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Review Article

A review of the use of oral anticoagulants in individuals with atrial fibrillation who had experienced intracranial hemorrhage in the past

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Abstract: Atrial fibrillation (AF) is the most prevalent arrhythmia, significantly increasing the risk of stroke and thromboembolism. Oral anticoagulants (OACs), including direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs), have been shown to reduce these risks effectively. However, the administration of OACs carries a notable risk of spontaneous intracranial hemorrhage (ICH), a severe complication associated with high morbidity and mortality. Patients with a history of ICH face a complex decision regarding the resumption of anticoagulation therapy, as the likelihood of recurrence is heightened in this population. Current literature reveals inconsistencies in research findings regarding the safety and efficacy of restarting OACs after ICH. A lack of definitive guidelines addressing this issue leaves clinicians uncertain about optimal management strategies. This systematic review aims to analyze existing observational studies and randomized controlled trials (RCTs) to evaluate the safety and effectiveness of resuming OACs in patients with AF who have experienced ICH. The review underscores the urgent need for high-quality research to inform clinical practices and develop comprehensive guidelines for managing anticoagulation therapy in this vulnerable group.

Keywords: Atrial fibrillation, intracranial hemorrhage, direct oral anticoagulant, oral anticoagulants, vitamin K antagonist

Introduction

Atrial fibrillation (AF) is the most commonly encountered arrhythmia by clinicians, accounting for approximately 1% of cases globally [1]. Stroke and thromboembolism risks are five times higher in patients with AF [2]. It has been shown that the administration of oral anticoagulants (OACs), either direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs), can decrease the risk of stroke, systemic embolism and death in patients with AF in comparison to placebo or control treatments [3]. However, spontaneous intracranial hemorrhage (ICH) is one of the most debilitating and potentially fatal side effect of OACs [4].

Compared to the general population, ICH recurrence is more likely to occur in AF survivors with ICH, and ICH related to OAC therapy has a higher mortality risk; therefore, the effects of OAC on these patients remain unclear [5]. Anticoagulant use in AF patients is linked to a number of possible side effects, including: The main issue is bleeding, since 2-4% of patients experience significant bleeding annually [6]. In contrast to VKAs, some DOACs are more likely to cause gastrointestinal bleeding. Despite being less common, intracranial hemorrhage is the most feared bleeding consequence because of its high rate of death and morbidity. Bleeding episodes are more likely to occur in patients with greater peak anticoagulant levels. Persistent minor bleeding can also happen [7, 8]. Moreover, thromboembolism is a possibility, especially when anticoagulation medication is stopped or interrupted. Stopping anticoagulation also increases the risk of myocardial infarction. Crucially, even brief disruptions lasting seven days or longer significantly increase the risk of myocardial infarction, stroke/systemic embolism, and all-cause death [9].

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Due to the absence of high-quality data in this population, it is difficult to identify whether re-initiating anticoagulation or permanently avoiding it is the most effective long-term treatment for patients with AF who have experienced ICH. A comparison between the risk of thromboembolism and the possibility of recurrent ICH is something that clinicians need to do. However, individual research that has attempted to address this topic has not been able to provide conclusive guidance on this matter. This is because the findings of these studies have been inconsistent. Following the ICH, it is currently unknown whether restarting OACs is effective and safe due to the absence of specific guidelines and the scarcity of high-quality research [10-12].

In this systematic review, first, we review an overall characteristic of ICH and then evaluate the comprehensive analysis of observational studies and recent randomized controlled trials (RCTs) that assess the safety, effectiveness, and optimal timing for resuming OACs in individuals with AF who have survived ICH.

Materials and methods

Search strategy

We have conducted a literature review evaluating the use of OAC in AF patients with a history of ICH. The research was performed in compliance with the PRISMA criteria, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the Flow Diagram is shown in **Figure 1**. The research was conducted in the PubMed, MEDLINE, Web of Science, and Google Scholar databases between 2020 and 2024. It used the Advanced Search Builder, and the keywords were searched in [Title OR Abstract]. We filtered only research articles published in the English language and using the combination of keywords and medical subject heading (MeSH), adjusted for each database, including: '(Atrial fibrillation OR AF) AND (Anticoagulant OR Direct oral anticoagulants OR DOACs OR Non-vitamin K antagonist oral anticoagulants OR Novel oral anticoagulants OR NOACs OR Dabigatran OR Rivaroxaban OR Apixaban OR Edoxaban OR Vitamin K antagonists OR VKAs OR Warfarin) AND (Intracranial hemorrhage OR Intracranial bleeding OR ICH OR Intracerebral hemorrhage OR Hemorrhage stroke)'.

Inclusion and exclusion criteria

As described below, the population, intervention, comparison, and outcome (PICO) format was used as guidelines for the inclusion criteria. (P): adult patients (age > 18 years old) with AF who had survived a presumably nontraumatic spontaneous ICH before; (I): OAC and (C): antiplatelets, placebo, or no treatment; (O): the rate of thromboembolic events, recurrent intracranial hemorrhage, and all-cause mortality. All included studies were either RCTs or observational studies that reported the baseline characteristics of patients. Also, we included review articles that evaluating the use of OAC in AF patients with a history of ICH. Furthermore, we excluded case studies, animal studies, and articles whose complete text was unavailable in English.

Data extraction

A.M. reviewed the titles and abstracts of various studies. Data was extracted from selected studies based on survey standards and inclusion/exclusion criteria. We also looked at references in previous review papers and included relevant studies. In total, we found thirteen valid published research articles. For some of these articles, we focused only on the key conclusions relevant to our study (see **Figure 1**).

Quality assessment

The quality of the published interventions was evaluated independently by two authors (A.M. and A.S.). A third author (O.C.) made sure that any disagreements were settled. In order to determine the possibility of bias in each of the included studies, the QUADAS-2 instrument was utilized to evaluate the population, technique, analysis, and reporting requirements of each study [13]. The instrument comprises four primary domains: flow and timing, reference standard, index test, and patient selection. Each domain was rated as "low", "high", or "unclear" for each specific investigation. Then, the ratings for every domain are shown, along with a subjective judgment on the overall quality of the included studies.

Outcome measures

Our review aimed to guide clinical practices and shape future research on anticoagulation man-

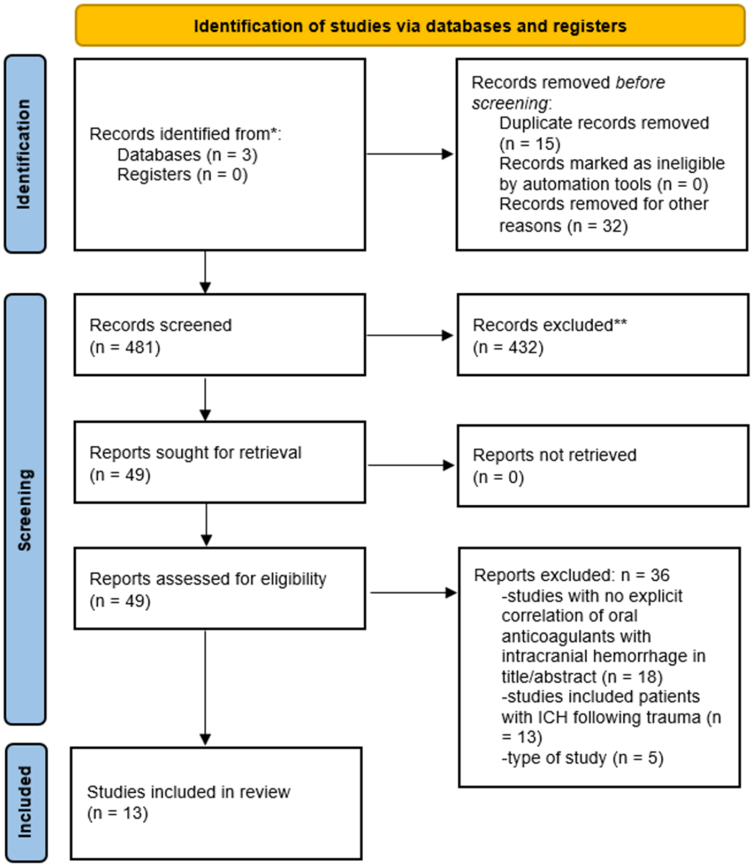

Figure 1. PRISMA flow diagram for enrollment of studies.

agement for patients with AF who have experienced an ICH. This was accomplished by gathering data on death rates, thromboembolic incidents, recurring ICH, and how the timing of OAC reinitiation affected patient outcomes.

Results

Study selection

After conducting a thorough search, we found 671 articles by October 2024. We removed 161 duplicate articles, leaving us with 510 studies to screen based on their titles and abstracts. After screening, we excluded 410 studies and were left with 49 to assess their full texts. Finally, 11 studies were included in our systematic review. The study selection process is illustrated in **Figure 1**. In this review, we assess 2 RCTs [14, 15] and 9 observational studies [16-24] and summarized the information in **Table 1**.

Quality assessment

Overall, the studies exhibit variability in methodological severity across the evaluated domains. While some studies, like Wang et al. and Suda et al., maintain low risks of bias, others, such as Lin et al. and Newman et al., display significant weaknesses that could compromise the validity and generalizability of their findings (**Figure 2**). Addressing these biases is crucial for improving the reliability of clinical implications drawn from this research, ensuring that outcomes can be confidently applied in clinical settings.

Study characteristics and outcomes

Abrantes et al. [17] conducted a study in 2021 to assess the safety and efficacy of OACs in patients with AF after ICH. Among the 95 patients, 40 resumed using OAC. During the follow-up, 10% of patients experienced at least one significant hemorrhagic episode, with 60% of them being anticoagulated. Additionally, 20% of the patients had at least one large thrombotic event, all of whom were not anticoagulated. Furthermore, 20% of the patients died. The ICH score was the only variable associated with the risk of hemorrhage. The mortality rate of patients who initiated anticoagulation was lower than that of those who did not. A history of ICH and elevated CHA2DS2-VASc levels were both linked to increased mortality. Based on the study, anticoagulation has been shown to decrease mortality and thrombotic events in patients with ICH and AF, without significantly increasing the risk of hemorrhage. In 2021, the SoSTART trial [15] compared starting OAC versus avoiding it in cases with AF after spontaneous ICH. Two hundred and three patients were entered into this study 101 patients started OAC, and 102 avoided OAC. The main focus of the study was to determine the recurrence of symptomatic spontaneous ICH. This study

Table 1. Characteristics of the included articles in our study

Study	Year	Study type	Regions	Sample size	Age, year	Gender, male (%)	Type of ICH in AF patients	Intervention	Comparison	Time of OACs restarting	Average of Follow-up	Primary outcomes	Conclusion
Wang et al. [17]	2024	Retrospective cohort study	China	296	74.96	61.5%	Spontaneous non-traumatic ICH	OAC with or without antiplatelet therapy (n = 166)	Antiplatelet or no therapy (n = 130)	56 days	4 years	Mortality	Antithrombotic medication, particularly DOAC, has been correlated to a reduced fatality rate.
Suda et al. [16]	2023	Retrospective cohort study	Japan	160	77	67.5%	Lobar, nonlobar, brain stem, cerebellar, and intraventricular ICH	DOAC (n = 108)	No anticoagulation therapy (n = 52)	7 days	-	Thromboembolic and bleeding events	Resuming OAC for non-valvular AF after ICH was safe. Discharge functional results were related to OAC resumption and timing.
Abrantes et al. [13]	2022	Retrospective cohort study	Portugal	95	75.2	51.6%	Spontaneous ICH	DOAC or VKA (n = 55)	No therapy (n = 40)	-	2 years	The occurrence of major thrombotic/hemorrhagic events and death	Antithrombotic medication reduced thrombotic events and overall mortality.
Lin et al. [12]	2022	Retrospective cohort study	Taiwan	2640	76.4	58.7%	ICH	Warfarin or DOAC (n = 821)	Antiplatelet or no therapy (n = 1819)	42 days	0.6 year	The occurrence of ischemic stroke, recurrent ICH, and all-cause mortality	OACs reduced the risk of ischemic stroke with no increase in the risk of subsequent ICH.
Moon et al. [20]	2022	Retrospective cohort study	Korea	4964	63.83	55%	ICH	DOAC or VKA (n = 878)	Antiplatelet (n = 2070) or no therapy (n = 2016)	6-8 weeks	-	The occurrence of severe bleeding and thrombosis	Continued anticoagulants and antiplatelets reduced severe bleeding and thrombosis after ICH. DOACs also reduced thrombosis risk compared to warfarin.
Schreuder et al. (APACHE-AF trial) [34]	2021	RCT	Netherlands	101	78	54%	Lobar, nonlobar, brain stem, cerebellar, and intraventricular ICH	Apixaban (n = 50)	Antiplatelet or no therapy (n = 51)	46 days	1.9 years	Non-fatal stroke or vascular death	Resumption or avoiding OAC both had high annual risks of non-fatal stroke or vascular death.
Salman et al. (SoSTART trial) [11]	2021	RCT	UK	203	79	64%	Lobar and non-lobar spontaneous intracerebral, non-aneurysmal subarachnoid, intraventricular or subdural hemorrhage	DOAC or VKA (n = 101)	Antiplatelet or no therapy (n = 102)	115 days	1.2 years	Recurrent symptomatic spontaneous intracranial hemorrhage	Restarting OAC was non-inferior to avoiding it.

Lee et al. [18]	2020	Retrospective cohort study	Korea	5712	72.4	56.9	ICH	DOAC (n = 3278)	Warfarin (n = 2434)	3.1 ± 2.8 years	0.6 year	Ischemic stroke, ICH, and composite outcomes	Compared to warfarin, DOAC use was linked with a 23% lower risk of ischemic stroke, a 34% lower risk of ICH, and a 27% lower risk of composite outcome.
Tsai et al. [19]	2020	Retrospective cohort study	Taiwan	4540	76	58.4%	ICH	DOAC (n = 3493)	Warfarin (n = 1047)	-	5 years	Clinical and safety endpoints (all-cause mortality, ischemic stroke, severe hemorrhage, adverse events) annual risk	DOACs reduced ICH and severe bleeding compared to warfarin.
Sadighi et al. [15]	2020	Prospective cohort study	USA	93	77.2	46.3%	Spontaneous non-traumatic ICH	Warfarin or DOAC (n = 38)	No therapy (n = 55)	56 days	28.8 months	Rate of recurrent ICH, ischemic stroke/systemic symbolism, death	Restarting OAC was non-inferior to avoiding it.
Newman et al. [14]	2020	Retrospective cohort study	USA	1502	-	43.7%	ICH	Warfarin or DOAC	Antiplatelet or no therapy	6 weeks	780 days	Rate of ischemic stroke, TIA, thromboembolism, recurrent ICH, and all-cause mortality	Resuming OAC did not correlate with an increased risk of recurrent ICH in AF patients who had survived an ICH.

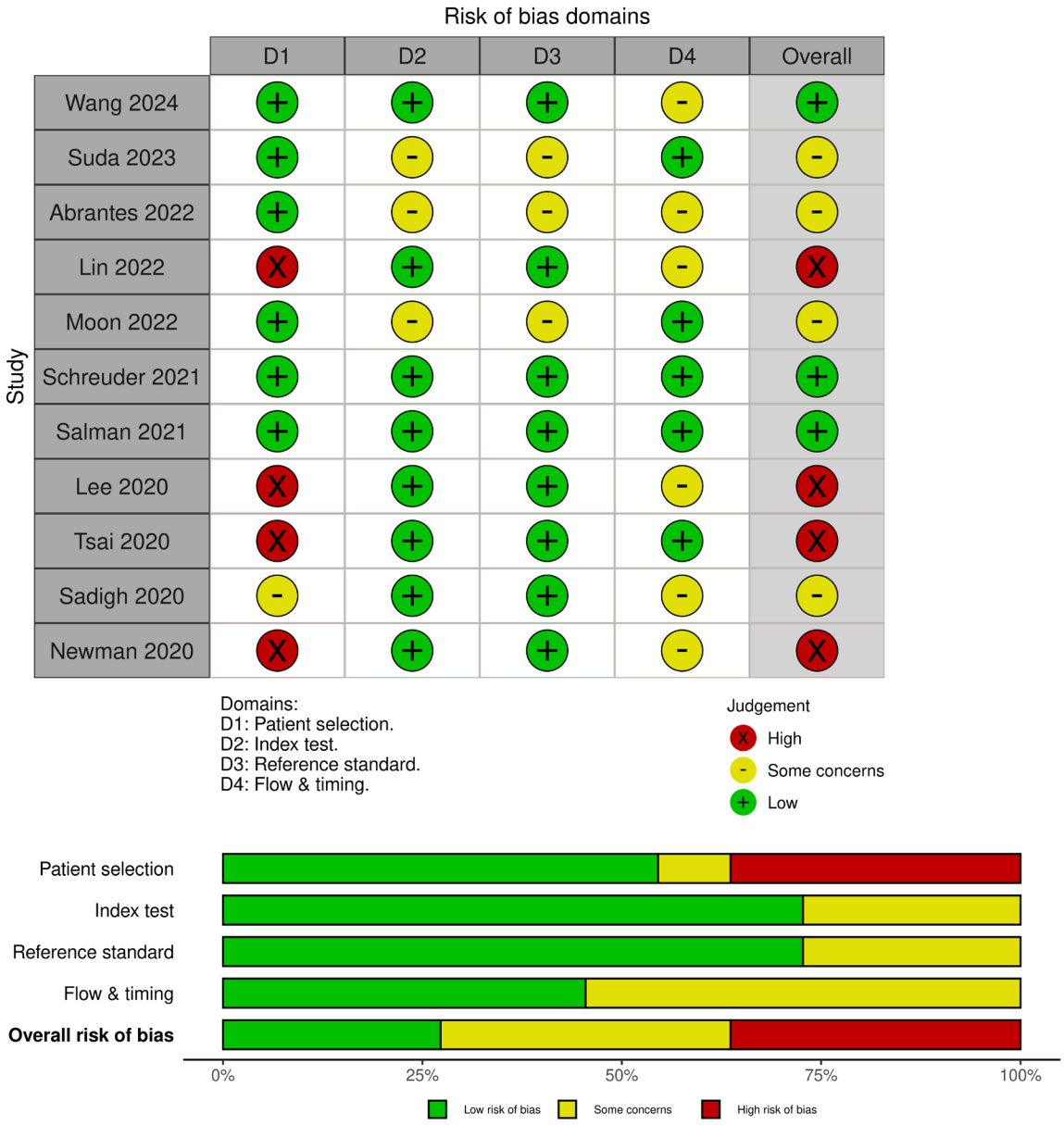

Figure 2. Quality assessment and bias risk assessment in the investigations included in the systematic review.

found no evidence that initiating OAC was inferior to averting it. Of all the participants, 8% of those who initiated OAC had a recurrent ICH, while only 4% of those who avoided anticoagulation experienced the same. However, there is weak evidence to suggest that starting OAC may be more effective than avoiding it in preventing major vascular events, stroke, and stroke or vascular death (composite secondary outcomes). Another major flaw and restriction of this study was its failure to assess the safety and effectiveness of warfarin compared to other OACs in AF patients. As a result, the authors stated that additional study is required to ascertain how OACs' risks and benefits compare for individuals with AF following ICH.

In another trial named APACHE-AF [14], the researchers evaluated the use of apixaban or avoidance of OAC on the rates of non-fatal stroke or vascular death in patients with AF who had survived an anticoagulation-associat-

ed ICH. Out of 101 patients, 50 patients received apixaban and 51 patients avoided receiving any anticoagulants. During a median follow-up of 1.9 years, 26% of individuals taking apixaban experienced a non-fatal stroke or vascular mortality, while 24% of those not taking anticoagulants faced similar risks. The annual incident rate for the apixaban group was 12.6%, compared to 11.9% for the avoid anticoagulation group. There was no statistically significant difference between the two groups, as indicated by the adjusted hazard ratio (HR) of 1.05 (P = 0.90). Moreover, 58% of those allocated to apixaban and 57% of those assigned to avoid anticoagulation experienced major adverse events unrelated to the primary outcome. The study concluded that there was no statistically significant difference in the risks of vascular death or non-fatal stroke between those treated with apixaban and those who did not take anticoagulation following an anticoagulant-associated ICH. The findings emphasize the significance of conducting additional studies to identify subgroups of individuals who may benefit from continuing or avoiding anticoagulation following such an occurrence.

In 2020, Lee et al. [22] compared the effectiveness and safety of NOACs to warfarin in Asian patients with non-valvular AF and a history of ICH. Among the 5,712 patients, 2,434 were treated with warfarin, and 3,278 were treated with NOACs. The use of NOACs was related to a decreased risk of ischemic stroke, ICH, and fatal stroke when compared to the use of warfarin. Also, NOACs demonstrated a reduced risk of fatal ICH compared to warfarin, but this was not statistically significant. NOACs were found to be related to a decreased risk of death from any cause when compared to warfarin. Although this study has provided valuable insights, it has several limitations. This study focused on an Asian population; therefore, the findings may not be directly applicable to populations in other regions or ethnicities. Also, while the study compared warfarin to NOACs as a group, it did not differentiate between different NOAC agents. Therefore, further research was necessary to validate the results and address these gaps.

In similar study conducted by Tsai et al. [23], they proposed that NOACs may be the optimal treatment for stroke prevention in patients with AF and previous instances of ICH. Among 4,540 patients, 1,047 received warfarin and 3,493 received NOACs. The findings demonstrated a statistically significant reduction in the risk of severe bleeding, ICH, and all-cause mortality when NOAC use was compared to warfarin use. Nevertheless, the two groups exhibited comparable rates of ischemic stroke.

In 2022, Moon et al. [24] investigated the risks and benefits of resuming anticoagulant medication in AF patients who experienced an ICH. Among the 4,964 patients studied, 17.7% used anticoagulants, and 41.7% utilized antiplatelet medications. Both anticoagulant and antiplatelet users had a decreased incidence of severe thrombotic and hemorrhagic events compared to non-antithrombotic users (for both groups: P < 0.0001). Resuming anticoagulant medication 6-8 weeks after ICH resulted in the lowest risk of all-cause mortality. Nevertheless, the risk for individuals using anticoagulants and antiplatelets was not significantly different. However, beginning anticoagulants 4 to 6 weeks after ICH onset resulted in the highest risk of severe hemorrhagic incidents. Overall, the study concluded that continuing anticoagulant and antiplatelet medication after ICH in AF patients can minimize thrombotic and hemorrhagic events. In addition, NOACs may provide advantages over warfarin in terms of reducing the incidence of thrombotic events.

In 2020, Sadighi et al. [19] evaluated the long-term outcomes of patients with AF who either resumed or did not resume OAC therapy after experiencing an OAC related to ICH. Of 115 patients with AF and OAC related to ICH, 93 were included in the analysis. 38 (40.9%) patients resumed OAC after the ICH event, while 55 (59.1%) did not. The mean time to OAC resumption was 56.0 ± 52.5 days, with over 70% of patients restarting within two months. There was no significant difference in the incidence rates of recurrent ICH, ischemic stroke/systemic embolism, or death between both groups. Nevertheless, there was an increased risk of recurrent ICH in the long term among patients who restarted OAC treatment. However, the difference was not statistically significant. The authors note several limitations of the study, including its retrospective nature, small sample size, and lack of randomization in the decision to resume OAC. Overall, this

observational study did not find a clear benefit or harm associated with resuming OAC after OAC related to ICH in patients with AF.

In 2020, Newman et al. [18] evaluated the effectiveness and safety of resuming OAC in patients with non-valvular AF who survived an anticoagulant-related ICH. Of 1502 patients, 976 participants (69%) restarted OAC within 6 weeks of the event. Among those who restarted OAC, 83% used warfarin. The study found no significant difference in the risk of ischemic stroke or transient ischemic attack (TIA), thromboembolism, or the composite of ischemic stroke or TIA and thromboembolism between patients who resumed OAC and those who did not. However, the resumption of OAC was associated with a lower risk of recurrent ICH and all-cause mortality compared to non-OAC use. Although this study provides valuable insights into the outcomes of the resumption of OACs, they did not evaluate the use of each NOAC separately due to the lack of sample size.

In a similar study, Wu et al. [25] evaluated the risk of mortality, ischemic stroke, systemic embolism, and recurrent ICH of resuming OACs in AF patients with prior ICH at six months and one year of follow-ups. Among 604 patients, 408 discontinued OAC therapy, while 196 resumed it within 6 weeks after ICH. The results showed that patients who resumed OAC therapy had significantly lower risks of composite outcomes of mortality, ischemic stroke, and systemic embolism compared to patients who discontinued OAC therapy at six months and one year of follow-ups ($P = 0.006$ and $P = 0.025$, respectively). However, no significant difference in recurrent ICH and major bleeding was observed between the two groups.

In 2022, Lin et al. [16] compared the efficacy and tolerability of various treatment options following an episode of ICH, such as OACs, antiplatelet agents, and no specific treatment. The study's findings showed that starting OACs again considerably lowered the risk of ischaemic stroke while not affecting the risk of ICH. Additionally, they demonstrated that OACs dramatically decreased the risk of ICH and thromboembolic events compared to antiplatelet medications. When it comes to preventing ischaemic stroke, NOACs are no more effective than warfarin, but their survival rate was higher. Resuming antiplatelet therapy raised the risk of ICH but did not lower the risk of ischaemic stroke when compared to no treatment.

In another study, Ivany et al. [64] evaluated factors such as age, CHA2DS2-VASc score, HAS-BLED score, type of OAC prescribed pre-ICH, OAC adherence, history of falls, and previous quality of VKA control, to decide whether to use antithrombotic therapy in patients with AF who survived ICH.

In another study, Suda et al. [20] demonstrated that out of the 160 patients with non-valvular AF included, 108 (68%) resumed OAC treatment at a median of 7 days after the ICH began. At discharge, the 52 patients who remained did not restart their OAC medication and had greater rates of hematoma expansion and modified Rankin Scale (mRS) ratings. The resumption rate was higher in patients with mRS scores of 0-4 compared to those of 5. The timing of resumption was also longer in patients with higher mRS scores. There was an increase in the occurrence of thromboembolic and bleeding events in the group that resumed treatment, including new-onset ICH, symptomatic hematoma enlargement, systemic embolism, deep venous thrombosis, and gastrointestinal bleeding. However, there were no significant differences between the resumption and non-resumption groups ($P > 0.05$). Overall, the study suggests that early resumption of OAC treatment in patients with non-valvular AF after ICH may be safe and associated with better functional outcomes.

In 2024, Wang et al. [21] assessed the efficacy of OAC with or without antiplatelet therapy for 296 AF patients who had survived ICH. Through a 4-year follow-up period, they showed that the use of DOACs was related to a lower fatality rate. However, the study concluded that future RCTs are needed to determine the positive net therapeutic impact of DOAC therapy.

Discussion

Intracerebral hemorrhage classification

Non-traumatic ICH originates in the brain parenchyma and can extend to the subdural, subarachnoid, or ventricular areas. The etiology and location of ICH can be used to classify it. The SMASH-U [26] categories roughly categorize the primary causes of ICH as follows: medi-

cation (M), amyloid angiopathy (A), systemic disease (S), hypertension (H), structural vascular lesions (S), or undetermined (U) factors that are not known at the time of assessment. Between 70% and 88% of ICH cases result from the rupture of tiny blood arteries that have already been compromised by degenerative changes brought on by either cerebral amyloid angiopathy (CAA) or hypertension [27, 28]. CAA is characterized by beta-amyloid build-up in the walls of small and medium-sized arteries in the cortical and leptomeningeal regions. It is less frequent to develop ICH due to structural lesions, systemic illness, or other factors [29]. Due to its unique treatment needs and variable recurrence rates, it is often left out of the studies discussed in this review.

Depending on location, ICH can also be categorized as lobar or deep. Approximately one-third of all ICH are lobar ICHs located inside the brain cortex, produced mainly by hypertension-related arteriolosclerosis and CAA. Roughly two-thirds of all ICH are deep ICH, primarily located in the brainstem, cerebellum, internal capsule, or basal ganglia, and primarily caused by arteriolosclerosis related to hypertension. Risk factors for ICH brought on by hypertension and CAA include age, male gender, excessive alcohol use, genetics influencing apolipoprotein E (APOE) metabolism, inflammation, and endothelial integrity [30, 31]. OAC treatment has been linked to an increased risk of hypertension and CAA-induced ICH. However, it is doubtful that the drug is the leading cause of the ICH.

Epidemiology

ICH is a major worldwide cause of diseases and fatalities, making it a major public health concern. There has been a steady increase in ICH event cases during the last few decades. Although ICH is less common than ischemic stroke, it is associated with a higher risk of morbidity and fatality, placing an increasing strain on medical facilities and economies.

According to the Global Burden of Disease Study 2019, 27.9% of all new stroke cases were related to ICH. About 3.5 million people globally have ICH (42 instances per 100,000 person-years), with low-income nations and regions of Southeast Asia and Oceania having the highest incidence. Individuals residing in low-income countries or regions have an almost twice higher proportion of ICH (29.5% vs 15.8% of all stroke cases in 2019) than people residing in higher-income countries or areas [2]. Between 1990 and 2013, the number of individuals aged 20 to 64 who had ICH nearly doubled globally, from 1.9 million to 3.7 million. This rise could be explained by more access to imaging and an aging population that uses antithrombotic agents more frequently [32].

Between 1990 and 2019, ICH accounted for an estimated 3 million deaths, moving up from ninth to fourth place on the list of causes of premature death. The most significant number of deaths occurred in regions of Central Asia, Oceania, and sub-Saharan Africa. The higher incidence and mortality rates of ICH in low- and middle-income countries may be attributable, in part, to a lack of healthcare access and public education regarding preventative strategies (such as the detection and treatment of arterial hypertension) [33]. An estimated 70 million disability-adjusted life years (DALYs) were lost in 2019 due to ICH. DALYs are the sum of years lost due to premature death and years lived with disability. However, ischaemic stroke is estimated to have caused the loss of around 65 million DALYs [34].

While ICH can still strike young people, the risk of ICH rises with age. Men were more likely than women to have it, accounting for 2 to 5 cases per 100,000 people. Furthermore, ICH affects Asians about twice as frequently as it does Black or White persons [35]. Moreover, ICH was diagnosed 10 years earlier among Black and Hispanic participants in a US study than in White participants. Because of a complex sex-based interplay between age, ethnicity, and underlying risk factors, ICH may be more common in males than women [36].

Risk factors of primary and recurrent intracranial hemorrhage

There is a lack of knowledge regarding the incidence and risk factors of ICH recurrence, which differ amongst research populations. The recurrence rate of ICH is predicted to be between 1.3 and 4.0% in the first year and 4.0 to 9.6% within five years following the initial incident [5]. The probability of ICH recurrence varies depending on the cause of the stroke, its location, and how modifiable risk factors are managed [37]. The risk of ICH recurrence is

Table 2. Factors that increase the possibility of recurrent ICH

Risk factors of recurrent ICH	Type of ICH	Mechanism of ICH	Size of ICH	Cerebral microbleedings	CAA	Type of anticoagulant	Age > 75 years	Uncontrolled HTN
Low risk	Subdural and epidural ICH	Traumatic	Mild (i.e. volume) < 30 ml	No	No	DOAC	No	No
High risk	Subarachnoid and lobar ICH	Spontaneous	Moderate to severe	Yes	Yes	Warfarin	Yes	Yes

ICH: intracranial hemorrhage, CAA: cerebral amyloid angiopathy, DOAC: direct oral anticoagulant, HTN: hypertension.

elevated in lobar hemorrhages, which are typically associated with CAA, in part due to the proliferation of cerebral amyloid. On the other hand, if hypertension is not adequately treated, deep hemorrhages, which often accompany hypertension, might have recurrence rates that are comparable to or even higher [38, 39].

High blood pressure, also known as hypertension, is the most significant factor that can be changed to reduce the chances of a recurrence of ICH. The recurrence of ICH can also be caused by modifiable risk factors such as diabetes, smoking, excessive alcohol consumption, and certain drugs such as selective serotonin inhibitors [40-42]. On the other hand, there are risk factors for ICH recurrence that cannot be changed, such as age, gender, CAA, presence of APOE metabolism-related alleles, race/ethnicity, and ICH location. These risk factors are similar to those that increase the likelihood of the first ICH occurrence [43].

Several studies have used various methodologies to assess an individual's risk of ICH recurrence [41, 44, 45]. Pinho et al. [41] identified a significant increase in recurrent ICH in individuals with or without CAA who had lobar microbleeds compared to those who did not. The same group created a risk score to predict ICH recurrence based on an MRI assessment of a small vascular disease load. Biffi et al. [44] used MRI indicators of cortical superficial siderosis, cerebral microbleeds, and APOE genotyping to predict ICH recurrence. While several interesting prognostic scores are available, they have not yet been validated in large cohorts, and there are no standardised approaches available to objectively estimate the risk of ICH recurrence at this time.

The initial ICH incident is closely correlated with antithrombotic medication; however, its effect on the likelihood of recurrent ICH is unknown. Because of the high probability of recurrence, particularly in lobar sites, and the potential risk to CAA, an early decision analysis was advised against administering oral antiplatelets and anticoagulants following ICH [46]. Nevertheless, according to recent observational studies, individuals who start or continue oral antiplatelets or anticoagulation after ICH do not appear to have higher recurrence risks [1, 47-49]. The hazards and advantages of OACs following ICH have only been assessed in a few clinical trials despite increasing observational studies. Also, we demonstrated the factors that increase the possibility of recurrent ICH in **Table 2**.

Prevalence of atrial fibrillation in patient who experienced intracranial hemorrhage

Several studies have shown that AF is highly prevalent in individuals with ICH. Nevertheless, the frequency depends on the research population's characteristics, particularly age and ethnicity. Researchers in Dijon, France, found that among individuals with their first ICH, 21.9% (mean age 75) had a diagnosis of AF [50]. In most cases (87%), AF had already been diagnosed before ICH. Over time, the incidence increased from 17.2% (2006-2011) to 25.8% (2012-2017). Between 2012 and 2017, one in every four patients had AF. Similar investigations from this time period revealed that the prevalence of AF in patients with ICH ranged from 16% to 31% [50].

Two recent UK population-based cohort studies found that 22% of patients with ICH also had a diagnosis of AF, with a mean age of 74.7 years old [37]. People with ICH had lower incidences of AF, according to other research. According to a longitudinal study using prospectively gathered claims data on hospitalizations in Florida, New York, and California from 2005 to 2014, 13% of patients with nontraumatic ICH also had AF [51].

In a cohort investigation of patients with ICH admitted to a hospital in Ontario, Canada, from

2009 to 2019, it was found that 10.8% of the patients (mean age 71.3 years) had a documented history of AF [52]. Reduced rates in these reports could be due to a younger average age; the prevalence of AF usually rises with advancing years. Younger patients with lower CHADS-VASc2 scores are less likely to utilize OAC. Ethnicity is another immutable variable that could affect the incidence of AF in the ICH population. The observed disparity in the mean age of patients with ICH between White patients and Asian, Black, and Hispanic populations suggests that age at ICH onset likely mediates this effect [53, 54]. Finally, the increase in the percentage of AF-associated ICH could be attributed to the increased use of anticoagulation in AF patients, including the elderly, over the last few decades [55, 56].

The impact of oral anticoagulants on individuals with atrial fibrillation and previous experience of brain hemorrhage

Evaluating OAC therapy in patients with AF following an ICH reveals a nuanced landscape of benefits and risks across various studies. Abrantes et al. [17] found that patients who resumed OAC therapy had lower mortality rates despite experiencing some major hemorrhagic events. This study highlighted the ICH score as a significant predictor of hemorrhage risk, underscoring the need for individualized patient assessments when considering anticoagulation resumption.

In contrast, the SoSTART Trial assessed the safety of initiating OACs after ICH. No significant difference in recurrent ICH rates was found between patients who started OACs and those who avoided them. This suggests that initiating OAC therapy may be viable; however, the study's lack of comparison between different OAC types limits the ability to draw definitive conclusions regarding their safety [15]. Similarly, APACHE-AF focused specifically on apixaban and reported no significant differences in non-fatal stroke or vascular mortality between apixaban users and those who avoided anticoagulation, reinforcing the idea that resuming OAC therapy may not lead to adverse outcomes [14].

The comparative safety of newer oral anticoagulants (NOACs) versus warfarin was explored in studies by Lee et al. [22] and Tsai et al. [23], which found that NOACs were associated with lower risks of ischemic stroke and ICH. This suggests that NOACs may be preferable for patients with AF and a history of ICH, aligning with the findings of Moon et al. [24], who examined the timing of anticoagulation resumption. This investigation indicated that initiating treatment 6-8 weeks post-ICH minimized mortality risk without significantly increasing hemorrhagic incidents, highlighting the critical importance of timing in treatment strategies.

Further supporting the safety of OAC resumption, both Sadighi et al. [19] and Newman et al. [18] reported no significant differences in recurrent ICH or ischemic stroke between patients who resumed OACs and those who did not. However, Newman's study noted a lower risk of recurrent ICH among those who restarted therapy, suggesting potential benefits to resuming anticoagulation. Wu et al. [25] reinforced these findings by demonstrating that patients who resumed OAC therapy had lower risks of mortality and stroke compared to those who discontinued therapy, further adding to the body of evidence advocating for anticoagulation.

Lin et al. [16] indicated that reinitiating OACs significantly reduced the risk of ischemic stroke without increasing ICH risk, supporting the argument for their use in managing AF after ICH. Meanwhile, Suda et al. [20] suggested that early resumption of OACs could be safe and improve functional outcomes, although they acknowledged the potential for associated risks. Lastly, Wang et al. [21] investigated the efficacy of OACs with or without antiplatelet therapy, finding that DOACs were linked to lower fatality rates while calling for further randomized controlled trials to clarify these findings.

In summary, the collective outcomes of these studies indicate that while there are risks associated with OAC therapy in patients with AF after ICH, the potential benefits - particularly in terms of reduced mortality and stroke risks - often outweigh these concerns. The studies collectively advocate for a nuanced approach that incorporates patient history, timing of resumption, and the choice of anticoagulant to optimize therapeutic outcomes.

Decision on the oral anticoagulant resumption: safety and efficacy

It is a common clinical challenge to decide whether to restart OACs following ICH because there is not enough data on the topic. Prompt resumption of OACs is necessary for individuals with AF who have experienced ICH because of the risk of thrombosis. Once the primary source of the bleeding has been treated, anticoagulation can usually be maintained if a secondary or reversible cause, like a tumor or physical trauma, causes the bleeding. Because incorrectly prescribed anticoagulants can raise the risk of rebleeding, the topic of resuming oral anticoagulants is contentious. There is currently no definitive agreement regarding the optimal timing for the reinitiation of OACs for individuals with AF and a history of ICH in clinical practice.

Resuming OAC medication appears to have net therapeutic advantages and is supported in published clinical trials for most individuals with AF and prior ICH.

Results of a study included 5712 Asian people with non-valvular AF and ICH history who started using anticoagulant medications showed that DOACs were linked to notably lower risks of ICH, ischemic stroke, and death when compared to warfarin [22]. Similar conclusions were drawn in 2020 from a cohort analysis involving 4540 cases with AF and past ICH [23]. In addition, a recent retrospective investigation indicated that, in comparison to no treatment, OACs reduced the risk of ischaemic stroke without raising the risk of recurrent ICH. Comparing DOACs to warfarin, all-cause mortality is significantly decreased [57, 58].

Because DOACs have a reduced chance of repeat ICH and better functional recovery than VKAs, they might be the better and preferred therapeutic choice for stroke prevention [59-61]. Therefore, it is advised that OACs be restarted in patients with AF who have previously experienced ICH. However, most of these studies were retrospective, and despite their high quality, there are currently no guidelines for resuming OACs after ICH. The SoSTART study included 203 patients with ICH and AF and a CHA2DS2-VASc score of 2 or above. Random assignments were made to start or stop OAC for the participants. According to the trial's results, the restart group experienced an increased incidence and death rate of recurrent ICH compared to the avoid group, and resuming OAC did not result in any beneficial outcomes [15]. There was a significant annual risk of non-fatal stroke or vascular death for both the apixaban and avoid groups, according to another randomized trial (APACHE-AF) [14]. Overall, there is a dearth of high-quality data to support the resumption of anticoagulant therapy, which leads to significant variation and uncertainty in clinical treatment approaches [62].

As measured by the CHA2DS2-VASc and HAS-BLED scores, thromboembolism and ICH recurrence risks must be considered in determining whether to resume OACs after ICH [63]. Concerns about ICH recurrence are the primary reason for avoiding continuing OACs [64]. A patient's risk-benefit evaluation regarding the resumption of OACs is influenced by the following risk factors: age, blood pressure, consumption of anticoagulants and concurrent antiplatelet drugs, acute or worsening renal failure, multiple cerebral microbleeds, the type of bleeding (spontaneous or caused by trauma), the extent of the bleeding, and the extent and place of the haematoma [16, 65].

Moreover, there is an increased chance of acquiring ICH in those with CAA; as a result, it is recommended that all patients with CAA and OAC-related ICH refrain from receiving anticoagulation, especially long-term anticoagulation medication. On the other hand, no RCTs have been published investigating the consumption of anticoagulants in individuals with CAA. Patients who are taking aspirin at the same time and have poorly managed hypertension, a lobar ICH site, or any other risk factors for rebleeding should delay anticoagulant treatment until their arterial pressure is under control or until these issues are resolved.

Restarting OACs in patients with non-lobar ICH should be assessed according to OAC indications, changes in risk factors, and bleeding characteristics. However, because of the extremely high risk of rebleeding, patients with lobar ICH should proceed with great caution while beginning OACs. If the risk of rebleeding becomes insignificant compared to the likelihood of future ischemic events, OAC may be continued. It should be noted, too, that the

timely resumption of OAC strongly influences the prognosis of patients with OAC-related ICH.

Furthermore, patients who are at a significantly higher risk of thromboembolism - for example, due to a mechanical heart valve prosthesis, valvular or non-valvular atrial fibrillation (AF), TIA or ischaemic stroke within three months, venous thromboembolism (VTE) within three months, or recurrent or cancer-related VTE - may benefit from returning to oral anticoagulants. Once hemostasis has been achieved and stable clinical signs have developed, rehabilitation should start as soon as possible. Keep in mind that occlusion devices or left atrial appendage closure (LAAC) are nonpharmacological interventions that can be considered to reduce the risk of thrombosis in AF in patients with mild risk of rebleeding or thromboembolism and absolute or relative contraindications to starting OACs (e.g., life-threatening bleeding from untreatable causes).

When should oral anticoagulants be resumed?

It is currently unclear when OACs should be resumed after reversal therapy for cases with anticoagulant-associated ICH. Finding a balance between stopping VTE and preventing recurrent ICH is especially challenging in the early stages after ICH [4, 66]. According to the most recent guidelines, a multiparametric examination should be carried out before a clinician decides to resume oral anticoagulation. This assessment should consider multiple viewpoints, such as cardiovascular, neurological, neurosurgical, and neuroimaging. Additionally, the strategy employed should be principally determined by a risk assessment that weighs the risks of ischemic stroke and ICH recurrence [60, 67]. Although the CHA2DS2-VASc score can be utilized to assess the ischemia risk profile, estimating the risk of recurrent ICH is more difficult because of the considerable variation in reported incidences, which range from 1.3% to 7.4% [32]. ICH's etiology, location, and imaging features can be used to predict the likelihood of a recurrence (**Table 1**) [60].

Published guidelines do not agree on when to restart OAC in cases with AF following ICH. Therefore, we consult the most recent guidelines and published studies to decide when to use OAC in this patient population.

The duration of OAC resumption following ICH varied between 115 and 45 days in the SoSTART and APACHE-AF trials, respectively [14, 15]. A different study that involved surveying 163 practitioners revealed that 36.6% of them continued OAC for those with AF more than 30 days after the ICH began, 24.2% resumed between days 15 and 30, and 16.3% resumed in the first 10 to 14 days following the ICH [64]. In 2023, El Naamani et al. [49] conducted a meta-analysis of 13 studies, including 1637 AF patients with a history of ICH. They discovered that the average duration for OAC resumption following ICH was approximately 31 days. However, this study included investigations with a study population of AF patients who presented with traumatic ICH. In a recent retrospective investigation by Suda et al. [20], OACs were resumed in 108 (out of 160 patients) of acute ICH survivors at a median of 7 days. Regardless of age, HAS-BLED score, or CHA2DS2-VASc score, the findings of this study suggested that the decision to resume therapy appeared to depend on the severity of the discharge mRS score. This was the case regardless of whether the patient was also receiving treatment. Specifically, mRS 5 substantially accelerated the healing process and decreased the time needed to recuperate before returning to work. Resumption rates, measured in days to resumption, were more significant in the mRS 0-4 group compared to the mRS 5 group.

In Korea, a retrospective study conducted recently revealed that the safest course of action for reducing all-cause mortality was to resume OAC therapy 6-8 weeks after ICH, whereas continuing treatment beyond 4-6 weeks after ICH had a higher risk of bleeding [24]. Also, another study found that there was no significant association between patients who discontinued OAC after ICH and those who resumed OAC within six weeks after ICH in terms of recurrent ICH and significant bleeding [25].

A meta-analysis evaluated the safety of restarting using OAC in AF patients within two weeks after ICH. This study measured the rate of complications restarting/avoiding OAC, such as mortality, hemorrhage, and thromboembolic events. A notably decreased frequency of recurrent ischemia episodes and mortality events was linked to starting OAC two weeks or one

month following ICH. There is also no evidence that early recovery from OAC correlates with an increased risk of hemorrhagic episodes [47].

Almost all evaluations of the optimal timing for resuming OAC after ICH have been observational. Hence, more RCTs are required in the future.

The 2020 guidelines from the European Society of Cardiology (ESC) state that resuming OAC in patients with AF at high risk of thromboembolism should be based on a multidisciplinary approach that weighs the treatment's benefits and drawbacks. Additionally, DOACs ought to be chosen above VKA. The recommended time to begin OAC therapy after ICH is 4 to 8 weeks, provided the bleeding source is controlled. Additionally, having recently gone through a high-risk bleeding event - like an ICH - is considered a complete contraindication to OACs (within two weeks). Also, LAAC might be considered for AF patients who have a very high risk of recurrent ICH. More specifically, for individuals with AF and cerebral bleeding that does not have a reversible cause, LAAC may be a viable treatment choice [60].

Guidelines from the European Heart Rhythm Association (EHRA) state that a multidisciplinary evaluation should be performed 4 to 8 weeks before restarting OAC. LAAC occlusion is strongly advised if it is deemed unsuitable [67]. According to American Heart and Stroke Association guidelines, individuals with spontaneous ICH with non-valvular AF should be evaluated for the possible resumption of anticoagulant medication, provided that the benefits and risks are balanced. This will help to prevent thromboembolic events and lower all-cause mortality. To achieve the optimal risk-benefit balance, patients who are contemplating restarting OAC may begin taking it approximately seven to eight weeks after ICH, taking into consideration their individual characteristics [68]. Despite aligning with the resumption of the OAC statement in the US guidelines, the most current Japanese national medical guidelines do not specify when OAC can be resumed [69].

Overall, the management of OACs in AF patients post-ICH necessitates a nuanced approach, balancing the risk of recurrent ICH against the benefits of stroke prevention and reduced mortality. While resuming OACs carries inherent short-term risks, long-term data suggest that the advantages of preventing thromboembolic events may outweigh these risks, particularly with careful monitoring and individualized assessment. Optimal timing appears crucial, with evidence suggesting a 6-8 week delay post-ICH minimizes mortality without significantly increasing hemorrhagic events. NOACs may offer a safer alternative to VKAs, demonstrating lower risks of ischemic stroke and ICH. However, a significant gap remains in high-quality research, emphasizing the need for larger, well-designed, randomized controlled trials to further define optimal strategies and identify patient subgroups who may benefit most from continued anticoagulation. Ultimately, shared decision-making between clinicians and patients is essential to optimize anticoagulation therapy in this vulnerable population.

Conclusion

Clinicians continue to face difficulty in managing OAC after ICH in AF patients. Patients with AF following ICH who received OAC demonstrated superior efficacy profiles without an increased risk of recurrent ICH or severe hemorrhage. In comparison to VKA, DOACs were discovered to have a greater advantage in preventing stroke and mortality, as well as a reduced incidence of recurrent ICH. The optimal timing for resuming OAC after ICH encompassed a range of 7 days to 3.1 years, as indicated by the observational studies this review examined. However, additional research is needed to determine whether DOAC is superior, as the few RCTs lack evidence.

Disclosure of conflict of interest

None.

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