Effect of oral anticoagulation therapy in atrial fibrillation patients with a history of intracranial hemorrhage: a systematic review and meta-analysis

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Background: Use of oral anticoagulants (OACs) among atrial fibrillation (AF) patients surviving intracranial hemorrhage (ICH) represents a challenge due to the difficult balance between thrombosis and hemorrhage.

Methods: We performed a systematic review and meta-analysis to evaluate the effectiveness and safety of OACs resumption in AF patients with a history of ICH during long-term follow-up. The outcome measures were ischemic stroke (IS), IS or systemic embolism (SE), all-cause death, recurrent ICH and major bleeding. Meta-analyses of pooled odds ratios (ORs) were conducted with random-effects models.

Results: A total of 2 randomized controlled trials (RCTs) and 9 observational studies were included, covering 18,115 patients with AF and a history of ICH. The risk of IS was not statistically different between the group of patients receiving OAC therapy and the no-OAC group (OR: 0.41, 95% CI: 0.16 to 1.0, P=0.05). The rate of IS or SE (OR: 0.42, 95% CI: 0.27 to 0.70, P=0.0008), all-cause death (OR: 0.54, 95% CI: 0.41 to 0.70, I²=42%, P<0.00001) were significantly decreased in patients receiving OAC therapy compared to those with no-OAC therapy. The pooled OR estimates for ICH recurrence (OR: 1.46, 95% CI: 0.94 to 2.26, P=0.09) and major bleeding (OR: 1.35, 95% CI: 0.86 to 2.11, P=0.19) were not significantly increased in the OAC therapy group. There was heterogeneity between the results of observational studies and RCTs in terms of all-cause death (I²=83.4%).

Conclusions: Considering the heterogeneity in results between observational studies and RCTs, as well as the limited number and small size of RCTs, high grade evidences are needed. Pooled analysis is required when more RCTs are completed in the future to resolve this therapeutic dilemma.

Keywords: Oral anticoagulants (OACs); atrial fibrillation (AF); intracranial hemorrhage (ICH); thromboembolic events; bleeding

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Introduction

Atrial fibrillation (AF) increases the risk of stroke and thromboembolism five-fold (1). The use of oral anticoagulants (OACs), either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs), has been demonstrated to reduce stroke, systemic embolism (SE) and mortality in AF patients when compared to control or placebo treatments (2). However, one of the most disabling and life-threatening complication of OACs is spontaneous intracranial hemorrhage (ICH) (3), although the risk is lower with DOACs (4). Results of most randomized clinical trials were not stratified by the history of ICH. This leads to a therapeutic dilemma as to whether starting or permanently avoiding anticoagulation is the best long-term strategy for AF patients after ICH. Clinicians have to weigh the risk of thromboembolism against the risk of recurrent ICH (5,6). Individual studies have attempted to address this challenge but have not yet been able to provide clear guidance on this issue because of conflicting results. Due to the current paucity of high-quality evidence and the absence of definitive guidelines in this area (7), the effectiveness and safety of restarting OACs after ICH remain unclear.

This is a systematic review and meta-analysis of observational studies as well as the latest randomized controlled trials (RCTs) to evaluate the effectiveness and safety of restarting OACs in ICH survivors with AF. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-582/rc) (8).

Methods

Literature search

PubMed, Embase, Cochrane Library, and ClinicalTrials.gov were systematically searched from the inception of each database till December 29, 2021, under MeSH terms and random words. Keywords used to query the databases included: 'atrial fibrillation', 'intracranial hemorrhage or intracerebral hemorrhage', and 'oral anticoagulants'. No linguistic restrictions were applied. Searching strategies are listed in the Supplementary file (Appendix 1). Additional records were procured by a hand-search of the references of primitive literature so as to not miss any eligible studies.

Definitions of outcomes

Our outcome measures were ischemic stroke (IS), IS or SE, and all-cause death for the evaluation of effectiveness; and recurrence of ICH, and major bleeding for the assessment of safety.

All of the studies identified outcomes according to the *International Classification of Diseases (ICD-9 or ICD-10)* diagnosis codes. Major bleeding event was defined according to the International Society on Thrombosis and Hemostasis criteria, including fatal bleeding and/or symptomatic bleeding in a critical area of organ (e.g., intracranial, intraspinal, intraocular, and retroperitoneal) and/or bleeding causing a decrease of ≥20 g/L (≥1.24 mmol/L) in the hemoglobin level or leading to transfusion of ≥2 U of whole blood or red cells (9).

Eligibility criteria and study selection

All published studies comparing oral anticoagulation therapy versus no anticoagulation in AF patients who had survived a non-traumatic ICH were included. Specifically, the criteria for inclusion were as follows: (I) design: prospective or retrospective observational cohorts, RCTs; (II) participants: non-traumatic ICH survivors with persistent or paroxysmal AF as indication for anticoagulation treatment with ICH including intracerebral, subarachnoid, and subdural hemorrhage; (III) intervention: OACs, including VKA or DOACs, regardless of the type, dosage and time interval of OAC prescription for stroke prevention; (IV) control: avoiding OAC after surviving ICH; (V) Outcome measures: long-term outcomes including IS, IS or SE, all-cause death, ICH recurrence and major bleeding events ≥3 months after exposure to OACs or avoiding OACs. For those studies that considered 3 different types of antithrombotic medication exposure (OACs, antiplatelet agents, and no antithrombotic medication), the latter two categories combined were regarded as the no-OAC group in this study. Studies were excluded if at least one of the following situations applied: (I) no relevant data provided (e.g., unfinished studies, reviews, commentaries, case reports, small case series); (II) studies focused on traumatic ICH; (III) single-arm studies without a comparison group; (IV) studies without follow-up or report of outcomes.

Two of the authors (Mei Liu and Yue Hou) carried out the initial selection separately, first based on titles and abstract and then on the full text of all possible candidate studies, according to the criteria above. Wherever there was a disagreement in the lists of studies to be included that the two authors produced separately, the whole research team met for discussions till a consensus was eventually reached.
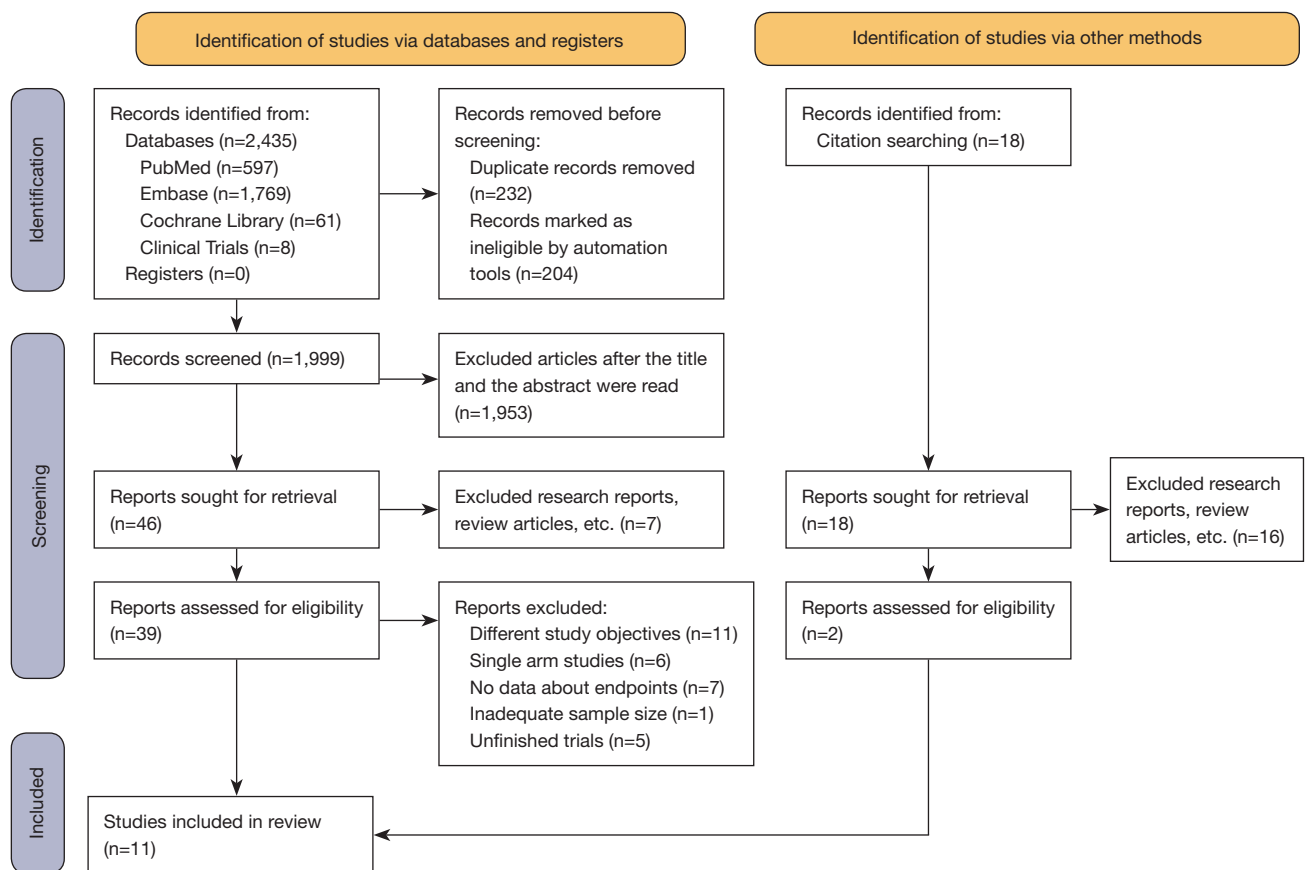
Figure 1 PRISMA flowchart: study selection.

Data extraction and study quality assessment

Data were extracted independently by two of the authors (Mei Liu and Yue Hou) using a common extraction form. Study characteristics including the following data were documented: first author, year of publishing, study design, demographic and clinical characteristics of the patients, sample size, type of hemorrhage, type of OACs, CHA_2DS_2-VASc and HAS-BLED scores, timing of OAC start after hemorrhage, and follow-up duration. The quality of the studies was assessed according to the Cochrane handbook (10).

Statistical analysis

All statistical analyses were performed using Review Manager (Version 5.2) and Stata (Version 12.0). The numbers of events and sample size of each group were collected. The odds ratio (OR) with a 95% confidence interval (CI) was calculated for each included study, and then pooled by a random-effect model using the Mantel-Haenszel (M-H) method. Subgroup analysis was performed based on the type of study (non-RCT, RCT). The Cochrane Q tests and I^2 statistics were used to evaluate heterogeneity, where $I^2 > 50\%$ indicated significant heterogeneity. If heterogeneity was detected, single-variable meta-regression was performed to explore underlying factors. The method of excluding one study at a time was used for sensitivity analysis. Publication bias was assessed using the funnel plots and further calculated by the egger's tests, with $P < 0.05$ considered an indicator of statistical significance.

Results

Study selection

The flow chart of document retrieval was presented in *Figure 1*. A total of 2,453 articles from four databases and citation searching were evaluated. After initial screening based on title and abstract, and after research reports and review articles were excluded, the full texts of 39 articles

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from databases and 2 articles from citation searching were assessed for eligibility. Two of the authors then assessed them separately, and 30 were excluded due to the following reasons: (I) 11 excluded because of a difference in their study objectives with ours; (II) 6 excluded because of an absence of a comparison group; (III) 7 excluded because of lack of data about endpoint; (IV) one feasibility study excluded because of inadequate sample size; and (V) 5 excluded as unfinished studies. Finally, 11 studies were included in our current meta-analysis: 2 completed RCTs (11,12) (APACHE-AF, NCT02565693 and SoSTART, NCT03153150) and 9 observational studies [2 prospective observational (13,14) and 7 retrospective studies (15-21)].

Study characteristics

This meta-analysis covered a total of 18,115 patients (43.6% female) who had AF and a history of ICH from 11 studies. A total of 2,818 (15.6%) of these patients received OACs, and 15,297 (84.4%) did not. Two studies (11,15) included only patients with intraparenchymal hemorrhage as the index ICH, while others widened coverage to include subdural and subarachnoid hemorrhages. Three studies (13,16,18) enrolled patients who received VKAs as the OAC agent, one RCT (11) used apixaban and the other seven studies included patients that used DOACs or VKA as the anticoagulation therapy. For the evaluation of ischemic stroke or SE, all-cause death, 10 studies were eligible (11-15,17-21). There were 10 studies included for the evaluation of ICH recurrence (11-13,15-21). For the evaluation of ischemic stroke (11,12,15,16,18) and major bleeding (11,13-15,18,19,21), 5 and 7 studies were included respectively. Characteristics of the included studies were described in detail in *Table 1*.

Study results

Effectiveness outcomes of OAC therapy *vs.* no-OAC therapy
IS
A total of 5 studies compared the occurrence of IS among patients who received OAC therapy and patients who avoided it. Neither the subgroup analysis of the observational studies nor that of the RCTs showed statistical significance between the OAC therapy group and no-OAC group, while the overall pooled estimate indicated that the risk of IS was not statistically different between the OAC group and the no-OAC group, though the upper CI was

on the borderline (5 studies, 13,744 participants, OR: 0.41, 95% CI: 0.16 to 1.00, I^2=77%, P=0.05) (*Figure 2A*).
IS or SE
When it came to IS or SE events, 10 studies were pooled for analysis with the M-H random model. Within these 10 studies, OAC therapy was found to be associated with a lower risk only in the subgroup of 8 observational studies (4,894 participants, OR: 0.44, 95% CI: 0.26 to 0.75, I^2=57%, P=0.002), while analysis of the 2 RCTs showed no result of statistical significance (304 participants, OR: 0.37, 95% CI: 0.05 to 2.79, I^2=81%, P=0.34). To sum up, as shown in *Figure 2B*, the overall results indicated a better protective effect in the OAC group than in the no-OAC group regarding IS or SE (10 studies, 5,198 participants, OR: 0.42, 95% CI: 0.26 to 0.70, I^2=59%, P=0.0008).
All-cause death
A total of 10 studies compared the all-cause mortality between patients who received OAC and those who did not. No statistical significance could be observed in the subgroup analysis of RCTs (2 studies, 304 participants, OR:1.18, 95% CI: 0.60 to 2.33, I^2=10%, P=0.63), while the subgroup of observational studies revealed a significantly lower risk of all-cause mortality in the OAC group than the no-OAC group (8 studies, 4,894 participants, OR: 0.49, 95% CI: 0.40 to 0.60, I^2=9%, P<0.00001). There was significant heterogeneity between the result of subgroup studies of observational studies and RCTs in terms of all-cause death (I^2=83.4%). As was shown in *Figure 2C*, the overall pooled OR of all-cause mortality was significantly lower for patient receiving OAC therapy than for those avoiding it (10 studies, 5,198 participants, OR: 0.54, 95% CI: 0.41 to 0.70, I^2=42%, P<0.00001).

Safety outcomes of OAC therapy *vs.* no-OAC therapy
ICH recurrence
For ICH recurrence, 10 studies were included for analysis. Neither the included 2 RCTs (304 participants, OR: 2.50, 95% CI: 0.85 to 7.35, P=0.10) nor the 8 observational studies (17,665 participants, OR: 1.36, 95% CI: 0.84 to 2.21, P=0.22) revealed statistically significant difference between the OAC and the no-OAC groups. To sum up, the rate of ICH recurrence was not significantly increased in patients receiving OAC compared with those avoiding it (10 studies, 17,969 participants, OR: 1.46, 95% CI: 0.94 to 2.26, I^2=66%, P=0.09). The detailed data were shown in *Figure 3A*.
##### Major bleeding event
Seven studies provided data that allowed for a comparison of the occurrence of major bleeding events in the OAC

Table 1 Characteristics of the studies included in the meta-analysis

Study	Location	Design	Type of hemorrhage	Total number	Age, mean/ median, y	Female, %	HAS-BLED, median	CHA₂DS₂-VASc, median	FU, medium, mo	Time internal to resumption, medium (SD/IQR)	OAC Group Therapy	OAC Group Number	No-OAC Group Therapy	No-OAC Group Number
Abrantes 2022, (15)	Portugal	Retrospective observational	Spontaneous intracerebral hemorrhage	95	75.2	48	4	4	24	N/A	DOAC/VKA	40	No-OAC	55
Chao 2016, (16)	Taiwan	Retrospective observational	Spontaneous ICH	12,917	74.7	43	N/A	6	39.6	N/A	VKA	1,154	APA/no-ATM	11,763
Nielsen 2015, (17)	Denmark	Retrospective observational	OACs-associated ICH	1,752	78	38	3.2	3.9	12	34 d	DOAC/VKA	303	APA/no-ATM	1,449
Nielsen 2017, (13)	Denmark	Prospective observational	Spontaneous ICH	1,325	76.8	43.3	3.6	4.1	9.2	81.3 (62.8) d	VKA	377	No-OAC	948
Park 2016, (18)	Korea	Retrospective observational	ICH	428	68.4	65.9	3.5	3.3	39.5	117.5 (235.7) d	VKA	254	No-OAC	174
Perreault 2019, (19)	Canada	Retrospective observational	ICH	683	83	53.1	2.6	3.9	12	N/A	DOAC/VKA	260	No-OAC	423
Poli 2018, (14)	Italy	Prospective observational	ICH	146	77	39.7	N/A	4.2	18	1–3 months	DOAC/VKA	55	APA/no-ATM	91
Sadighi 2020, (20)	US	Retrospective observational	OACs-associated ICH	93	76.2	46	N/A	4	26	56 (52.5) d	DOAC/VKA	38	No-OAC	55
Salman 2021, (12)	UK	RCT, open-label	Spontaneous ICH	203	79	36	2	4	14.4	115 [49–265] d	DOAC/VKA	101	No-OAC	102
Schreuder 2021, (11)	Netherland	RCT, open-label	OACs-associated intracerebral hemorrhage	101	78	46	N/A	4	22.8	46 [21–71] d	Apixaban	50	No-OAC	51
Wu 2021, (21)	Taiwan	Retrospective observational	OACs-associated ICH	372	71	52.1	2.5	4.2	12	Within 6 weeks	DOAC/VKA	186	No-OAC	186

HAS-BLED score includes poorly controlled hypertension (1 point), abnormal renal (1 point), abnormal liver function (1 point), prior stroke (1 point), prior major bleeding or predisposition (1 point), elderly (age >65; 1 point), and concomitant drugs with antiplatelet effect (anti-platelets or NSAIDs, 1 point), and excessive alcohol usage (1 point). CHA₂DS₂-VASc score: a score for predicting the risk of stroke or thromboembolism in atrial fibrillation, based on congestive heart failure (1 point); hypertension (1 point); age ≥75 years (2 points); diabetes (1 point); previous stroke, transient ischemic attack, or thromboembolism (2 points); vascular disease (1 point); age 65–74 years (1 point); and sex category (1 point for female). FU, follow-up; SD, standard deviation; IQR, interquartile range; OAC, oral anticoagulants; N/A, not available; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; ICH, intracranial hemorrhage; APA, anti-platelet agent; ATM, antithrombotic medication; RCT, randomized controlled trial; NSAID, nonsteroidal anti-inflammatory drug.
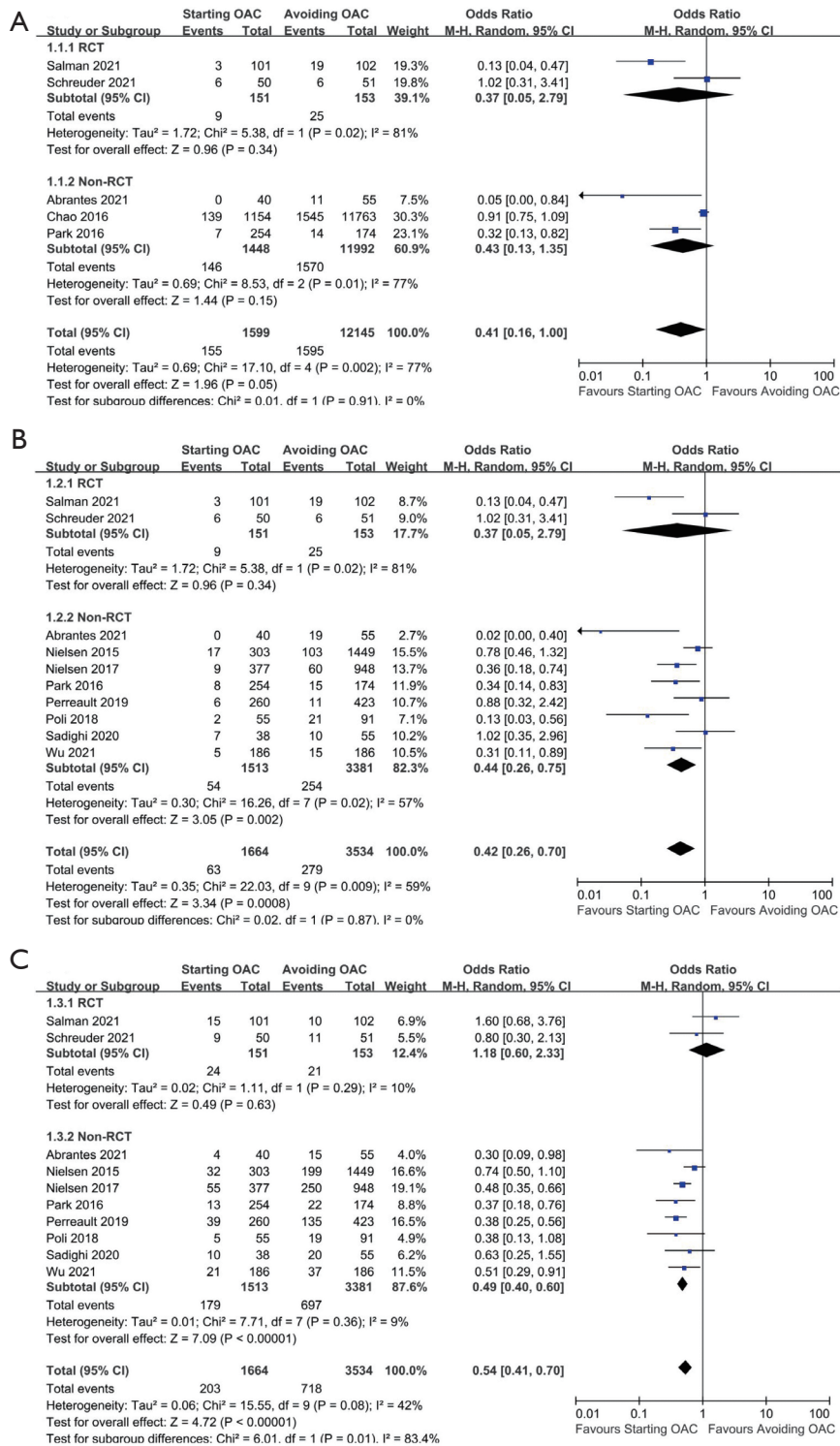
Figure 2 Forrest-plot of efficacy outcomes. (A) Ischemic stroke; (B) ischemic stroke or systemic embolism; (C) all-cause death. OAC, oral anticoagulants; M-H, Mantel-Haenszel test; CI, confidence interval; RCT, randomized controlled trial.
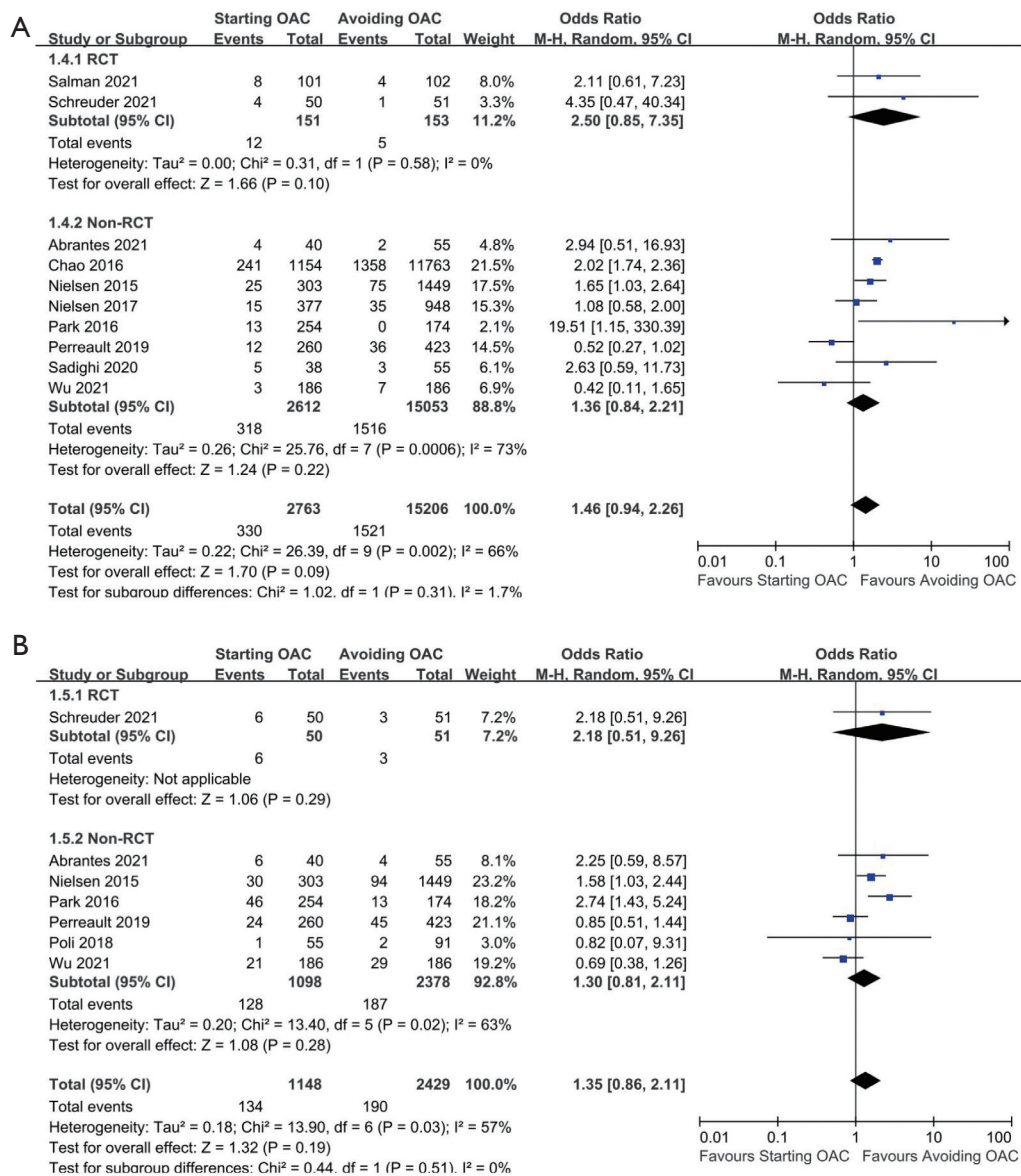
Figure 3 Forrest-plot of safety outcomes. (A) Intracranial hemorrhage recurrence; (B) major bleeding. OAC, oral anticoagulants; M-H, Mantel-Haenszel test; CI, confidence interval; RCT, randomized controlled trial.

group and the no-OAC group. Neither the included RCT, APACHE-AF (101 participants, OR: 2.18, 95% CI: 0.51 to 9.26, P=0.29) nor the remaining 6 observational studies (3,476 participants, OR: 1.30, 95% CI: 0.81 to 2.11, P=0.28) revealed statistically significant difference. The overall results, shown in *Figure 3B*, indicated no significant increase in the rate of major bleeding events in patients receiving OAC compared to those avoiding it (7 studies, 3,577 participants, OR: 1.35, 95% CI: 0.86 to 2.11, I²=57%, P=0.19).

Publication bias and quality assessment

Publication bias was determined using the funnel plots (*Figure 4*). Symmetry funnel plots of each outcome measure could be obtained from visual inspection of relevant test results. In addition, the egger's test was conducted to precisely detect the publication bias and no statistically significant bias was observed (detailed information provided in Figure S1).

Overall, 8 out of 11 (72.7%) studies reported consecutive
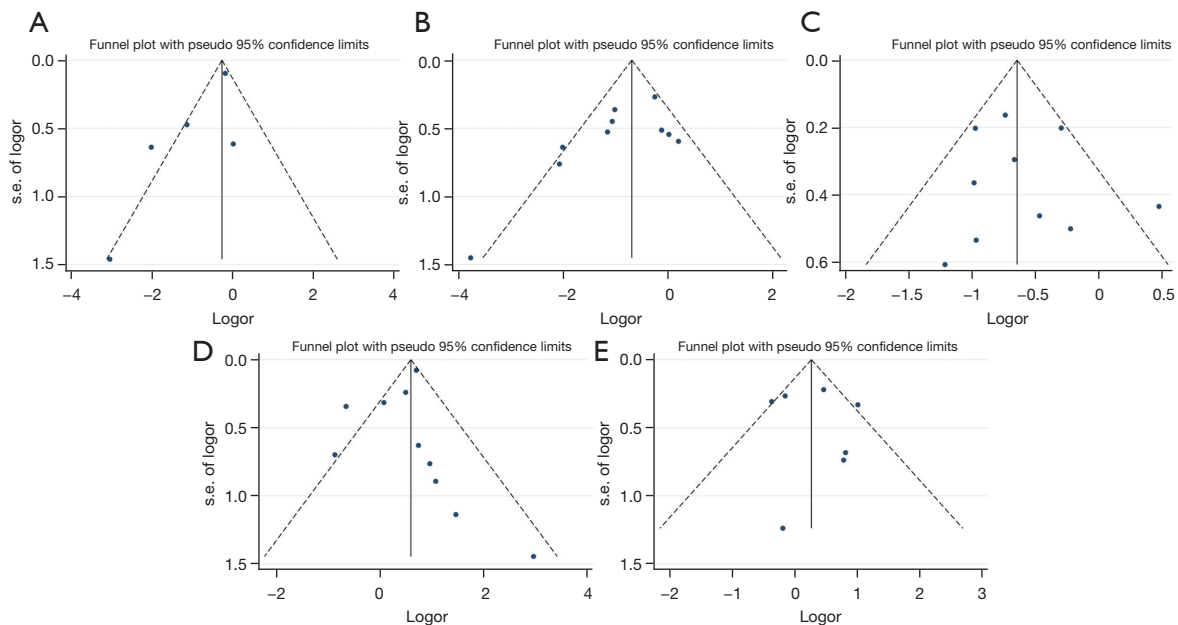
Figure 4 Funnel-plot of assessing publication bias. (A) Ischemic stroke; (B) ischemic stroke or systemic embolism; (C) all-cause death; (D) intracranial hemorrhage recurrence; (E) major bleeding.

recruitment. Selection bias was minimized in 2 studies through the random selection of patients in RCTs. Blinding of outcome assessment was performed in these 2 RCTs. The investigators were not blinded to the anticoagulant status in any of the included studies. Attrition bias was found in one study. The risk of a reporting bias was low in all studies. Potential risks of bias are presented in Table S1.

Sensitivity analysis and investigation of heterogeneity

Sensitivity analysis was performed by excluding one study a time. As a result, the pooled effect did not change substantially. Given the moderate to significant heterogeneity in the random effects model assessing all the outcomes, a meta-regression was performed to identify factors that could have caused the heterogeneity. Studies were appraised based on potential factors such as mean age, gender (percentage of female), type of ICH (inclusion of intraparenchymal hemorrhages only), CHA_2DS_2-VASc score, and type of OACs (VKAs only or VKAs/DOACs). Each of these factors was assessed individually. Consequently, gender was found to be a potential confounding factor that may contribute to the heterogeneity in the evaluation of all-cause death (coefficient =0.969, SE =0.012, t=−2.54, 95% CI: 0.942 to 0.997, P=0.035, adjusted

R^2=0.93). Detailed information of the meta-regression was presented in Table S2 and Figure S2.

Discussion

For AF patients who survived ICH, whether to prescribe OACs is a dilemma that clinicians usually face, as it is difficult to balance between the risk of thromboembolism and a recurrent hemorrhage. Anticoagulation therapy for AF patients surviving ICH was still a controversial issue and decisions are mainly based on observational studies and expert consensus (2,5,6,22). Therefore, we performed this most comprehensive meta-analysis, the first of this kind to include two most recently published RCTs (11,12), investigating the optimal therapeutic strategy and comparing the effectiveness and safety of starting OAC therapy and avoiding OAC in AF patients with a history of ICH during long-term follow-up. In this systematic review and meta-analysis of 11 studies with more than 18,000 AF patients surviving ICH, we found that starting OAC therapy after ICH was associated with a lower occurrence of IS or SE, and all-cause death than avoiding OAC therapy, without increasing ICH recurrence or major hemorrhage event significantly.

As for effectiveness outcome, our meta-analysis showed

that starting OACs after ICH was associated with a significant decrease in the occurrence of IS or SE, and all-cause death, by 58% and 46% respectively compared to avoiding OAC therapy. However, subgroup study of non-RCTs and RCTs showed heterogeneity: starting OAC was only revealed to have a lower risk in the observational studies, while for RCTs, the result had no statistical significance between starting OAC and avoiding OAC in terms of the risk of IS/SE and all-cause death. The included observational studies are highly prone to selection bias and confounding by indication because clinicians may avoid the prescription of OAC in patients with a short life expectancy or at a higher risk of death. Randomization procedure secured well balanced patient and imaging characteristics in RCTs, while in observational studies, people with larger intracerebral hemorrhage volumed were less likely to be prescribed with OAC. What is more, in the retrospective observational studies, some deaths may be attributed to undiagnosed stroke and some minor strokes may have remained undetected, making it possible that the risk of IS was underreported.

When it comes to the safety outcome, the main concern regarding OAC resumption is the recurrence of ICH. Previous research showed that ICH survivors carried a significant risk of recurrent ICH when treated with VKA (23). We found no significant increase in the risk of a recurrent ICH or major bleeding for those receiving OAC, although the point estimate for the pooled OR was 46% and 35% higher than when OAC was avoided. Subgroup analysis showed consistency in the RCT group and the non-RCT group. However, certain limitations of published studies, especially the fact that most of them are observational studies, may have influenced this finding. In particular, the results might be influenced by confounding by indication and selection bias in the observational studies, in which patients at a higher perceived risk of bleeding may have been less likely to be prescribed with OAC, while those with smaller hematomas or a lower risk of bleeding are more likely to receive OAC. Moreover, not all studies provided information on hematoma volume and hematoma location, or if the ICH was a first-time bleed or recurrent hemorrhage. The lack of data on baseline information regarding ICH precluded further evaluation.

The optimal timing of starting anticoagulant treatment after ICH with AF patients was inconclusive. A cohort study suggested that anticoagulant treatment might be initiated 7 to 8 weeks after ICH in ICH survivors with AF to balance benefits from the treatment against the risk of a recurrent

bleeding (24). In the studies included in our meta-analysis, the time interval between ICH and the start of the OAC therapy varied from 34 days to 117.5 days. However, such information was not provided in some of the studies, which precluded further evaluation.

Three studies included in our systematic review enrolled only patients who used VKAs as the OACs, while patients in 7 studies were prescribed with DOACs or VKAs as the anticoagulation therapy. Further subgroup analyses to compare the effect of DOACs with that of VKA or to compare the effect of different types of DOACs were not possible because relevant information was missing in several studies. DOACs have been shown to be associated with a significantly lower risk of hemorrhagic complications including ICH compared to VKA (1,25,26). Apixaban significantly reduces the risk of stroke and SE compared to aspirin without increasing the risk of ICH (27). Therefore, DOACs could be a better option for AF patients surviving ICH. One of the RCTs included in our meta-analysis, Apixaban Versus Antiplatelet Drugs or no Antithrombotic Drugs After Anticoagulation-Associated Intracerebral Hemorrhage in Patients with Atrial Fibrillation (APACHE-AF) pilot study (11), addressed stroke prevention with apixaban in ICH survivors with AF. However, the result showed that the risks of IS or recurrent ICH were similar in participants allocated to apixaban and in those assigned to avoiding anticoagulation. This study had a small sample size of 101 patients, and as a result, event rates of the outcome had a wide 95% CI and the assessment of the efficacy and safety of OACs was inconclusive. This highlights the importance of meticulous interpretation of the aggregate results and the subgroup results of RCTs.

Our study shed light on the limitations of existing studies focusing on OAC use in AF patients with ICH. First, most of the studies were observational studies lacking randomization, which might affect the reliability of the results, although there were two completed open-label RCTs. Therefore, this meta-analysis was subject to the limitations of the non-blinded, mostly retrospective observational design of the included studies. Secondly, the two RCTs included in our meta-analysis, which has a low risk of selection bias and little indication confounding, nevertheless, also had limitations in that the sample sizes were small and as a result, the assessment of the efficacy and safety of OACs was inconclusive. Thirdly, there existed heterogeneity among the included studies, including considerable heterogeneity between RCTs and non-RCTs in terms of evaluating all-cause mortality. Meta-

regression found that gender might be a confounding factor attributing to the heterogeneity in the evaluation of all-cause death. Besides, wide variations in the demographics of enrolled patients and study designs, including the different follow-up durations in the individual studies, time interval before starting OAC, or the existence of co-morbidities, might have contributed to the heterogeneity. Fourthly, the selection criteria may vary across individual studies as some included only patients with intraparenchymal hemorrhage while others widened their coverage to include also subdural and subarachnoid hemorrhages. Lastly, information on blood pressure control, which was a known risk factor of ICH recurrence and might affect the outcome (28), was not provided in all the included studies.

Considering the heterogeneity of the existing studies, more high-grade evidences are needed to solve the clinical dilemma, and there are five ongoing pivotal RCTs: STATICH (NCT03186729), A3ICH (NCT03243175), ASPIRE (NCT03907046), ENRICH-AF (NCT03950076), and PRESTIGE-AF (NCT03996772). It is our hope that these will provide more substantial evidences in the field of anticoagulation in AF patients with a history of ICH (Table S3). Pooled analysis is probably required when more RCTs are completed in the future to resolve this therapeutic dilemma.

Conclusions

This meta-analysis of OAC therapy in AF patients with a history of ICH suggested that starting OAC therapy after ICH was associated with lower rates of IS, IS or SE, and all-cause mortality than avoiding OAC, without increasing ICH recurrence or major hemorrhage events significantly. Considering the heterogeneity between the results of observational studies and RCTs, as well as the limited number and small sample size of the RCTs, high-grade evidences, including more RCTs with larger sample sizes, are needed to better inform clinical decisions regarding anticoagulation therapy in AF patients with ICH.

Acknowledgments

Footnote

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## Appendix 1

Search strategies

1.1 PubMed Search Query

"atrial fibrillation"[MeSH Terms] AND ("brain hemorrhage"[Title/Abstract] OR "intracerebral hemorrhage"[Title/Abstract] OR "cerebral hemorrhage"[Title/Abstract] OR "intracranial hemorrhage"[Title/Abstract]) AND ("Anticoagulants"[MeSH Terms] OR "warfarin"[Title/Abstract] OR "vitamin k antagonist"[Title/Abstract] OR "NOAC"[Title/Abstract] OR "novel oral anticoagulant"[Title/Abstract] OR "non vitamin K anticoagulant"[Title/Abstract] OR "DOAC"[Title/Abstract] OR "rivaroxaban"[Title/Abstract] OR "edoxaban"[Title/Abstract] OR "apixaban"[Title/Abstract] OR "dabigatran"[Title/Abstract])

1.2 EmBase Search Query

#1. 'atrial fibrillation'/exp
#2. 'brain hemorrhage':ab,ti
#3. 'intracranial hemorrhage':ab,ti
#4. 'intracerebral hemorrhage':ab,ti
#5. 'cerebral hemorrhage':ab,ti
#6. #2 OR #3 OR #4 OR #5
#7. 'anticoagulant agent'/exp
#8. 'warfarin':ab,ti
#9. 'vitamin k antagonist':ab,ti
#10. 'noac':ab,ti
#11. 'novel oral anticoagulant':ab,ti
#12. 'non vitamin k anticoagulant':ab,ti
#13. 'doac':ab,ti
#14. 'rivaroxaban':ab,ti
#15. 'dabigatran':ab,ti
#16. 'apixaban':ab,ti
#17. 'edoxaban':ab,ti
#18. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19. #1 AND #6 AND #18

1.3 Cochrane Search Query

#1   MeSH descriptor: [Atrial Fibrillation] explode all trees
#2   MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#3   ("intracerebral hemorrhage"):ti,ab,kw
#4   (cerebral hemorrhage):ti,ab,kw
#5   #2 or #3 or #4
#6   MeSH descriptor: [Anticoagulants] explode all trees
#7   (anticoagulation):ti,ab,kw OR (NOAC):ti,ab,kw OR (novel oral anticoagulant):ti,ab,kw OR (non vitamin k antagonist):ti,ab,kw AND ("Warfarin"):ti,ab,kw (Word variations have been searched)
#8   (DOAC):ti,ab,kw OR (rivaroxaban):ti,ab,kw OR (edoxaban):ti,ab,kw OR (apixaban):ti,ab,kw AND (dabigatran):ti,ab,kw (Word variations have been searched)
#9   #7 or #8
#10   #1 and #5 and #9

https://dx.doi.org/10.21037/apm-22-582
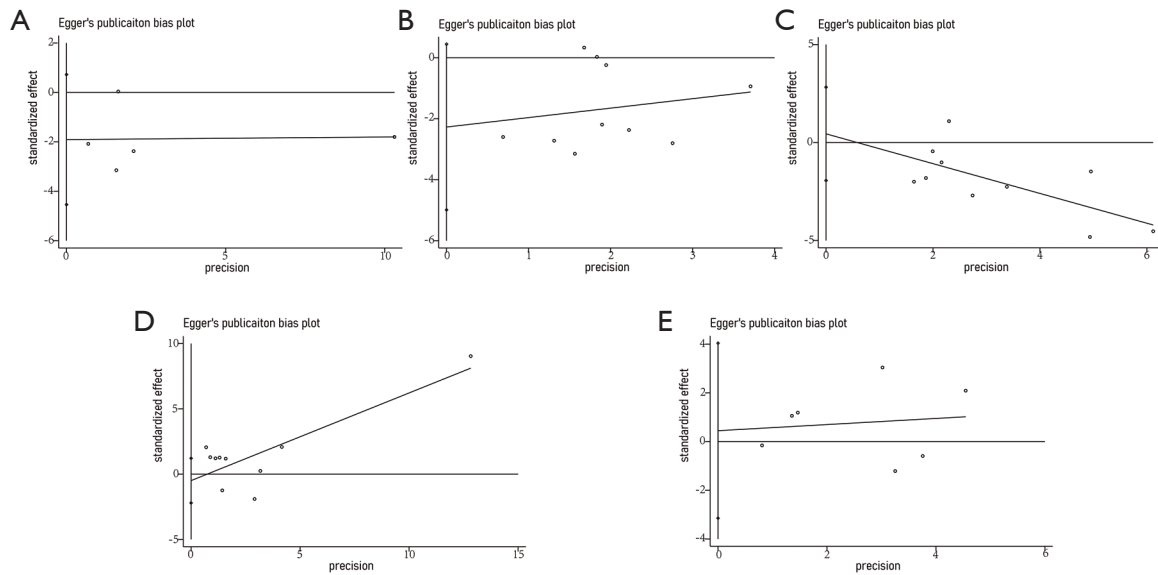
Figure S1 Egger's tests of the reported outcomes. (A) Ischemic stroke (P=0.104); (B) Ischemic stroke or systemic embolism (P=0.09); (C) All-cause death (P=0.680); (D) Intracranial hemorrhage recurrence (P=0.520); (E) Major hemorrhagic event (P=0.762).
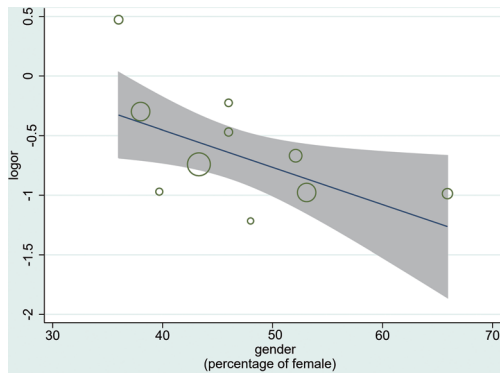
Figure S2 Meta-regression analyses of gender on all-cause death. Regression line and its prediction intervals (95% CIs) were presented in the figure. Coefficient =0.969, SE =0.012, t=−2.54, 95% CI: 0.942 to 0.997, P=0.035, adjusted R^2=0.93.

Table S1 Quality assessment of studies included in the meta-analysis

	Selection bias			Blinding of participants and personnel		Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Consecutiveness	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Abrantes 2022	−	−	−	−	−	+	+
Chao 2016	−	−	+	−	−	−	+
Nielsen 2015	−	−	+	−	−	+	+
Nielsen 2017	−	−	+	−	−	+	+
Park 2016	−	−	+	−	−	+	+
Perreault 2019	−	−	−	−	−	+	+
Poli 2018	−	−	+	−	−	+	+
Sadighi 2020	−	−	+	−	−	+	+
Salman 2021	+	+	+	−	+	+	+
Schreuder 2021	+	+	+	−	+	+	+
Wu 2021	−	−	−	−	−	+	+

+, low risk of bias; −, high risk of bias.

Table S2 Results from single variable meta-regression analyses on all outcomes

Meta-regression (P value)	By age	By gender (female%)	By type of ICH	By CHA$_2$DS$_2$-VASc score	By type of OACs
IS	0.968	0.953	0.949	0.372	0.53
IS or SE	0.455	0.812	0.923	0.918	0.738
All-cause death	0.658	0.035*	0.856	0.539	0.397
ICH recurrence	0.183	0.488	0.57	0.799	0.553
Major bleeding	0.522	0.698	0.834	0.063	0.147

*, $P<0.05$. IS, ischemic stroke; SE, systemic embolism; ICH, intracranial hemorrhage; OACs, oral anticoagulants.

Table S3 Ongoing clinical trials evaluating effect of oral anticoagulants in atrial fibrillation patients with a history of intracranial hemorrhage

Study title	NCT identification number	Study population	Intervention	Comparator	Primary outcomes	Estimated enrollment number	Estimated completion date
STATICH	NCT03186729	Adults with intracerebral hemorrhage and an indication for antithrombotic drugs	Anticoagulant or antiplatelet drugs	No antithrombotic treatment	Fatal or non-fatal symptomatic intracerebral hemorrhage	500	Jun-23
A3ICH	NCT03243175	Adults with AF and recent spontaneous intracerebral hemorrhage	Apixaban/LAAC	No intervention	Composite of all fatal or non-fatal major cardiovascular/cerebrovascular ischemic or haemorrhagic intracranial/extracranial events	300	Dec-23
ASPIRE	NCT03907046	Adults with AF and recent spontaneous intracerebral hemorrhage	Apixaban	Aspirin	Stroke or death	700	Apr-24
ENRICH-AF	NCT03950076	Adults with AF and recent spontaneous intracranial hemorrhage	Edoxaban	Non-anticoagulant medical therapy	Stroke, Major hemorrhage	1200	Jul-23
PRESTIGE-AF	NCT03996772	Adults with AF and recent spontaneous intracerebral hemorrhage	Apixaban/Dabigatran/Edoxaban/Rivaroxaban	Antiplatelet or no antithrombotic drugs	Ischemic stroke, intracerebral hemorrhage	654	May-22

AF, atrial fibrillation; LAAC, left atrial appendage closure.