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Research article

Percutaneous or surgical LAAO for stroke prevention in patients with atrial fibrillation: A network meta-analysis

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A R T I C L E I N F O

Keywords:
Atrial fibrillation
Stroke prevention
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Surgical left atrial appendage occlusion
Network meta-analysis

A B S T R A C T

Background: Stroke, which is mainly caused by thrombus formation in the left atrial appendage, represents the most prevalent complication of atrial fibrillation (AF). Both percutaneous left atrial appendage occlusion (p-LAAO) and surgical LAAO (s-LAAO) are used to treat AF and prevent stroke events. However, no head-to-head randomized controlled trials (RCTs) compared these strategies.
Objective: To examine the efficacy and safety of diverse strategies for reducing stroke risk using a network meta-analysis (NMA).
Methods: PubMed, EMBASE, and Cochrane repositories were explored to identify RCTs involving p-LAAO or s-LAAO, and five were included for NMA. This investigation adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses. The NMA was pooled using the Bayesian random effect framework. All findings were expressed as odds ratios accompanied by a 95 % confidence interval.
The primary efficacy endpoint was any stroke (AS), and the secondary efficacy endpoint was combined AS and systematic embolism (AS/SE). The primary and secondary safety endpoints were major bleeding (MB) and all-cause death (ACD), respectively.
Results: Our meta-analysis incorporated 6337 individuals diagnosed with AF. The NMA demonstrated a reducing trend in AS and AS/SE for s-LAAO versus p-LAAO, while p-LAAO showed a benefit in reducing MB and ACD.
Conclusions: and Relevance: s-LAAO could potentially benefit individuals at elevated risk for stroke, whereas p-LAAO may be linked to a reduced likelihood of bleeding.

1. Introduction

Atrial fibrillation (AF) stands as the most prevalent arrhythmia linked to elevated rates of illness and death [1]. Moreover, with the progress of population aging and the improvement of detection methods, the incidence of AF is expected to increase by 2–3 times in the future, which may have major public health implications [2]. Stroke, mainly caused by thrombus formation in the left atrial appendage

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(LAA), represents the most prevalent clinical issue. Although the efficacy and safety of oral anticoagulants (OACs), encompassing vitamin K antagonists and direct oral anticoagulants (DOACs), have been widely clarified in previous studies [3,4], unavoidable bleeding events [5], and nonadherence [6,7] limit their application.

LAA occlusion (LAAO) serves as an alternative approach to stroke prevention. Previous research has shown the viability of transcatheter left atrial appendage (t-LAAC) utilizing devices such as the Amplatzer-Amulet [8] or Watchman [9]. A recently published randomized study revealed the effect of a surgical left atrial appendage (s-LAAO) [10]. These new strategies highlight the need to reconsider their comparative efficacy and safety by evaluating the new evidence. However, no direct head-to-head comparisons between s-LAAO and p-LAAO have been reported. Therefore, we searched for high-level evidence published over the past decade and performed a meta-analysis.

2. Methodologies

This systematic review and meta-analysis was recorded in the International Prospective Register of Systematic Reviews (CRD 42021277272) and was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplement 1).

2.1. Study selection criteria

Clinical investigations evaluating approaches for stroke prevention among AF patients were incorporated in this meta-analysis. The selection criteria for our research encompassed [1] randomized controlled trials (RCTs) published in the last decade (from January 2013 to June 2023) with at least two comparator arms [2], primary data on clinical endpoints, including the occurrence of stroke and bleeding events, and [3] follow-up duration of at least 12 months. Review papers, single-arm investigations, redundant studies, mechanistic research, abstracts, and conference presentations were omitted. No constraints regarding language, publication date, or publication status were enforced. We additionally examined references from systematic reviews and meta-analyses of associated studies.

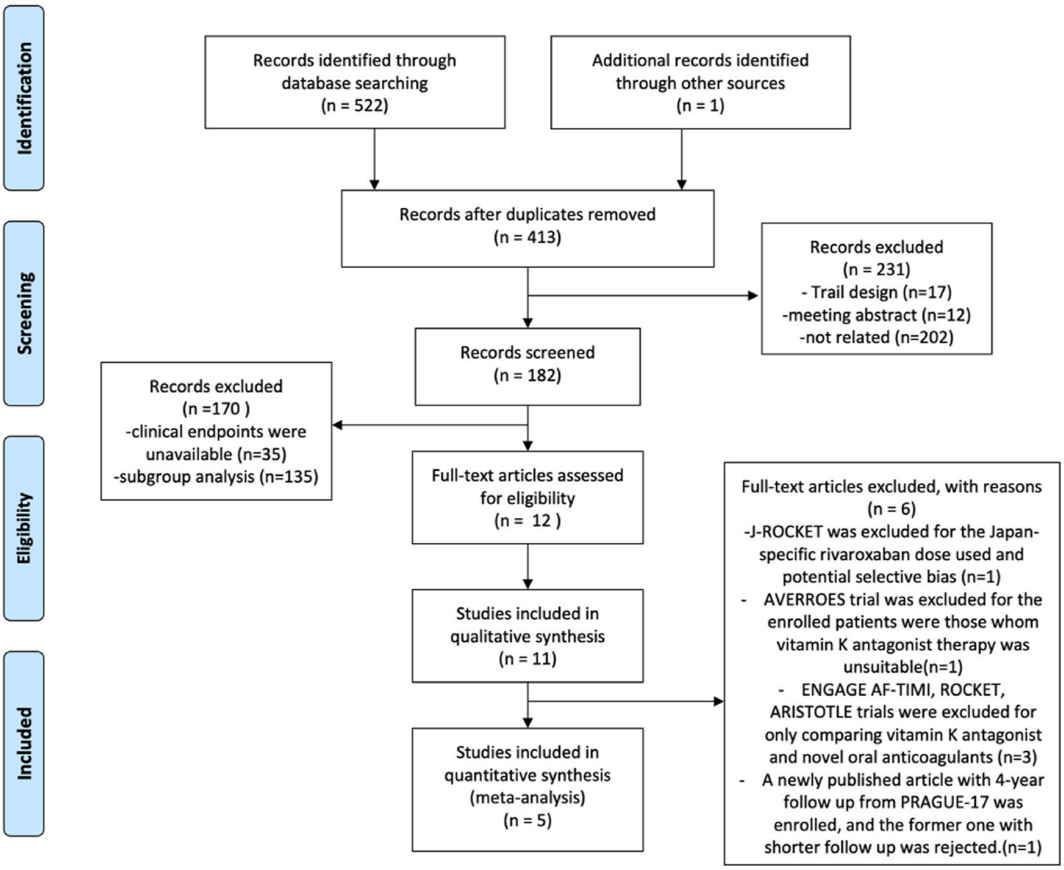

Fig. 1. Flow chart of the study design.

2.2. Exploration approach and data resources

We employed search terms associated with AF and LAA occlusion to explore the PubMed, EMBASE, and Cochrane repositories spanning from January 2013 through June 2023. The keywords for the search strategy are provided in Supplement 2, and the study flow diagram is shown in Fig. 1. In the end, we included 5 studies.

2.3. Endpoint measures

The primary efficacy endpoint was any stroke (AS), and the secondary efficacy endpoint was combined AS and systematic embolism (AS/SE). The primary and secondary safety endpoints were major bleeding (MB) and all-cause death (ACD), respectively. We also analyzed the composite endpoints (including major adverse events [MAE] and net adverse clinical events [NACE]). An MAE was defined as a composite of stroke, embolism, and death. NACE was a combination of ischemic and bleeding events. We prioritized utilizing information from the most extended available monitoring duration as the long-range results. More detailed information on the endpoint definitions can be found in Supplement 7.

2.4. Statistical analysis

Initially, we conducted a Bayesian random-effects NMA to concurrently evaluate various stroke prevention approaches. We calculated the odds ratios (ORs) of the treatment impacts for the two strategies and their corresponding 95 % credible intervals utilizing Markov chain Monte Carlo techniques. All computations were executed using the gemtc package (version 0.8–7) and rjags package (version 4–10) in R (version 3.6.1). We presumed that the direct and indirect evidence for a treatment comparison exhibited no discrepancy, a concept referred to as evidence consistency. To address effect heterogeneity across studies, we incorporated random effects in the NMA and quantified the extent of heterogeneity. We employed the package's default configurations, including non-informative prior distributions with four parallel chains, where each chain comprised 50,000 samples following a 20,000-sample burn-in period.

Moreover, to assess and order treatment protocols, we computed probability rankings (i.e., the likelihood of a strategy being optimal, second-best, or least effective for a given outcome) and the Surface under the Cumulative Ranking (SUCRA). SUCRA serves as a quantitative summary that considers both the magnitude and uncertainty of the estimated effect for each protocol. A higher SUCRA value signified superior outcome performance.

Sensitivity assessment was conducted employing a leave-one-out approach to determine if the aggregated findings were affected by any individual study. Additionally, we implemented a trial sequential analysis (TSA) [11,12] to evaluate the susceptibility of the current meta-analysis's effect magnitude to potential future data alterations, thus examining the risk of type I error and the necessity for subsequent research.

Table 1
Study design and baseline characteristics of patients.

Study characteristics					Baseline characteristics of patients			
Trial name	Study design	Number	Follow-up[a]	Treatments#	Age (years)	Male (%)	CHA2DS2-VASc score$	Permanent AF (%)&
LAAOS III	randomized	4770	3.8 years	Occlusion	71.3 ± 8.4	68.0	4.2 ± 1.5	29.1
				Control	71.1 ± 8.3	67.0	4.2 ± 1.5	29.6
PRAGUE-17	open-label, randomized, non-inferiority	402	4 years	DOAC	73.4 ± 6.7	66.7	4.7 ± 1.5	41.3
				LAAC	73.2 ± 7.2	64.7	4.7 ± 1.5	35.8
PROTECT AF	randomized, unblinded, non-inferiority	707	5 years	Device Group	71.1 ± 8.8	70.4	2.2 ± 1.2	34.6
				Warfarin Group	72.7 ± 9.2	70.1	2.3 ± 1.2	38.1
PREVAIL	randomized, unblinded, non-inferiority	407	5 years	Device Group	74.0 ± 7.4	67.7	3.8 ± 1.2	15.6
				Warfarin Group	74.9 ± 7.2	74.6	3.9 ± 1.2	15.9
LAAOS II	randomized open trial	51	1 year	Occlusion	77.4 ± 76.8	76.9	/	15.4
				no occlusion	74.6 ± 7.6	76.0	/	20.0

[a] In order to obtain the data from a long-term follow-up, we extract the outcome from a new meta-analysis (Reddy VY et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. Journal of the American College of Cardiology 2017; 70:2964–2975.) combined PROTECT AF and PREVAIL trial.

3. Results

3.1. Studies and patient characteristics

A combined 6337 individuals with AF from five RCTs were enrolled in our meta-analysis. LAAOS III [10], PRAGUE-17 [13], PROTECT AF [14], PREVAIL [15], and LAAOS II [16], directly compared non-pharmacologic strategies (LAAO) and pharmacologic strategies (OAC), while no head-to-head trial directly estimated the difference between p-LAAO and s-LAAO. Therefore, we conducted an NMA to obtain these outcomes. A summary of the studies and patients' baseline characteristics is shown in Table 1.

3.2. Results for TSA

The TSAindicated that the findings derived from the accessible data supported our investigation into AS prevention (Fig. 2A), as the Z-value trajectory fell within the beneficial zone. Consequently, despite not reaching the target sample size, it seems improbable that subsequent research would alter this outcome. Regarding the MB occurrence, the existing data also favored LAAO and proved conclusive, given that the Z-value trajectory resided in the zone of substantial benefit, and the necessary sample size was attained (Fig. 2B). The TSA for the other endpoints is shown in Supplement Figs. 2–4.

3.3. Results for NMA

We conducted a head-to-head comparison among the four strategies (s-LAAO, p-LAAO, DOACs, and control groups); the network is shown in Supplement Fig. 5.

The NMA demonstrated a reducing trend in efficacy endpoints (OR for AS 0.69; OR for AS/SE 0.74) for s-LAAO versus p-LAAO (Fig. 3A), but the effect was not statistically significant. Of the four treatment strategies, s-LAAO, which had the highest SUCRA value (8.4), was ranked as the most effective in reducing the efficacy endpoints. (Supplement 10.4). p-LAAO showed the best performance in improving safety endpoints compared with s-LAAO (OR for MB, 0.48; OR for ACD, 0.68) (Fig. 3B).

Rank probability and SUCRA analyses yielded similar results (Supplement 10.4). A 2-dimensional forest plot of ORs for the primary efficacy and safety endpoints is presented in Fig. 4. The results of composite endpoints can be found in Fig. 3C. The detailed analyses are presented in Supplement 10.

As depicted in Supplement 10.7, multiple supplementary sensitivity analyses are executed. We found that excluding the data of the three studies that compared the DOACs and control groups as part of the sensitivity assessment yielded outcomes comparable to those of the primary analysis (Supplement 10.7.1). We also found similar outcomes when combining DOACs and controls in the OAC regime (Supplement 10.7.2). All fitted models converged well (Supplement 10.5), and our NMA showed no indications of statistical inconsistency (Supplement 10.6).

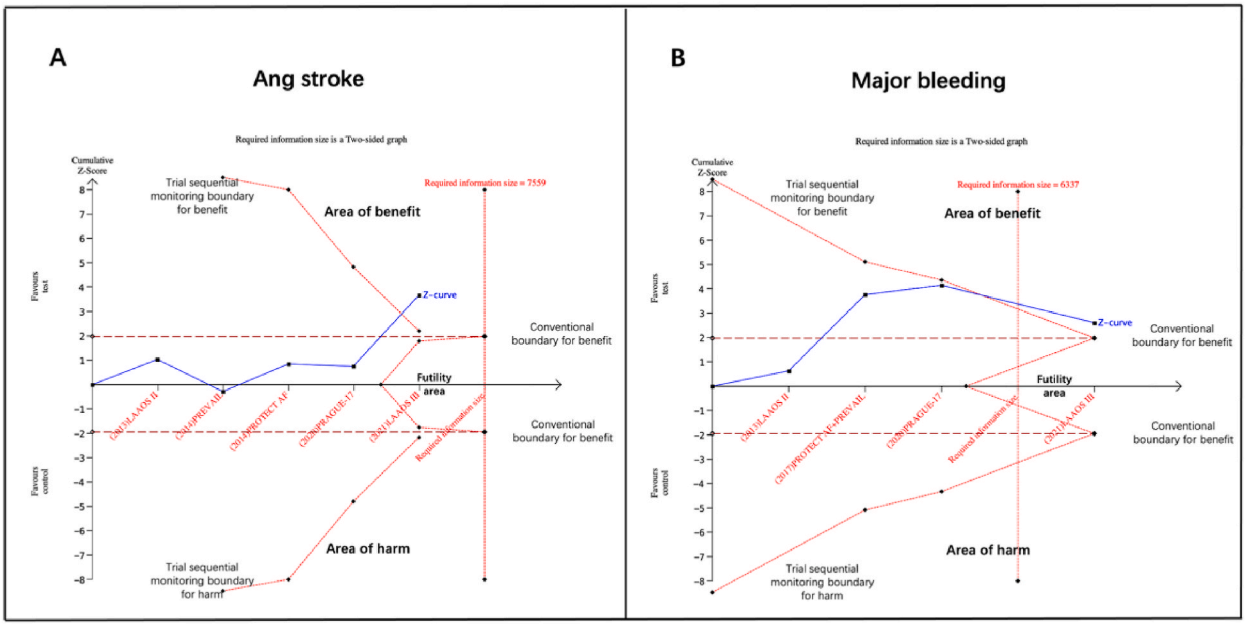

Fig. 2. Trial sequential analysis for Ang stroke (A) and Major bleeding (B) end points.

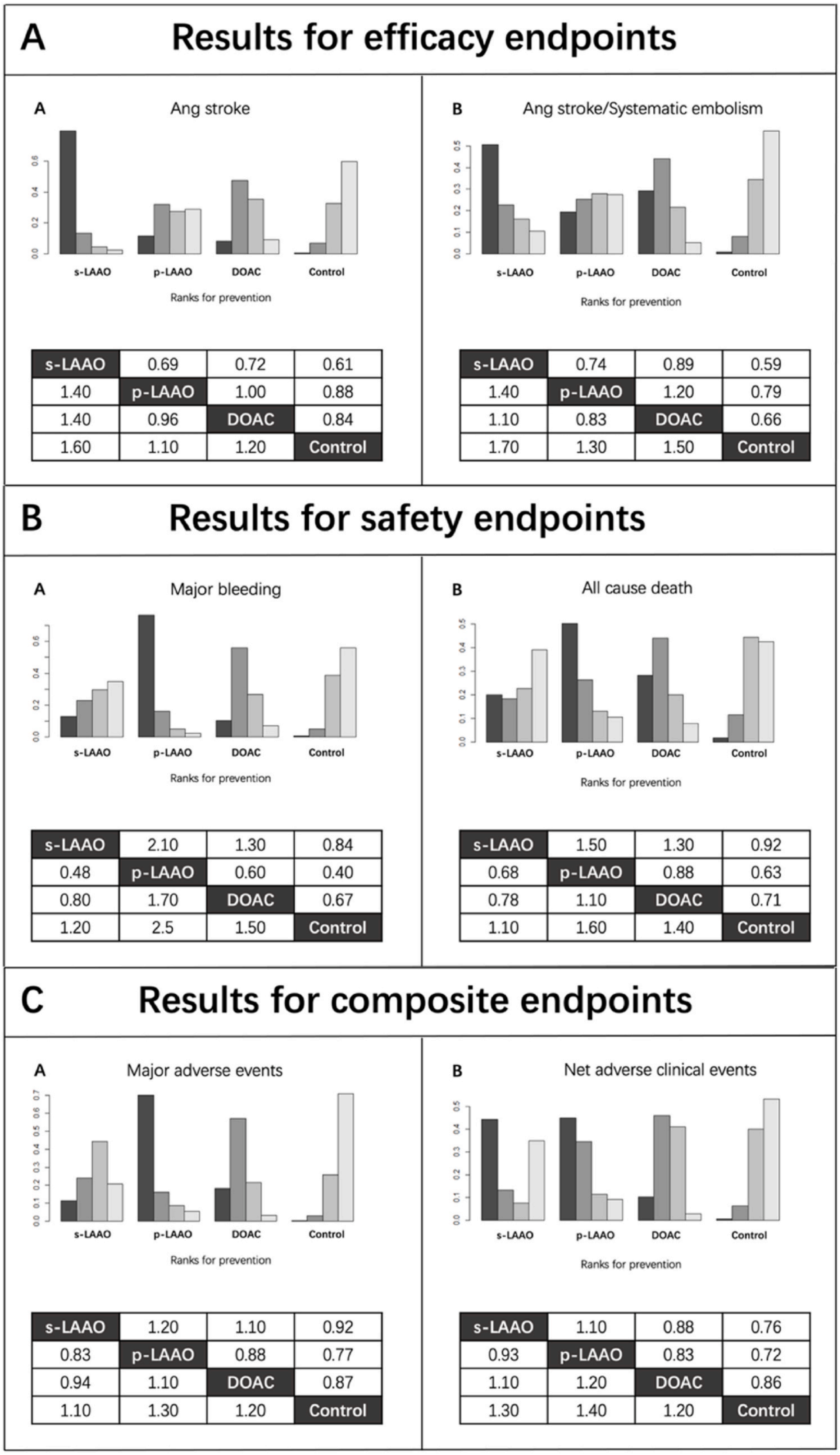

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Fig. 3. Pooled results for clinical endpoints from network meta-analysis. Odds ratio (95 % credible intervals) between row and column treatment strategies are reported. Rank probabilities were also provided for each endpoint.

4. Discussion

LAAO is not recommended as a first-line treatment for stroke prevention in the latest guideline [17,18] for AF management. LAAO is considered an alternative strategy only when patients are at high bleeding risk and contradictory to OACs. The Watchman device and surgical exclusion of LAA alone showed non-inferiority when directly compared to OACs. A large RCT(10) on patients with an associated cardiac surgical procedure has been published, and other data on new devices [19] for p-LAAO are also available. Therefore, conducting a meta-analysis of existing data is necessary to provide a basis for future revisions of the guidelines and new research directions.

We noticed that data comparing p-LAAO and OACs were available, and the LAAOS II and LAAOS III studies also provided evidence for s-LAAO. However, no direct head-to-head comparisons between s-LAAO and p-LAAO have been reported. NMA provides an extension beyond the traditional PMA, which allows for comparisons of different treatments that lack head-to-head studies. As demonstrated by our NMA, s-LAAO performed better than p-LAAO in reducing the efficacy endpoints and was ranked as the most effective among the four strategies. However, this situation was reversed in terms of the safety endpoints. This result was similar to the sensitivity analyses identified for PMA.

There are several possible reasons for this discrepancy. First, the Watchman device employed in the PROTECT AF and PREVAIL trials consisted of a self-expanding nitinol frame with fixation anchors, which has been available commercially since 2009 [20]. Recent advancements in medical device effectiveness have led to the gradual adoption of Next Generation Watchman FLX Devices in clinical settings. Research by Matthew et al. demonstrates that transcatheter LAAO utilizing the Watchman FLX exhibits reduced in-hospital MAE rates compared to its predecessor. This finding could positively impact the risk-benefit balance of p-LAAO for stroke prevention in atrial fibrillation patients [21]. Despite the demonstrated efficacy of p-LAAO in stroke prevention, there are some concerns regarding size mismatch and subsequent residual cavities. In Domenico's research, a strong agreement was found in LAA sizing between pre-procedural transesophageal echocardiography (TEE) and periprocedural three-dimensional intracardiac echocardiography (3D-ICE). 3D-ICE proved markedly superior efficacy relative to traditional two-dimensional intracardiac echocardiography (2D-ICE) in determining FLX dimensions and could potentially provide enhanced guidance throughout the implantation process. The adoption of these innovative technologies and devices could potentially influence our experimental outcomes [22]. However, as of now, s-LAAO has achieved better LAA closure. Although patients with LAAO III (4.2) had a higher CHA2DS2-VASc score than those in the PROTECT AF (2.2) and PREVAIL (3.8) studies, s-LAAO still performed better than p-LAAO in stroke prevention according to our NMA, and 70 % of patients were still on OAC treatment after the s-LAAO procedure for a long time [10]. Patients implanted with an LAA closure device were treated with anti-platelet drugs. Different postoperative antithrombotic therapies could also affect the clinical outcomes. Next, patients in LAAOS III and LAAOS II were slated for cardiac procedures due to separate indications, which primarily pertained to surgical closure of the appendage executed as an accompanying intervention rather than an isolated surgical or endovascular occlusion. Potential differences among participants against p-LAAO could also affect the final results.

Although roughly 90 % of left atrial thrombi are found in the LAA [23], all of the above findings highlight that therapy at the site of thrombus formation is necessary and effective for stroke prevention in individuals with AF. Moreover, AF is an independent risk factor for stroke events that cannot be eliminated by LAA closure, and postoperative OAC treatment seems to be somewhat effective. LAA

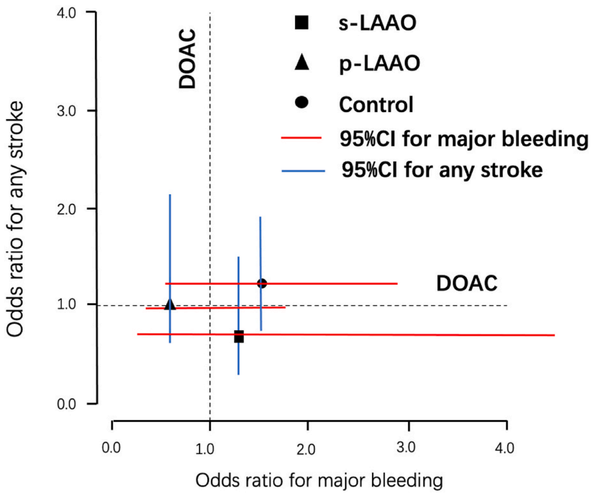

Fig. 4. Bivariate end point plot for primary endpoints (ang stroke and major bleeding). In this plot, the relative effects of different stroke prevention regimens vs DOAC (set as reference, dotted lines) in Fig. 2 both in terms of any stroke (vertical axis) and major bleeding (horizontal axis) are contemporary plotted. The points with different shape indicate the odds ratios, whereas the colored lines indicate the CIs.

occlusion diminishes stroke risk through a distinct mechanism relative to anticoagulant medications. Therefore, in LAA closure, both s-LAAO and p-LAAO should not be treated as only an "alternative" treatment for patients' intolerance to OACs, which seems to present additional protection against stroke risk when OAC is co-administrated. Clinicians should treat the LAAO strategy as a complement to OAC rather than as a replacement.

To the best of our understanding, this meta-analysis represents the initial head-to-head comparison of different stroke prevention strategies. We found that s-LAAO may be suitable for individuals at elevated stroke risk, whereas p-LAAO may be linked to a reduced bleeding risk. We hope our research will introduce new ideas and directions to the field of LAAO. The new-generation LAA closure device, Watchman FLX, features a length reduction of 10–20 % compared to its predecessor, allowing it to accommodate a broader spectrum of LAA anatomical variations, encompassing those with shallow configurations. Furthermore, the extended polyethylene terephthalate fabric contributes to optimal sealing and reendothelialization [24]. We noticed that PROTECT AF and PREVAIL were designed to establish non-inferiority to OAC, and we call for a large-scale RCT to verify the superiority of these new devices. Moreover, further exploration of the optimal postoperative anticoagulation regimen is warranted to balance stroke prevention and bleeding risk.

5. Conclusion

Our head-to-head NMA indicated that s-LAAO is better than p-LAAO in diminishing stroke risk yet appears to elevate bleeding risk. However, p-LAAO was associated with fewer bleeding events than s-LAAO. Our results indicate that LAAO performed better as a stroke-reducing approach in individuals with AF. In terms of the operational strategy selection, s-LAAO is suitable for individuals with elevated stroke risk, while p-LAAO correlates with reduced bleeding risk.

Ethics approval and consent to participate

Not available.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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CRediT authorship contribution statement

Zihan Zhao: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Changjiang Yang:** Visualization, Validation, Software, Investigation. **Wenchang Zhang:** Writing – review & editing, Formal analysis, Conceptualization. **Changjian He:** Visualization, Investigation, Formal analysis. **Guojie Ye:** Software, Formal analysis, Data curation. **Tengfei liu:** Software, Investigation, Data curation. **Chunhua Ding:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

AF	atrial fibrillation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ORs	odds ratios
CI	confidence intervals
SUCRA	Surface under the Cumulative Ranking
RCTs	Randomized Controlled Trials
PMA	pairwise meta-analysis

NMA	network meta-analysis
LAAO	left atrial appendage occlusion
OAC	Oral anticoagulants
DOAC	direct oral anticoagulants
AS	any stroke
AS/SE	any stroke and systematic embolism
MB	major bleeding
ACD	all cause death

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37730.

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