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Comparison of early and delayed anticoagulation therapy after ischemic stroke in patients with atrial fibrillation: a systematic review and meta-analysis

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Abstract
The optimal initiation timing of oral anticoagulants (OACs) remains controversial in patients with atrial fibrillation (AF)-related acute ischemic stroke (AIS). The aim of this study is to compare the efficacy and safety of early OACs initiation with that of the delayed initiation for AIS and AF.We searched systematically the following mainstream databases: PubMed, Embase, and Web of Science from the inception to July 2023 for studies that compared the early initiation with the delayed initiation of OACs for AF-related AIS patients. Outcome measures were the incidence of hemorrhagic events, ischemic events, and combined outcomes, as well as all-cause mortality.There were 12 eligible articles included (10 cohort studies and 2 RCT), involving 11421 patients (5690 patients in the early-initiation group and 5731 in the delayed-initiation group). Meta-analysis revealed that patients receiving OACs at the early stage of stroke had a lower incidence of ischemic events (OR: 0.68; 95% CI: 0.55,0.84; p = 0.0003) and combined outcomes (OR=0.74, 95% CI (0.57,0.95), p=0.02). No significant differences were identified in the incidence of hemorrhagic events (p = 0.26) and all-cause mortality (p = 0.20) between the groups.Early initiation of anticoagulation therapy would be preferable in lowering the incidence of ischemic events and combined outcomes in AIS patients with AF. It is safe compared to the delayed-initiation strategy. However, the conclusion of this study needs to be further validated by more well-designed RCTs.

Keywords Stroke · Atrial fibrillation · Anticoagulation · Secondary prevention · Therapy · OACs

Introduction

For patients suffering from acute ischemic stroke (AIS), concomitance with atrial fibrillation (AF) could typically increase the risk for recurrent ischemic stroke, especially in the early stage after the initial episode [1]. Statistical data have shown that the risk of recurrent stroke ranges from 0.5 to 1.3% per day in the first 14 days after the initial episode in patients receiving no anticoagulation therapies [2]. Previous studies conducted in multiple regions recommended vitamin-K antagonists (VKAs) as a first-line intervention for the prevention of recurrent stroke. Since 2010, 4 direct oral anticoagulants (DOACs) have been approved for medication in patients with non-valvular atrial fibrillation, including apixaban, dabigatran, edoxaban, and rivaroxaban [3], while the most preferable timing for the initiation of these agents after cardioembolic ischemic stroke remains controversial.

Warfarin is the most commonly-used anticoagulative agent in clinical practice. However, several randomized controlled trials (RCTs) have demonstrated that DOACs would be of similar efficacy compared to warfarin while of a lower risk for intracranial hemorrhage in patients with non-valvular AF (NVAF) [4]. The increasing application of DOACs could probably promote the change in the initiation timing of anticoagulation therapy.

There are many concerns and controversies over the initiation timing of OACs. Some studies suggest that the risk of recurrent ischemic stroke and intracranial hemorrhage is highest in the first few days after acute ischemic stroke [5]. The administration in the first few days after stroke could

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indeed reduce the incidence of recurrent stroke, whereas it might increase the incidence of hemorrhagic events such as symptomatic intracranial hemorrhage (ICH) and hemorrhagic transformation [6]. A study by Mizoguchi et al. has found no differences in the incidence of adverse events (recurrent stroke, systemic embolism, bleeding, and death) between early and delayed use of DOACs after AF-related ischemic stroke or transient ischemic stroke [4]. However, Baker et al. have reported that the incidence of ICH would be higher in patients receiving anticoagulation therapy early after stroke, compared with those who have delayed the initiation, while there were no significant differences in the incidence of other outcomes [7]. Another study by Matos Ribeiro showed that early anticoagulation therapy was associated with a lower recurrence rate of ischemic stroke and more favored functional outcomes at 3 months [8].

Therefore, to address the controversy over the initiation timing of anticoagulation therapy, we have conducted this systematic review and meta-analysis to critically compare the efficacy and safety of early initiation with delayed initiation of OACs (including VKA and DOACs) in patients with AIS and AF.

Materials and methods

This study is conducted and reported strictly following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, and the study protocol has been pre-registered on PROSPERO (registration No. CRD42023391978). The PRISMA checklist [9] is presented in Online Resource 1.

Literature search

The following mainstream electronic English databases were searched from the inception of the databases to July 2023: PubMed, Embase, and Web of Science, the detailed search strategy for each database was presented in Online Resource 2. Furthermore, the reference lists of retrieved articles were searched manually to avoid missing eligible studies. All the identified studies were independently screened by two review authors and any disagreement would be resolved through discussion.

Identification of eligible studies

The following inclusion criteria were defined for study inclusion:

(1) Study design: randomized controlled trial (RCT), cohort study, or case control study.
(2) Types of participants: patients with AIS and AF.
(3) Intervention: anticoagulation therapy initiated at an early or late stage of stroke.
(4) Reporting on more than one of the following outcome measures: ischemia recurrence rate, incidence of hemorrhagic events, and all-cause mortality.
(5) Providing sufficient data for calculating the weighted mean difference (WMD) and pooled odd ratio (OR).

Literature reviews, letters, case-report, comments, conference summaries, studies with full texts unavailable, and studies reported and published in non-English were excluded.

Data extraction

The data were extracted by two review authors independently, and the disagreements were settled by discussing with a third review author to make a consensus. The extracted contents were: name of the first author, date of publication, study period, nationality, study-design, number of recruited patients, follow-up duration, characteristics of the participants (age, gender, CHADS2 score, CHADS2-VASc score, HASBLED score, NHISS Score, etc.), and outcome measures (hemorrhagic events, ischemic events, combined outcomes, and all-cause mortality).

For continuous data reported in the original studies as median (range interquartile), the mean with the standard deviation (MD) would be calculated via a validated mathematical method [9, 10].

Quality assessment

Newcastle–Ottawa Scale (NOS) was adopted for assessing the quality of observational studies [11], and studies scored 7–9 were regarded as "high quality" [12]. As for RCTs, the Cochrane risk-of-bias tool was used [13]. Two review authors independently completed the process of quality assessment, with the disagreements settled through discussion.

Statistical analysis

Review Manager (RevMan) 5.4 software (Cochrane Collaboration, Oxford, UK) was adopted for data synthesis and meta-analysis. WMD and OR were applied as pooled statistics for continuous data and dichotomous data, respectively. The 95% confidential interval (95%CI) of each variable was provided. Chi-squared (χ^2) test and I^2 statistic were adopted for testing the heterogeneity among the studies [14]. A p value < 0.05 in χ^2 test with an $I^2 > 50\%$ indicated that evident heterogeneity existed, and thus a random-effect model

was used for meta-analysis. Otherwise (p value > 0.05 in χ^2 test with an $I^2 < 50\%$), a fixed-effect model was applied. One-way sensitivity analysis was also conducted to detect the effect of each included study on the pooled results. A funnel plot was produced to reveal the existence of publication bias.

Results

Study selection and characteristics

The PRISMA flow diagram of the literature searching and screening process is provided in Fig. 1.

The searches in PubMed(n = 4874), Embase (n = 1231), and Web of Science (n = 1217) retrieved 7322 articles. Following the process of duplicate-checking, the titles and abstracts of 5719 articles were browsed. A total of 12 studies meeting the inclusion criteria were included [4, 5, 7, 8, 15–22], involving 11,421 patients who had administered OACs after being diagnosed with AF-related IS. Among the included studies, 10 were cohort-design [4, 7, 8, 15–18, 20–22], and 2 was RCTs-design.[5, 19]. Characteristics and the score of quality assessment of the studies are presented in Table 1.

The included RCTs were graded as "low risk" in all the domains, and the 10 cohort studies were graded as "high quality", with a median score of 8 (7–8) [4, 7, 8, 15–18, 20–22]. Detailed results of the quality assessment are presented in Online Resource 3 and 4.

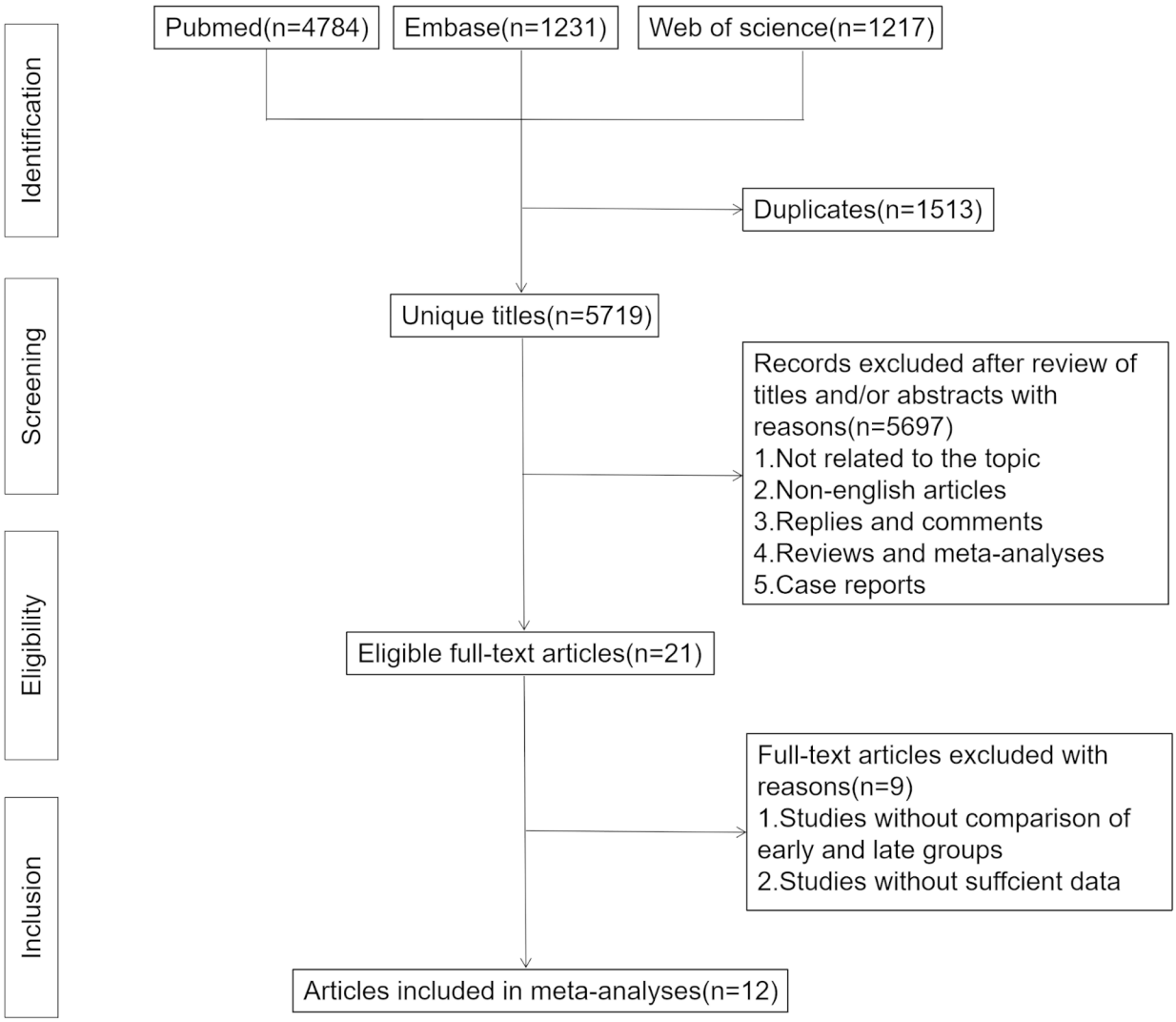

Fig. 1 Flow chart

Table 1 Baseline characteristics of include studies and methodological assessment

Authors	Study period	Country	Study design	Patients (n) Early/Late	Median follow-up	Quality score
Bakr 2020	2016–2018	Kingdom of Saudi Arabia	Cohort study	55/23	4.5months	8
Marchis 2022	2011–2018	Europe and Japan	Cohort study	1362/1188	30days	7
Kimura 2022	2011–2016	Europe and Japan	Cohort study	785/1012	90days	8
Kimura 2021	2013–2018	Japan	Cohort study	191/44	90days	7
MatosRibeiro 2022	2017–2019	Portugal	Cohort study	134/100	90days	8
Mizoguchi 2020	2011–2014	Japan	Cohort study	223/276	2 years	8
Oldgren 2022	2017–2020	Sweden	RCT	450/438	90days	-
Paciaroni 2020	2018–2019	Europe, North America and Asia	Cohort study	468/531	90days	7
Wilson 2019	-	UK and the Netherlands	Cohort study	358/943	90days	8
Yaghi 2020	2015–2018	United States	Cohort study	617/137	90days	8
Macha 2016	2011–2013	-	Cohort study	41/32	30days	7
Fischer 2023	2017–2022	Europe, the Middle East, and Asia	RCT	1006/1007	60days	-

Table 2 Demographics and clinical characteristics of included studies

Outcomes	Studies	No. of patients Early/Late	WMD or OR	95% CI	p-value	Heterogeneity			
						Chi^2	df	p-value	I^2 (%)
Age (years)	9	4414/5019	-0.00	[-0.78, 0.78]	1.00	21.09	8	0.007	62
Gender (female)	10	5031/5156	0.97	[0.89, 1.05]	0.4	6.10	9	0.73	0
CHADS2 Score	4	1254/1355	0.35	[-0.07,0.78]	0.1	47.56	3	< 0.00001	94
CHADS2-VASc Score	6	3925/4470	0.26	[-0.02,0.54]	0.07	81.63	5	< 0.00001	94
HASBLED Score	5	2616/2473	-0.27	[-0.45,-0.09]	0.003*	19.75	4	0.0006	80
NHISS Score	9	4382/4717	-4.01	[-6.65,-1.36]	0.003*	859.45	8	< 0.00001	99

* Statistically significant.

WMD, weighted mean difference; OR, odds ratio; CI, confidence interval.

Demographic characteristics

Between the two groups, no evident differences were identified in age (WMD:0.00; 95% CI: -0.78, 0.78; p = 1.00), gender (female/total, OR: 0.97; 95% CI: 0.89, 1.05; p = 0.40), CHADS2 Score(WMD:0.35; 95% CI: -0.07,0.78; p = 0.1), and CHADS2-VASc Score (WMD: 0.26; 95%CI: -0.02,0.54; p = 0.07).

There were evident differences in the HASBLED Score (WMD: -0.27; 95% CI: -0.45,-0.09;p = 0.003) and NHISS Score (WMD: -4.01; 95% CI:-6.65,-1.36;p = 0.003) between the groups (Table 2).

Hemorrhagic events

There were 10 studies reporting the incidence of hemorrhagic events [4, 5, 7, 8, 16–18, 20–22], involving 7903 participants (3840 in the early-initiation group and 4063 in the delayed-initiation group). The pooled results indicated no evident difference in the incidence of hemorrhagic events between the two groups (OR:0.72; 95% CI: 0.41, 1.27; p = 0.26). Significant heterogeneity existed among the studies (I^2 = 66%, p = 0.003) (Fig. 2). The funnel plot showed the presence of slight publication bias (Fig. 3A).

Ischemic events

There were 9 studies that reported ischemic events [4, 5, 7, 8, 16, 17, 20–22], with a total of 7830 patients (3799 in the early-initiation group and 4031 in the delayed-initiation group). The pooled results indicated that patients in the early-initiation group had an evidently lower incidence of recurrent ischemia (OR: 0.68; 95% CI: 0.55,0.84; p = 0.0003) (Fig. 4). No evident heterogeneity (I2 = 0%, p = 0.44) and publication bias was confirmed among the studies(Fig. 3B).

Combined outcomes

There were 5 studies that provided data on combined outcomes [15, 19, 20–22], with 6492 patients (3255 in the early-initiation group and 3237 in the delayed-initiation group). Meta-analysis revealed that patients receiving OACs at the early stage of stroke had an evidently lower incidence of combined outcomes (OR: 0.74; 95% CI:0.57,0.95; p = 0.02) (Fig. 5). No evident heterogeneity (I2 = 46%, p = 0.12) and publication bias was confirmed among the studies (Fig. 3C).

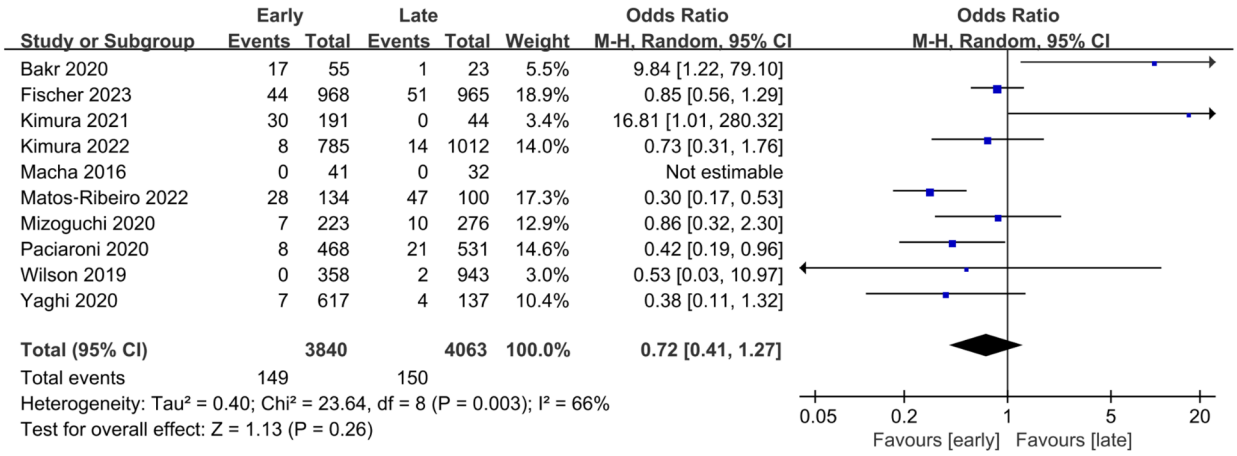

Fig. 2 Forest plot for Haemorrhagic

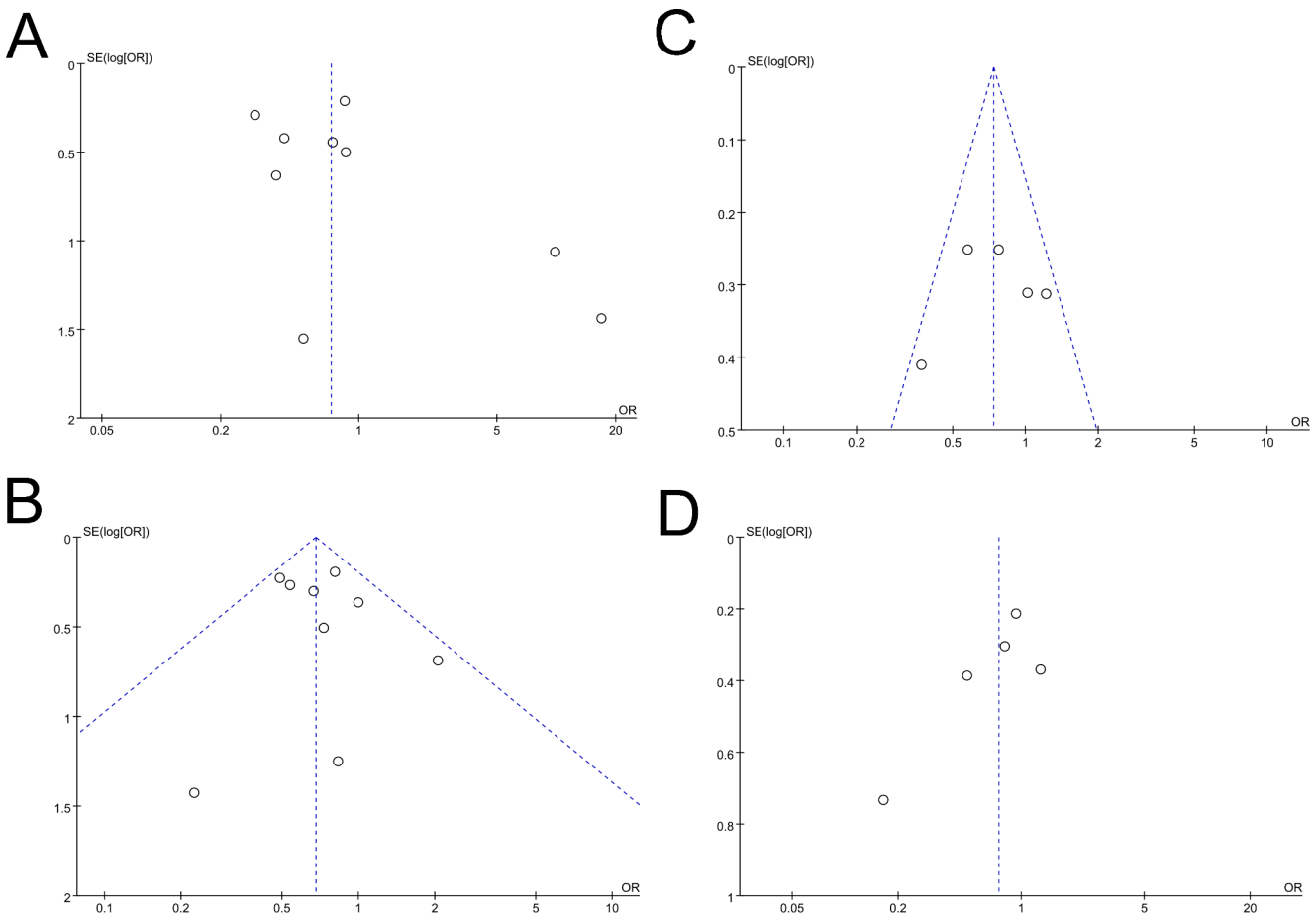

Fig. 3 Funnel plot for (**A**) Haemorrhagic endpoint, (**B**) Ischaemic endpoint, (**C**) Combined endpoint, (**D**) Mortality

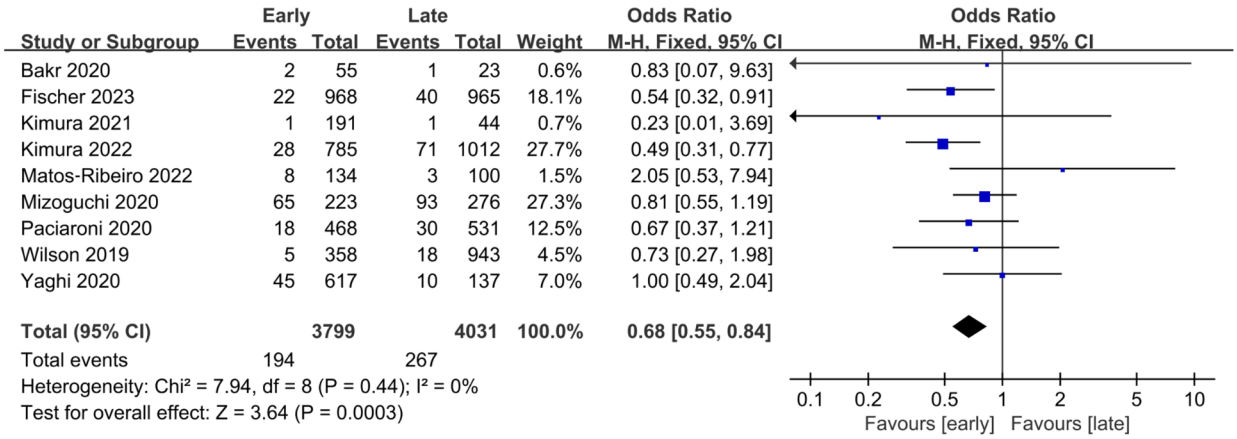

Fig. 4 Forest plot for Ischaemic

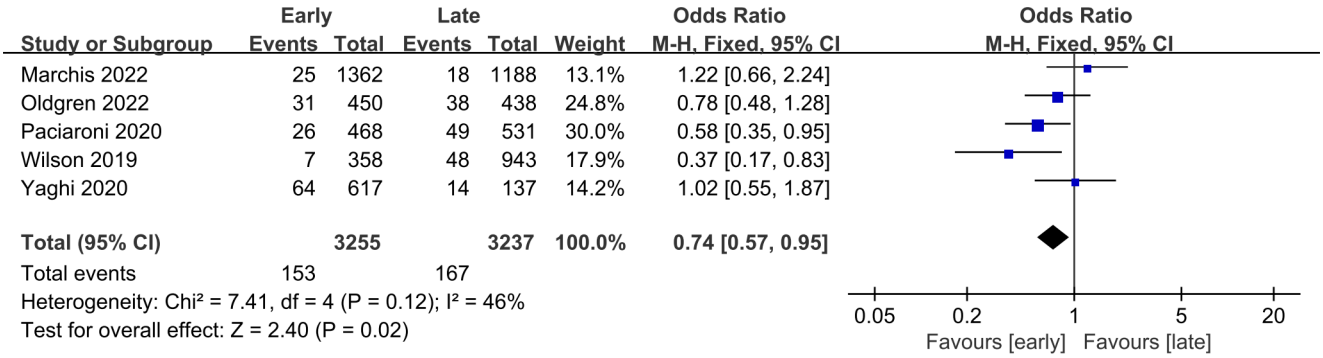

Fig. 5 Forest plot for Combined

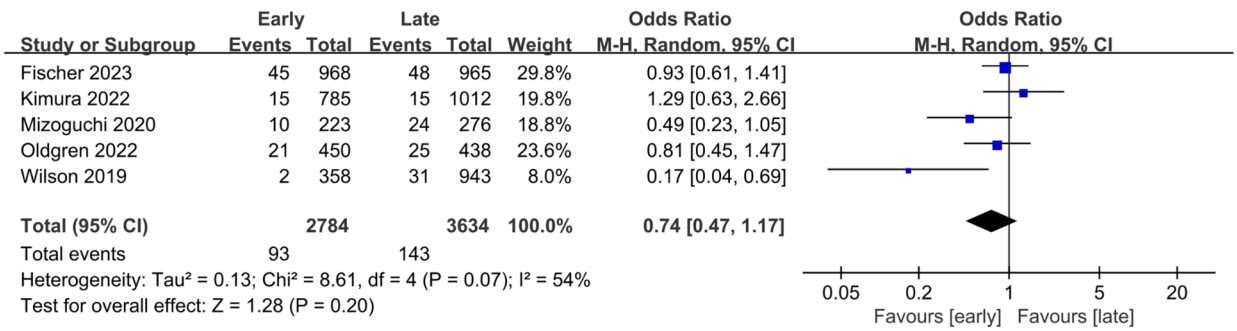

Fig. 6 Forest plot for Mortality

Mortality

There were 5 studies reporting the all-cause mortality of the patients [4, 5, 16, 19, 21], involving 6418 patients (2784 in the early-initiation group and 3634 in the delayed-initiation group). No evident difference was identified in all-cause mortality between the two groups (OR: 0.74; 95% CI:0.47,1.17; p = 0.20). Significant heterogeneity existed (I2 = 54%, p = 0.07) (Fig. 6), and no evidence of publication bias was confirmed through the funnel plot (Fig. 3D).

Sensitivity analysis

A one-way sensitivity analysis was performed for the incidence of hemorrhagic events (Fig. 7) and all-cause mortality (Fig. 8), so as to detect the effect of each study on the

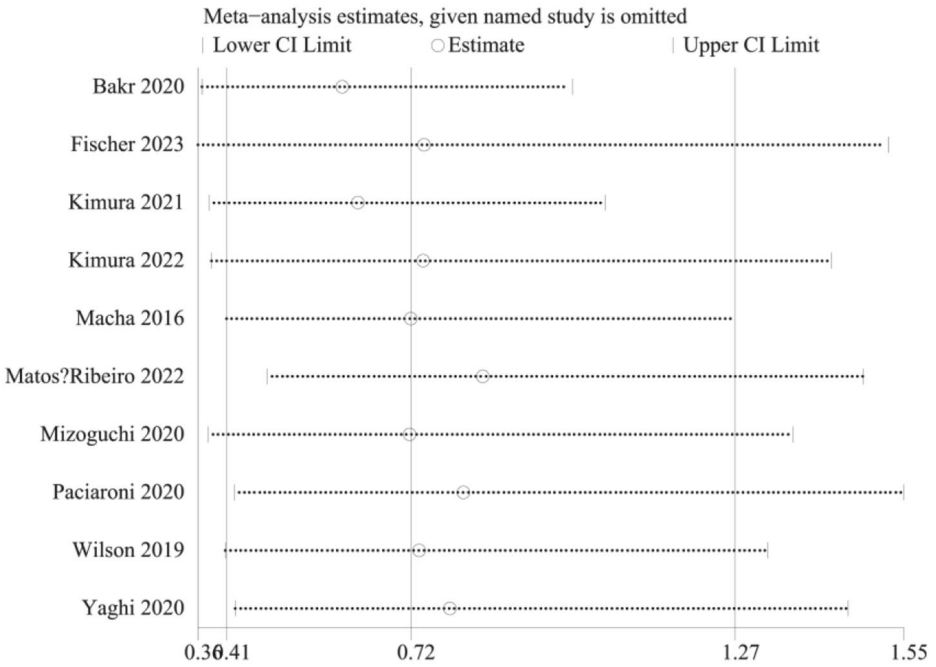

Fig. 7 Sensitivity Analysis diagram of Haemorrhagic endpoint

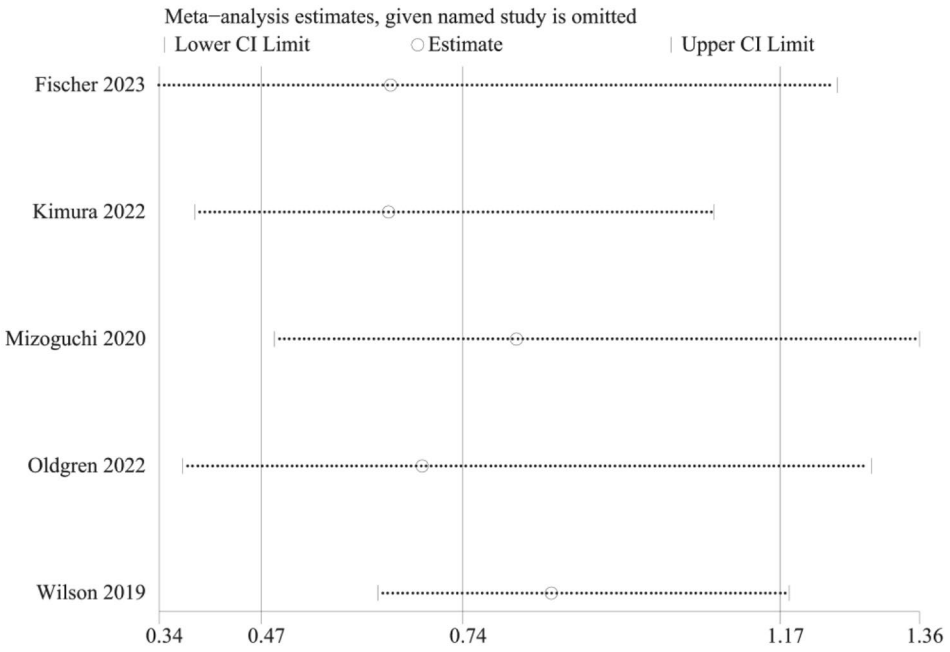

Fig. 8 Sensitivity Analysis diagram of Mortality

pooled results. After the one-by-one removal of the studies reporting hemorrhagic events, the pooled OR failed to be reversed.However, the exclusion of the study by Wilson et al. [21] resulted in decreased heterogeneity for the mortality ($I^2 = 14\%$, $p = 0.32$), suggesting that this study would be a source of heterogeneity.

Discussion

Episode of cardioembolic stroke in the setting of atrial fibrillation (AF) is of a significantly high risk of mortality. Those patients also have high morbidity of recurrent stroke in the first 90 days after the preliminary attack [23].

Direct oral anti-coagulants (DOACs) and Vitamin-K antagonists (VKAs) have been recommended for secondary prevention in patients with non-valvular AF [3].

Recent international guidelines provide no specific recommendations on the initiation timing of OACs after AF-related AIF due to the controversies over the benefits of early initiation and delayed initiation of OACs. According to the guideline released by the American Heart Association, OACs are recommended within 4 to 14 days after the episode of cardioembolic stroke [24]. However, such a recommendation is typically based on the results of observational studies that fail to consider several circumstances that might affect the clinical decision on the initiation of OACs after the episode of stroke [3, 21, 25, 26]. Guideline released by the European Stroke Organization (ESO) [27] recommends a delayed OACs administration, for patients with disabling ischemic stroke to at least 14 days after the episode of stroke, and the specific timing could be decided by clinicians. For non-disabling ischemic stroke, OCAs administration should be initiated no more than 14 days after the stroke. As for patients with TIA, anti-coagulation therapy is typically initiated immediately. Guideline released by the European Society of Cardiology guidelines [28] recommends that initiation of OACs is based on the infarct size at 1, 3, 6, or 12 days, which could be assessed by experts.

There have been multiple retrospective and observational studies published recently. These studies explored the early OACs administration in AIS patients, and found that early OACs administration did not increase the incidence of recurrent stroke or mortality [18, 25, 26, 29–32]. There are 4 ongoing RCTs (ELAN [NCT03148457] [33], OPTIMAS [NCT03759938] [34], TIMING [NCT0291348] [19], START [NCT03021928] [35]) that aim to evaluate the safety and efficacy of early OAC administration for ischemic stroke. The TIMING and ELAN studies have been recently completed, and the details will be elaborated on and discussed in the following part.

In view of the above situations, we conducted this study that included 12 comparative studies with a total of 11,421 participants,the conclusions are intended to provide a direction of clinical practice. The results showed that AIS patients receiving OACs in the early stage had a lower recurrence rate of ischemic events. However, this study did not consider the fact that patients receiving anti-coagulation therapy at the early stage often had lower HASBLED score and NHISS score, so selective bias would exist. Because of the limitations of the study, patients' characteristics varied to some extent between the early-OAC initiation group and the delayed-OAC initiation group. In most of the included studies, the condition of patients receiving OACs at the early stage was milder while those receiving OACs more than 1 week after the stroke were more severe. There are still 2 studies that had no significant differences in HASBLED score and NHISS score between the two groups after using some statistical methods. In the study by Kimura et al., the occurrence of systemic embolism and stroke was less common in the early-initiation group (n = 785) (defined as initiating DOACs within 1–4 days), compared with the delayed-initiation group (n = 1012) [(1.9% versus 3.9%), HR = 0.50, 95%CI (0.27, 0.89)], as well as the incidence of ischemic stroke [(1.7% versus 3.2%), HR = 0.54, 95%CI (0.27, 0.999)] [16]. The study by Oldgren et al. also showed that the early-initiation group had a lower incidence of ischemic stroke than the delayed-initiation group (3.11% versus 4.57%, risk difference=-1.46% [95% CI, -3.98–1.07%]) [19]. These studies firmly supported that the early administration of anticoagulants could effectively prevent the recurrence of ischemia.

On the other hand, analyses of the safety outcomes in the two groups found no significant difference in the incidence of hemorrhagic events and mortality, which was inconsistent with the previous studies that early administration of anticoagulants would be of higher risk for hemorrhagic events. However, the reason for these findings might be attributed to the increasing use of DOACs, but previous conclusions were largely based on studies of warfarin. Our meta-analysis combined VKA and DOAC studies, which provided stronger supporting evidence. Due to the small sample size, there are DOAC-only and OAC studies included. The results might be reversed if all included studies used DOACs. Different HASBLED score and NHISS scores also affect the accuracy of safety results. Similarly, we analyzed the 2 studies that had no significant differences in HASBLED score and NHISS score. In the study by Kimura et al., the incidence of major bleeding presented to be similar between the groups (0.8% versus 1.0%), as well as that of intracranial hemorrhage (0.2% in the early-initiation group and 0.6% in the delayed-initiation group) [16]. In the study conducted by Oldgren et al., the all-cause mortality of the patients was 4.67% in the early-initiation group and 5.71% in the delayed-initiation group [RD=-1.04%, (95% CI (-3.96, 1.88)]. There was no report regarding the occurrence of symptomatic intracerebral hemorrhage in the patients [19]. Therefore, early initiation of OACs would not be unsafer than the delayed initiation for AIS patients with AF.

Third, a pooled analysis of combined outcomes evaluated showed that the early group had less incidence rate of efficacy and safety outcomes. The present result contradicted the report of Palaiodimou et al [36], a similar meta-analysis published in recent years, which showed that OACs initiation within the first week after stroke might be of comparable efficacy and safety compared to the initiation within two weeks after stroke, while DOACs presented to be

more effective in reducing the incidence of recurrent stroke and improving the survival of the patients, compared with VKAs. Our study included more newly-published studies, with a larger sample size, which would make a difference.

Our study is the latest and largest meta-analysis that compares directly the efficacy and safety of OACs administration at different timing in AIS patients with AF. However, there is no doubt that several limitations exist. Firstly, our meta-analysis included just 2 RCTs (16.7%), whereas the other studies were retrospective or prospective cohort-design, without appropriate processing of confounding factors. As for the incidence of hemorrhagic events and all-cause mortality, evident heterogeneity was observed. Though sensitivity analysis was conducted to assess the robustness of the results, the sources of heterogeneity could not be identified. Given the potential confounding factors, the results of this study ought to be interpreted prudently. Finally, we failed to perform a more comprehensive assessment to specify the timing of early OACs administration in that the definition of the initiation timing varied among the studies.

Despite the limitations mentioned above, our study is the latest and largest meta-analysis regarding optimal initiation timing of OACs in AIS patients with AF. Most of the included studies were published between 2019 and 2022, especially 2 influential RCTs [5, 19] were published in 2022 and 2023, which makes the evidence more reliable. The evidence produced by our study further supported the superiority of early initiation of OACs for preventing the recurrence of stroke in AIS patients with AF, which has been reported in previous study. Meanwhile, we found that early initiation of OACs did not cause more hemorrhagic events. More well-designed and large-scale RCTs with a long follow-up duration are expected to further identify the optimal initiation timing of OACs.

Conclusion

The present meta-analysis indicates that early initiation of OACs could be more effective in preventing the recurrence of ischemic events and reducing the incidence of combined outcomes in AF-related AIS patients. And early-initiation of OACs would be of similar safety (hemorrhagic events and mortality) to the delayed initiation. These findings require further validation by more RCTs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-023-02872-0.

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Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare that they have no competing interest.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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