioperative complications. The incidence of perioperative complications was 10.8% (26/240) in the CA combined with LAAC group and 9.4% (43/459) in the CA alone group. No significant difference in the rate of perioperative complications was observed between the 2 groups (RR=1.62, 95% CI=0.99-2.63, $I^2=0%$, $P=.05$, Figure 4A). After an average follow-up ranging from 10.1 to 24 months, 2 patients in the CA combined with LAAC group and 7 patients in the CA alone group suffered from TEs. There was no significant difference in the rate of TEs between the 2 groups during the follow-up period (RR=0.67, 95% CI=0.15-3.11, $I^2=0%$, $P=.61$, Figure 4B). Three studies^{15,16,18} mentioned the safety outcome of bleeding events during follow-up, and there was no significant difference in the rate of these events between the 2 groups (RR=0.67, 95% CI=0.11-3.88, $P=.65$, Figure 4C).

Subgroup Analysis

We performed subgroup analysis by the type of AF, ablation energy, and type of study. There was no significant difference in the freedom from atrial arrhythmia rate, TEs, and bleeding events during follow-up (Supplemental Tables 1-3). However, subgroup analysis by the type of study showed that there was a significant difference in the rate of perioperative complications between the CA combined with LAAC group and the CA alone group in the observational study (RR=1.67, 95% CI=1.01-2.76, $P=.04$, Supplemental Table 3). This finding might be due to the inclusion of Ren et al's study

Table 1. Baseline Characteristics of Studies

Trial (Year)	Country	Ablation Energy	Group	Sample Size (n)	Age (Years)	Female (%)	PAF (%)	LAD (mm)	CHA ₂ DS ₂ -VASC Score	HAS-BLED Score	Occlusion Device	Mean Follow-Up (Months)	Design	NOS
Mo (2020)	China	Radiofrequency†	CA + LAAC	76	69.9 ± 7.9	48.7	48.7	42.7 ± 5.7	3.6 ± 1.3	3.3 ± 1.1	Watchman	24	Observed	7
			CA alone	76	69.5 ± 7.8	52.6	50.0	41.7 ± 4.9	3.4 ± 1.4	2.6 ± 0.9		24		
Pelissero (2017)	Italy	Radiofrequency or cryoballoon	CA + LAAC	21	66.86 ± 10.35	33.3	19.0	NA	2.8 ± 1.22	3.2 ± 0.83	Watchman/ACP	14.93 ± 10.05	Observed	7
			CA alone	21	68.42 ± 10.61	28.6	14.3	NA	2.01 ± 0.93	3.1 ± 0.95		14.93 ± 10.05		
Ren (2020)	China	Cryoballoon	CA + LAAC	42	70 ± 7.6	38.1	100	45.6 ± 5.8	3.8 ± 2.1	3.7 ± 1.2	Watchman/ Lefort/ Lacbes	20 ± 9	Observed	5
			CA alone	262	66.3 ± 9.5	45.8	100	40.4 ± 5.6	2.8 ± 1.9	2.7 ± 1.2		22 ± 11		
Romanov (2015)	Russia	Radiofrequency	CA + LAAC	45	60 ± 5	37.8	53.3	49 ± 6	2.2 ± 0.6	3.5 ± 0.8	Watchman	24	RCT	-
			CA alone	44	60 ± 6	40.9	56.8	48 ± 7	2.3 ± 0.7	3.4 ± 0.8		24		
Zhu (2020)	China	Radiofrequency or cryoballoon	CA + LAAC	56	65.2 ± 6.6	41.1	42.9	45.6 ± 6.3	4.3 ± 1.8	2.0 ± 1.3	Watchman/ Lambre/ Lagger/ACP	12.3	Observed	6
			CA alone	56	64.8 ± 8.5	39.3	53.6	44.5 ± 6.2	4.1 ± 1.7	1.8 ± 1.1		10.1		

ACP, Amplatzer Cardiac Plug; CA, catheter ablation; LAAC, left atrial appendage closure; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; NA, not available; NOS, Newcastle-Ottawa Scale; PAF, paroxysmal atrial fibrillation; RCT, randomized controlled trial.

†Due to CARTO or Ensite 3D electroanatomic mapping system was used for mapping and ablation in the article, we speculate that the energy should be radiofrequency.

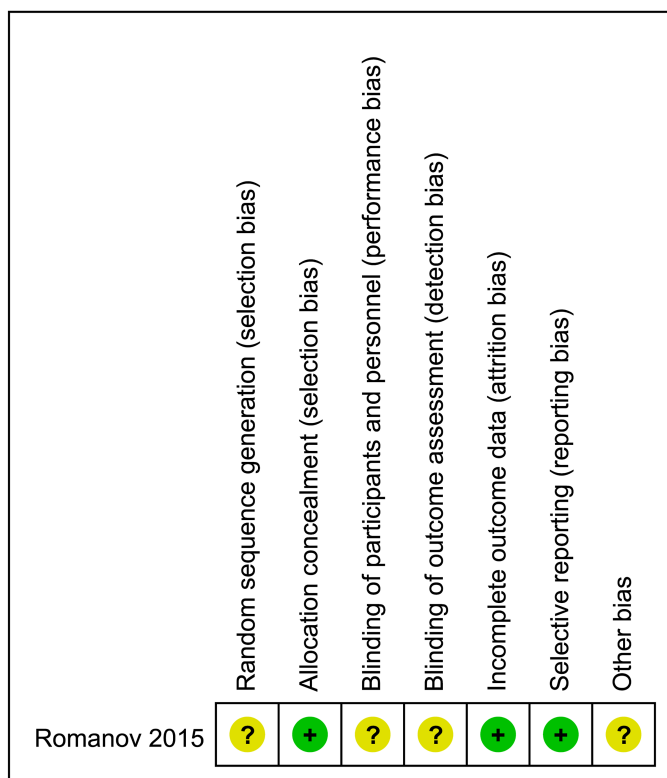


Figure 2. Risk of bias of included randomized controlled trial in the meta-analysis.

in the observational studies, which did not match with the basic characteristics of the included population (e.g., age, left atrial diameter, HAS-BLED score, CHA₂DS₂-VASc score, etc.), or because that the sample size of the 2 groups was different (42 vs. 262). These factors may have led to bias that affected the results.

In the subgroup analysis by the type of AF, ablation energy, and study type, the procedure time and fluoroscopy time showed significant differences between the groups (Supplemental Tables 4-6), which were similar to the results without subgroup analysis (Figure 3B, C).

Two studies (Romanov et al's and Zhu et al's studies)^{15,19} included patients with a high risk of stroke. In the subgroup analysis of patients with a high risk of stroke, no significant differences were observed in the freedom from atrial arrhythmia rate, perioperative complications, or TEs during follow-up between the groups (Supplement Table 7). During the follow-up, no severe bleeding events occurred in Romanov et al's study, and data of bleeding events were not reported in Zhu et al's study.

DISCUSSION

This meta-analysis showed similar freedom from atrial arrhythmia rate, perioperative complications, TEs, and bleeding events during follow-up in the CA combined with LAAC group compared with the CA alone group. Catheter ablation combined with LAAC appeared to have longer

procedure and fluoroscopy times. To the best of our knowledge, this is the first meta-analysis to compare the efficacy and safety of CA combined with LAAC and CA alone.

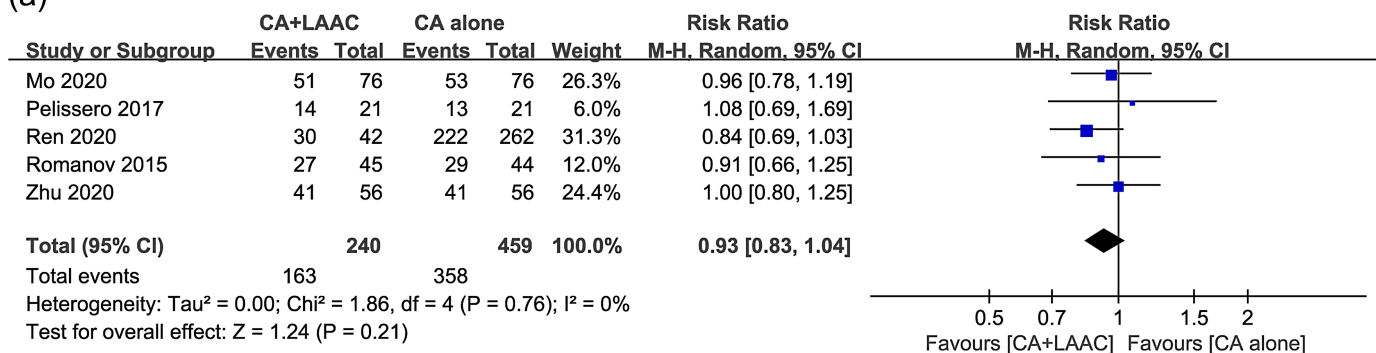
A previous meta-analysis showed that the recurrence rate of AF was 32.89% with the CA combined with LAAC strategy,²⁰ which is similar to our rate (32.08%). The authors of this previous meta-analysis speculated that the potential effect of long-term residual leakage on hemodynamics may affect the maintenance of sinus rhythm.²⁰ However, some of the excitatory foci of AF (including paroxysmal and persistent AF) originate from the LAA.²¹ Exclusion of the LAA can reduce the burden of AF.²² However, previous studies showed no difference in the AF burden between CA combined with LAAC and CA alone.^{15,18} A meta-analysis showed that LAA isolation reduced the recurrence of AF.²³ Our study showed no difference in the recurrence rate of AF between CA combined with LAAC and CA alone. This finding may be related to the fact that LAAC did not completely isolate LAA electrical activity. On the basis of combined strategy and LAA isolation, freedom from AF at 12 months was significantly higher than that of CA alone (95% vs 63%, $P=.036$).²⁴ However, the study had a small sample and was a non-RCT. Therefore, more studies are required to evaluate the efficacy and safety of the above-mentioned strategies.

Our study showed that the procedure and fluoroscopy times of CA combined with LAAC were longer than those of CA alone, which may be related to the process of different procedures. The operation of CA combined with LAAC involves the addition of LAAC to CA, leading to prolongation of the procedure and fluoroscopy times. These factors are also related to the type of AF (e.g., persistent AF may require more ablation), ablation energy, experience of the operator, and other factors.

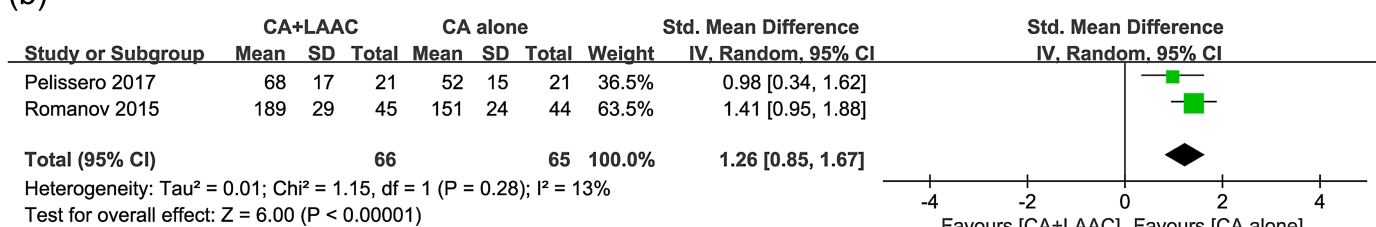
With regard to perioperative complications, because the combined strategy and CA alone use the same vascular approach, the main difference between the 2 methods is the process of LAAC. In early research of PROTECT AF, perioperative complications of LAAC reached 8.4%.²⁵ With the development of new products, optimization of the operation process, and improvement of experience, this rate has dropped to 2.7%²⁶ and even 1.44%.²⁷ In theory, ablation of the posterior wall of the left atrium and the use of transesophageal echocardiography may increase the incidence of esophageal injury, which is a perioperative complication.²⁸ However, we did not find any studies that reported the occurrence of esophageal injury or even atrial esophageal fistula.²⁹⁻³³ Postoperative gastroscopy may be able to detect and further evaluate the degree of esophageal injury. Our meta-analysis did not show a difference in perioperative complications between CA combined with LAAC and CA alone, which may be attributed to the low complication rate of LAAC itself.

The risk of stroke in patients with nonvalvular AF is significantly higher than that in patients without.³⁴ Anticoagulant therapy is an important measure for preventing thrombosis.

(a)



(b)



(c)

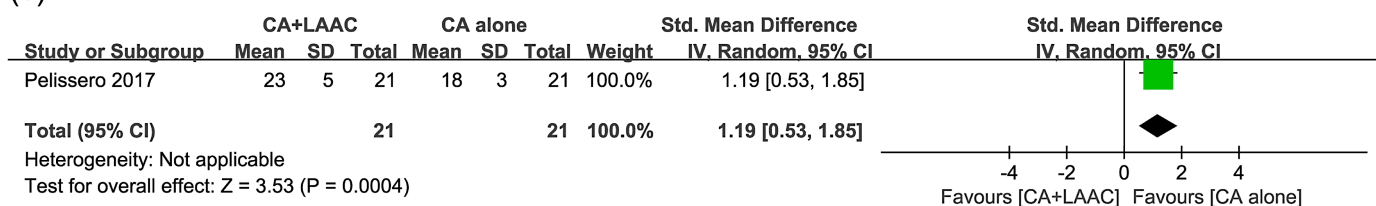


Figure 3. Forest plots of efficacy outcomes for CA + LAAC versus CA alone. (A) Freedom from atrial arrhythmia rate; (B) procedure time; (C) fluoroscopy time. CA, catheter ablation; LAAC, left atrial appendage closure.

However, some patients have a high risk of stroke and also have contraindications to anticoagulation therapy. In the 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) and 2020 ESC guidelines for the management of AF, LAAC is recommended for such a group of patients as class IIb.^{5,35} Catheter ablation for AF has been recommended by multiple guidelines.^{5,36} Various studies have examined the strategy of CA combined with LAAC.^{29,37-39} A 2-year follow-up study from 11 centers showed that the composite end-point ratio of transient ischemic attack, ischemic stroke, or systemic thromboembolism was 1.09/100 patient-years with CA combined with LAAC.⁴⁰ A meta-analysis that included 18 studies (2 of them were RCTs) to evaluate the efficacy and safety of CA combined with LAAC showed that the incidence of stroke/transient ischemic attack was 0.01,¹³ compared with 0.008 in our study. Another meta-analysis of 12 RCTs showed no significant difference in TEs between the CA group and the non-ablation group (2.25% vs. 2.88%,

P=.28).⁴¹ Our meta-analysis showed that the incidence of TEs in the CA alone group was 1.53%. The difference in rate between our study and the previous study may be due to the different numbers and types of literature that met the inclusion criteria. Moreover, our study showed that there was no difference in the incidence of TEs between the CA combined with LAAC and CA alone groups. Even in patients with the removal of the LAA and maintenance of sinus rhythm, atrial scarring caused by ablation injury or progression of the disease remains a risk of stroke.⁴² On one hand, thrombus formation in non-contractile left atrial space or appendage stump due to incomplete resection.⁴² On the other hand, we speculate that the LAA may be the “preferred site” for atrial thrombus formation. When the LAA is occluded, other atrial sites (e.g., the left atrial cavity and right atrial appendage) still have a risk of thrombus formation.

With regard to safety outcomes, the occurrence of bleeding events is related to anticoagulation or antiplatelet strategy.

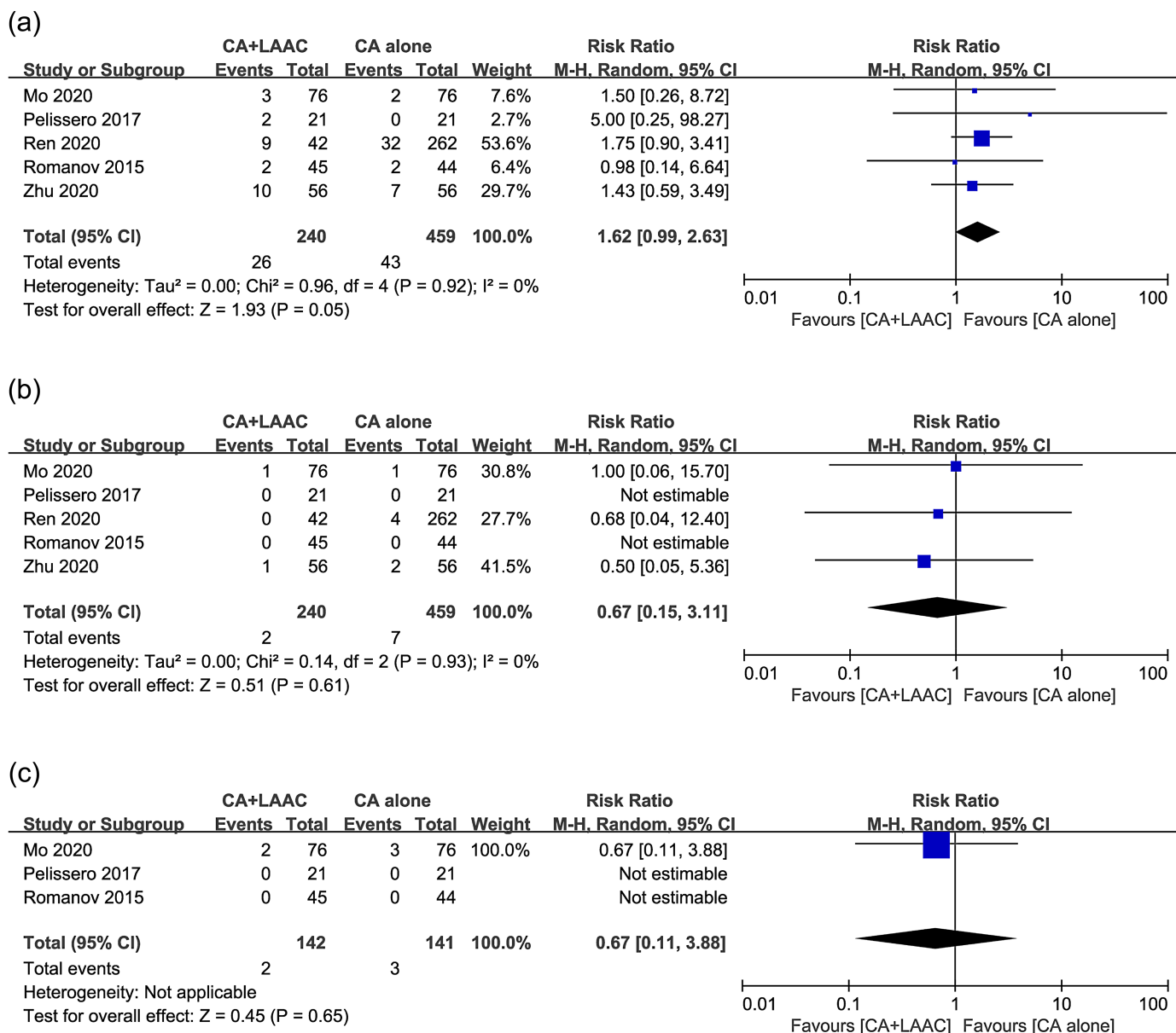


Figure 4. Forest plots of safety outcomes for CA + LAAC versus CA alone. (A) perioperative complications; (B) thromboembolic events during follow-up; (C) bleeding events during follow-up. CA, catheter ablation; LAAC, left atrial appendage closure.

In the CA combined with LAAC group, the final strategy after the operation is frequently long-term, single antiplatelet therapy (e.g., aspirin). In the CA alone group, the strategy with a high CHA₂DS₂-VASc score tends to be continuation of oral anticoagulants (OACs). Studies have compared aspirin with OACs, warfarin, and novel OACs for the risk of bleeding. In a multinational, population-based cohort study, no difference was found in the risk of gastrointestinal bleeding between aspirin and rivaroxaban overall and low-dose rivaroxaban (≤ 15 mg/day).⁴³ A meta-analysis showed that rivaroxaban 10 mg once daily or 5 mg twice daily and apixaban 5 mg twice daily were comparable to aspirin for intracranial hemorrhage.⁴⁴ A meta-analysis that included 29 studies showed a similar risk of bleeding between warfarin and novel OACs.⁴⁵ Our study did not show any difference in bleeding

events between the CA combined with LAAC and CA alone groups.

The purpose of performing LAAC is mainly expected to benefit patients who are at a high risk of stroke and bleeding. In our subgroup analysis of patients with a high risk of stroke, patients with CA combined with LAAC and those with CA alone had similar rates of freedom from atrial arrhythmia, perioperative complications, and TEs during follow-up. In the analysis of bleeding events during the follow-up period, one study did not show any severe bleeding events, and the other study did not report data on bleeding events. However, because this subgroup analysis only included 2 studies and the follow-up time was not long enough, we were not able to accurately assess the role of LAAC in this part of the population.

Study Limitations

Our study has the following limitations. (1) The number of articles in this meta-analysis and the sample size of each study were small. (2) Of the 5 studies included, 4 of them were observational studies and only 1 was an RCT. (3) Different CA techniques and occlusion devices used in each study may have led to bias, such as residual peri-device leakage after different occlusion devices. (4) The follow-up time of the included studies was insufficient. (5) The conclusion of fluoroscopy time was based on data from a single-center observational study. (6) Subgroup analysis of patients with a high risk of stroke only included 2 studies. All of the above-mentioned factors may have affected the evaluation of the outcome events. A larger sample size and multicenter RCTs are required to evaluate the combined strategy of CA with LAAC and CA alone.

CONCLUSION

Our meta-analysis shows no significant difference in freedom from atrial arrhythmia rate, perioperative complications, TEs, and bleeding events during follow-up in patients who have CA combined with LAAC compared with those who have CA alone. Catheter ablation combined with LAAC tends to have a longer procedure and fluoroscopy time than CA alone. More RCTs are required for further study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.W., G.Z.; Design – A.W., G.Z.; Supervision – G.Z.; Fundings – G.Z.; Materials – None; Data collection &/or processing – A.W., Z.X., J.J.; Analysis &/or interpretation – A.W., Z.X.; Literature search – A.W., J.J., Z.X.; Writing – A.W., G.Z.; Critical review – A.W., J.J., Z.X., G.Z.

Declaration of Interests: The authors declare no conflict of interest.

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Supplementary Material

1 SEARCH STRATEGY

- #1. Atrial Fibrillation [MesH]
- #2. atrial fibrillat* [title/abstract]
- #3. auricular fibrillat* [title/abstract]
- #4. atrium fibrillat* [title/abstract]
- #5. AF [title/abstract]
- #6. #1 or #2 or #3 or #4 or #5
- #7. ablat* [title/abstract] or isolat* [title/abstract]
- #8. "left atrial appendage" [title/abstract] or LAA [title/abstract]
- #9. occlu* [title/abstract] or clos* [title/abstract]
- #10. #8 and #9
- #11. #6 and #7 and #10

Supplement Table 1. Subgroup Analysis for Binary Variable Outcomes According to the Type of AF

Outcome	Trials	Participants	Risk Ratio (95% CI)	P
Freedom from atrial arrhythmia rate				
Paroxysmal AF	1	304	0.84 (0.69, 1.03)	.09
Paroxysmal/persistent/long-standing persistent AF	4	395	0.98 (0.85, 1.12)	.72
Test for subgroup differences $\chi^2 = 1.44$, $df = 1$, $P = .23$, $I^2 = 30.5\%$				
Perioperative complications				
Paroxysmal AF	1	304	1.75 (0.90, 3.41)	.10
Paroxysmal/persistent/long-standing persistent AF	4	395	1.47 (0.72, 3.00)	.29
Test for subgroup differences $\chi^2 = 0.13$, $df = 1$, $P = .72$, $I^2 = 0\%$				
Thromboembolic events during follow-up				
Paroxysmal AF	1	304	0.68 (0.04, 12.40)	.79
Paroxysmal/persistent/long-standing persistent AF	4	395	0.67 (0.11, 4.05)	.66
Test for subgroup differences $\chi^2 = 0.00$, $df = 1$, $P = .99$, $I^2 = 0\%$				
Bleeding events during follow-up				
Paroxysmal AF	-	-	-	-
Paroxysmal/persistent/long-standing persistent AF	3	283	0.67 (0.11, 3.88)	.65
Test for subgroup differences -				

AF, atrial fibrillation.

Supplement Table 2. Subgroup Analysis for Binary Variable Outcomes According to Ablation Energy

Outcome	Trials	Participants	Risk Ratio (95% CI)	P
Freedom from atrial arrhythmia rate				
Radiofrequency	2	241	0.95 (0.79, 1.13)	.54
Cryoballoon	1	304	0.84 (0.69, 1.03)	.09
Radiofrequency or cryoballoon	2	154	1.01 (0.83, 1.24)	.89
Test for subgroup differences $\chi^2=1.70$, $df=2$, $P=.43$, $I^2=0\%$				
Perioperative complications				
Radiofrequency	2	241	1.25 (0.32, 4.79)	.75
Cryoballoon	1	304	1.96 (0.86, 4.47)	.11
Radiofrequency or cryoballoon	2	154	1.74 (0.64, 4.68)	.28
Test for subgroup differences $\chi^2=0.32$, $df=2$, $P=.85$, $I^2=0\%$				
thromboembolic events during follow-up				
Radiofrequency	2	241	1.23 (0.34, 4.51)	.75
Cryoballoon	1	304	1.75 (0.90, 3.41)	.10
Radiofrequency or cryoballoon	2	154	1.58 (0.67, 3.72)	.29
Test for subgroup differences $\chi^2=0.23$, $df=2$, $P=.89$, $I^2=0\%$				
Bleeding events during follow-up				
Radiofrequency	2	241	0.67 (0.11, 3.88)	.65
Cryoballoon	-	-	-	-
Radiofrequency or cryoballoon	1	41	-	-
Test for subgroup differences -				

Supplement Table 3. Subgroup Analysis for Binary Variable Outcomes According to the Type of Study

Outcome	Trials	Participants	Risk Ratio (95% CI)	P
Freedom from atrial arrhythmia rate				
RCT	1	89	0.91 (0.66, 1.25)	.56
Observational studies	4	610	0.94 (0.83, 1.05)	.27
Test for subgroup differences $\chi^2=0.02$, $df=1$, $P=.88$, $I^2=0\%$				
Perioperative complications				
RCT	1	89	0.98 (0.14, 6.64)	.98
Observational studies	4	610	1.67 (1.01, 2.76)	.04
Test for subgroup differences $\chi^2=0.28$, $df=1$, $P=.60$, $I^2=0\%$				
Thromboembolic events during follow-up				
RCT	1	89	-	-
Observational studies	4	610	0.67 (0.15, 3.11)	.61
Test for subgroup differences -				
Bleeding events during follow-up				
RCT	1	89	-	-
Observational studies	2	194	0.67 (0.11, 3.88)	.65
Test for subgroup differences -				

RCT, randomized controlled trial.

Supplement Table 4. Subgroup Analysis for Continuous Variable Outcomes According to the Type of AF

Outcome	Trials	Participants	Standard Mean Difference (95% CI)	P
Procedure time (minutes)				
Paroxysmal AF	-	-	-	
Paroxysmal/persistent/long-standing persistent AF	2	131	1.26 (0.85, 1.67)	<.00001
Test for subgroup differences -				
Fluoroscopy time (minutes)				
Paroxysmal AF	-	-	-	
Paroxysmal/persistent/long-standing persistent AF	1	21	1.19 (0.53, 1.85)	.0004
Test for subgroup differences -				

AF, atrial fibrillation.

Supplement Table 5. Subgroup Analysis for Continuous Variable Outcomes According to Ablation Energy

Outcome	Trials	Participants	Standard Mean Difference (95% CI)	P
Procedure time (minutes)				
Radiofrequency	1	89	1.41(0.95, 1.88)	<.00001
Cryoballoon	-	-	-	
Radiofrequency or cryoballoon	1	42	0.98(0.34, 1.62)	.003
Test for subgroup differences $\chi^2 = 1.15, df = 1, P = .28, I^2 = 12.9\%$				
Fluoroscopy time (minutes)				
Radiofrequency	-	-	-	-
Cryoballoon	-	-	-	-
Radiofrequency or cryoballoon	1	42	1.19 (0.53, 1.85)	.0004
Test for subgroup differences -				

Supplement Table 6. Subgroup Analysis for Continuous Variable Outcomes According to the Type of Study

Outcome	Trials	Participants	Standard Mean Difference (95% CI)	P
Procedure time (minutes)				
RCT	1	89	1.41 (0.95, 1.88)	<.00001
Observational studies	1	42	0.98 (0.34, 1.62)	.003
Test for subgroup differences $\chi^2 = 1.15, df = 1, P = .28, I^2 = 12.9\%$				
Fluoroscopy time (minutes)				
RCT	-	-	-	-
Observational studies	1	42	1.19 (0.53, 1.85)	.0004
Test for subgroup differences -				

RCT, randomized controlled trial.

Supplement Table 7. Subgroup Analysis of Patients with High Risk of Stroke

Outcome	Trials	Participants	Risk Ratio (95% CI)	P
Freedom from atrial arrhythmia rate	2	201	0.97 (0.81, 1.16)	.74
Perioperative complications	2	201	1.34 (0.59, 3.00)	.48
Thromboembolic events during follow-up	2	201	0.50 (0.05, 5.36)	.57