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Effectiveness and safety of non-vitamin K oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke: A systematic review and meta-analysis

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Short Title: Effectiveness and safety of NOAC versus warfarin

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Abstract

Introduction: Current evidence regarding the clinical outcomes of non-vitamin K oral anticoagulants (NOACs) versus warfarin in patients with atrial fibrillation (AF) and previous stroke are inconclusive, especially in patients with previous intracranial haemorrhage (ICrH). We aim to undertake a systematic review and meta-analysis assessing the effectiveness and safety of NOACs versus warfarin in AF patients with a history of stroke.

Methods: We searched studies published up to 10th December 2022 on PubMed, Medline, Embase and Cochrane Central Register of Controlled Trials. Studies on adults with AF and previous ischemic stroke (IS) or IrCH receiving either NOACs or warfarin and capturing outcome events (thromboembolic events, ICrH, and all-cause mortality) were eligible for inclusion.

Results: Six randomized controlled trials (including 19489 patients with previous IS) and fifteen observational studies (including 132575 patients with previous IS and 13068 patients with previous ICrH) were included. RCT data showed that compared with warfarin, NOACs were associated with a significant reduction in thromboembolic events (OR 0.85, 95% CI 0.75-0.96), ICrH(OR 0.57, 95% CI 0.36-0.90) and all-cause mortality (OR 0.88, 95% CI 0.80 to 0.98). In analysing observational studies, similar results were retrieved. Moreover, patients with previous ICrH had a lower OR on thromboembolic events than those with IS (OR 0.66, 95% CI 0.46-0.95 versus OR 0.80, 95% CI 0.70-0.93) in the comparison between NOACs and warfarin.

Conclusions: Observational data showed that in AF patients with previous stroke, NOACs showed better clinical performance compared to warfarin and the benefits of NOACs were more pronounced in patients with previous IrCH versus those with IS. RCT data also showed NOACs are superior to warfarin. However, current RCTs only included AF patients who survived an IS and further large RCTs focus on patients with previous ICrH are warranted.

Introduction

The risk of stroke recurrence is particularly high in patients with atrial fibrillation (AF) and previous stroke (1). Oral anticoagulation (OAC) therapy showed better clinical performance for secondary stroke prevention compared with no treatment in these patients (2-4). Warfarin used to be the most common OAC worldwide, but it has several limitations such as a narrow therapeutic window and the need for frequent blood tests to monitor coagulation levels regularly. Moreover, risk of warfarin -related intracranial haemorrhage (ICrH) also limits its usage, especially in patients with AF who survived after ICrH (4). However, the situation changed with the availability of a newer class of OAC- non-vitamin K antagonists (NOACs). Previous meta-analysis showed that the rates of ICrH after NOACs were 0.55% versus 0.91% after warfarin(5). Evidence suggest that compared to warfarin, NOACs showed comparable efficacy and superior safety of reducing ICrH risk by 50% in patients(-6-7). As the guideline recommendation, NOACs are currently considered first choice treatment for secondary prevention due to their comparable efficacy, better safety and easier administration without the need for frequent blood tests (8-9).

Despite strong recommendations on NOACs over warfarin in patients with non-valvular AF and previous ischemic (IS) for secondary prevention of all events, the effectiveness and safety of NOACs compared with warfarin in patients with AF who survived an ICrH has rarely been evaluated. Previous systematic review and mate-analyses have reported the beneficial effects of OAC treatment on lowering the risk of ischemic stroke without increasing ICrH recurrence in these populations (10-11), but NOACs were not analysed as an anticoagulation treatment option in these studies. Therefore, data on whether NOACs are superior to warfarin in reducing the risk of recurrent ICrH in patients with a history of ICrH are lacking. In this study, a systematic review and meta-analysis was performed with the aim of comparing the effectiveness and safety of NOACs to warfarin in patients with non-valvular AF and previous IS or ICrH. We also aim to evaluate if patients with AF and a history of ICrH benefit more from NOACs when compared with patients with previous IS.

Method

This review was conducted in accordance with the PRISMA guidelines. The review protocol was registered with the PROSPERO database of systematic reviews: CRD42022382732.

Search strategy and selection criteria

The following four databases were searched for the systematic review from inception to 10th December 2022: PubMed, Medline, EMBASE and Cochrane Central Register of Controlled Trials. There were no restrictions on language or duration of follow-up. Details of the search strategy are shown in the Supplementary materials. We included randomized controlled trials(RCTs) or cohort studies that recruited participants (aged>=18years) with AF and a history of IS/ transient ischemic attack or nontraumatic spontaneous ICrH of any size and any type. Patients with a diagnosis of post-operative AF, valvular AF, AF associated with mechanical valve malfunction, AF associated with mechanical complication of heart valve prosthesis, or rheumatic AF were excluded. This study chose NOAC as interventions in the experimental group. Warfarin treatment was chosen as the intervention for the control group, regardless of dose and frequency. Control groups treated with a placebo, with no intervention or antiplatelet drugs such as aspirin were excluded.

Outcomes

The outcomes of interest were thromboembolic events, ICrH and all-cause mortality. Thromboembolic events were chosen to reflect the range of definitions used in the included studies (such as deep vein thrombosis, ischemic stroke, myocardial infarction or systemic embolism).

Data Extraction

One reviewer (MS) first scrutinized all titles and abstracts after removing duplicate papers and excluded clearly irrelevant articles. The remaining studies were read in full against the inclusion and exclusion criteria independently by the two investigators (MS and HW). Discussion between the two reviewers was used to resolve disagreements, and a third arbiter (YW) was available if resolution could not be reached. Extracted data included study design, participant characteristics, sample size, type and doses of anticoagulant, initiation and duration of anticoagulant, outcome measurements and length of follow-up.

Bias and quality assessment

The Newcastle-Ottawa Scale (NOS) tool was used to assess the quality of observational cohort studies (12) according to the selection of study groups, their comparability, and outcome assessment in the studies. The score could range

between 0 and 9. Cochrane Collaboration's tool was used for RCTs (13) for assessing risk of bias, assigning low, high, or unclear risk of bias based on the process of sequence generation, allocation concealment, blinding, data collection, and outcome reporting.

Data synthesis and statistical analyses

We performed two meta-analyses, one included the observationl studies comparing NOAC versus warfarin on the related outcomes, the other included only the RCTs. This study used both random-effects model (when heterogenity=0) and fix-effects model(when heterogeneity>0) to conduct a typical pairwise meta-analysis for each pairwise comparison of treatments to estimate all primary and secondary outcomes as odds ratio (OR) with associated 95% confidence intervals (CIs). For Q statistics, the I^2 statistic and p-value were used to calculate the proportion of variability across studies that may be attributed to heterogeneity. An I^2 value of less than 25% is viewed as low heterogeneity, 25% to 50% as moderate heterogeneity, and over 50% as high heterogeneity.

For studies with more than one follow-up point, results from the longest follow-up were included in the main analysis. With multiple publications from a single database, the study with the largest number of patients was selected to avoid duplication of data. Subgroup analyses were performed based follow-up period (<=1 year and > 1 year) and geographic locations (Asia, Europe and North America)

The software Review Manager (RevMan) Version 5.4 was used to perform pairwise analysis, forest plots and funnel plots. In this meta-analysis, a p-value <0.05 was considered statistically significant for all comparisons.

Results

A total of 8448 articles were identified through the searches. After eliminating duplicate records,5709 articles were screened by titles and abstracts for eligibility and 268 articles remained. By full-text review,21 articles were eventually included in the meta-analysis study. The flow chart is shown in Fig. 1.

Characteristics of the included studies

Randomized controlled trials

A total of 6 RCTs (14-19) comprising 19489 participants (mean age ranging from 70.1 to 79.4 years, 57.9% to 84.6% males, follow-up ranged from a median of 30 days to a median of 2.8 years) were included in the analysis.All the RCTs only included patients with AF and previous IS. Five studies (14,16-19) used CHADS2 to assess the risks of stroke recurrence. Two of them(14,18) had a mean score> 3 and the rest three(16,17,19) showed the proportion of patients with a score>3 ranged from 67%-92%. The other one study (15) with the mean HAS-BLED score <2. Baseline characteristics of each study are shown in Supplementary Table1.

Observational data

Fifteen observational studies(20-34)(n= 145643 patients) compared NOAC versus warfarin.The mean age of the patients ranged from 69.0 to 83.9 years, with male sex comprised 35.0% to 70.7%. Follow-up time were between a median of 16.1 days to a median of 5.4 years. Six studies (20,26-28,32,34) included participants with AF and a history of ICrH (one study only included AF patients with previous intracerebral haemorrhage (ICH)(32) and the other 4 studies included patients with both intracerebral and other types of ICrH), while nine studies (21-25,29-31,33) focused on AF patients with previous IS. One of the studies (34) included both patients with previous ICrH and those with previous IS. The risks of stroke recurrence differed significantly across the studies as shown either by the mean(SD) (21-23,26-30,34) or the median (IQR) (20,34)of CHA2DS2- VASc score. The medians of score ranged from 4 to 6 and the means were between 2.3 and 6.8. The risks of bleeing shown by HAS-BLED score varied from <2 to >4. NIHSS score were reported in 5 studies(21-23,29-30) to assess stroke severity. There was a great difference in the medians of the score with a range from 3 to 11. Baseline characteristics of each study are shown in Supplementary Table2.

Outcome of interest

Randomized controlled trials

Thromboembolic Events

Six studies (14-19) with 19489 participants reported on the outcome of ischemic stroke or systemic embolism. The results showed NOAC treatment was associated with a significant reduced risk of thromboembolic events compared with warfarin (OR 0.85, 95% CI [0.75 to 0.96]; P=0.01; I^2=0%) (shown in Fig.2).

Incident ICrH

Five studies (15-19), including 18677 participants, reported on the outcome of incident ICrH. The pooled analysis revealed a significant reduction in incident ICrH with NOAC compared with warfarin (OR 0.57, 95% CI [0.36 to 0.90]; P=0.02; I^2=70%)(shown in Fig.2).

All-cause mortality

Five studies (15-19) included 18677participants reported on all-cause mortality. The present results found that NOAC use was associated with a reduced risk of mortality compared with warfarin treatment (OR 0.88, 95% CI [0.80 to 0.98]; P=0.02; I^2=0%) (shown in Fig.2).

Subgroup analysis

When stratifying the RCTs by follow-up, 2 studies(14-15) (n=995) at follow-up <=1 year and 4 studies(16-19) (n=18494) at>1 year compared NOAC versus warfarin on thromboembolic events, one study(15) (n=183) at follow-up <=1 year and 4 studies(16-19) (n=18494) at>1 year on incident ICrH, and one study(15) (n=183) at follow-up <=1 year and 4 studies(16-19) (n=18494) at>1 year on all-cause mortality. The pooled odd ratios demonstrating that NOAC treatment significantly reduced the risks of thromboembolic events(OR 0.86, 95% CI [0.75 to 0.98]; P=0.02; I^2=0%) and incident ICrH (OR 0.49, 95% CI [0.32 to 0.75]; P=0.001; I^2=60%) at>1 year follow-up, while at<=1 year follow-up, the efficacy was comparable in these two treatments (thromboembolic events OR 0.72, 95% CI [0.45 to 1.15]; P=0.17; I^2=0%. incident ICrH OR 1.16, 95% CI [0.62 to 2.19]; P=0.64). NOAC therapy was also associated with lower risks of all-cause mortality compared to warfarin at>1 year follow-up.No observation of mortality in both NOAC treatment and warfarin treatment in the analysis of <=1-year follow-up. Results are shown in Fig. 3.

A subgroup analysis by geographic locations can't be performed since four out of six RCTs(16-19) were multi-center studies which included patients from several countries and the rest two studies only included Asian participants.

Observational data

Thromoembolic events

Thirteen studies (20-31,33) with 142304 participants (11412 patients with a history of ICrH and 130892 patients with a history of IS) reported on the outcome of any thromboembolic events. Four studies (20,26-28) included patients with previous ICrH, nine studies (21-25,29-31,33) reported on patients with a history of ischemic stroke. The results revealed a significant reduction in thromboembolic events with NOAC compared with warfarin (OR 0.76, 95% CI [0.66 to 0.87]; P<0.001; I^2=78%) (shown in Fig. 4). Moreover, AF patients with previous IS could have a 20% reduction in thromboembolic events after receiving NOAC (OR 0.80, 95% CI [0.70 to 0.93]; P=0.003; I^2=79%), while a 34% decrease in thromboembolic events was observed in AF patients with a history of ICrH (OR 0.66, 95% CI [0.46 to 0.95]; P=0.03; I^2=75%)(shown in Fig. 4).

ICrH

Ten studies (20-21,23-24,26-29,31-32), including 119817 participants, reported on the outcome of ICrH. Five studies (20,26-28,32) included 11756 patients with an index ICrH (intracerebral, subdural, subarachnoid, or epidural haemorrhage) and five studies (21,23-24,29,31) included 108061 patients with a history of ischemic stroke. Our results showed that NOAC treatment was associated with a significant decrease in the risk of IrCH recurrence compared to warfarin therapy in AF patients with previous stroke (OR 0.55, 95% CI [0.44 to 0.68]; P<0.001; I^2=36%). NOAC resumption was associated with a 47% reduction of recurrent ICrH in AF patients with previous haemorrhagic stroke (OR 0.53, 95% CI [0.40 to 0.70]; P<0.001; I^2=25%), which was similar to the effects (44% reduction in the risk of ICH) in patients with AF who survived IS (OR 0.56, 95% CI [0.38 to 0.81]; P=0.002; I^2=34%). Results are presented in Fig. 4.

All-cause mortality

Eleven studies (20-21,23-24,26,28-32,34) including 133949 participants (12473 patients with a history of ICrH and 121476 patients with a history of IS) reported on all-cause mortality. Six studies (21,23-24,29-31) included patients with previous IS, four studies(20,26,28,32) included patients with previous ICrH and one study included both patients with a history of IS and those with ICrH (34). The present results indicated that NOAC therapy could reduce mortality in AF patients with a history of stroke by 45% compared to warfarin therapy (OR 0.55, 95% CI [0.44 to 0.70]; P<0.001; I^2=92%) (shown in Fig. 4). The reduced mortality from NOAC therapy is similar in AF patients with previous ICrH(OR 0.58, 95% CI [0.40 to 0.83]; P=0.003; I^2=89%) and in patients with previous IS(OR 0.53, 95% CI [0.39 to 0.74]; P<0.001; I^2=93%)(shown in Fig. 4).

Subgroup analysis

Subgroup analyses were performed according to follow-up period(follow-up<=1 year versus follow-up >1 year) and geographic locations (Asia versus Europe versus Notrh America). Seven studies(20-21,24,27-28,31,33) with 113832 participants reported on any thromboembolic events at follow-up <=1 year, while six studies(22-23,25-27,30) with 24182 participants at follow-up > 1 year. Five studies(20-21,24,28,31) reported on ICrH at follow-up<=1 year, three

studies (23,26,32) at follow-up >1 year and one study(27) reported on the outcome at both periods. In total, 108905 patients reported on ICrH at follow-up <= 1 year and 6622 patients at >1 year. In terms of mortality, results at follow-up <=1 year were reported in six studies (20-21,24,28,31,34)(n=111375) and follow-up >1 year were reported in four studies (23,26,30,32)(n=129037). The results showed that NOAC treatment was associated with a significant reduction in the risk of ICrH and all-cause mortality at both follow-up<=1 year (ICrH: OR 0.62, 95% CI [0.53 to 0.73]; P<0.001; I^2=4%. Mortality: OR 0.72, 95% CI [0.62 to 0.83]; P<0.01; I^2=45%) and follow-up>1 year (ICrH: OR 0.61, 95% CI [0.42 to 0.90]; P=0.01; I^2=24%. Mortality: OR 0.42, 95% CI [0.26 to 0.68]; P<0.001; I^2=96%). NOAC had a significant decreased risks in thromembolic events at follow-up<=1 year(OR 0.65, 95% CI [0.54 to 0.77]; P<0.001; I^2=72%) , while this was not significant at follow-up>1 year(OR 0.91, 95% CI [0.79 to 1.06]; P=0.22; I^2=44%). Results are shown in Fig. 5.
Seven studies (20,22-24,26,28-31) included 113481 participants from Asia, three studies(21,25,27) with 7322 patients in Europe and two studies(30,33) with 16589 participants from North America were included in the pooled analysis of assessing the thromboembolic events after NOAC treatment versus warfarin. Regarding ICrH, results on Asian were reported in six studies (20,23-24,26,28,31) with 113380 patients and on Europen were reported in three studies(21,27,32) with 1525 participants. No study in North America reported on ICrH. Six studies (20,23-24,26,28,31) with 113380 participants from Asia, three studies (21,32,34) included 3995 patients and one study(30) with 11662 patients reported on all-cause mortality. The results demonstrated that NOAC treatment significantly reduce the risks of thromboembolic events(OR 0.71, 95% CI [0.57 to 0.89]; P=0.003; I^2=69%), ICrH(OR 0.56, 95% CI [0.45 to 0.70]; P<0.001; I^2=31%) and mortality(OR 0.44, 95% CI [0.30 to 0.66]; P<0.001; I^2=94%) for Asian patients, while the observed reduced risks were not statistically significant for European patients (Thromboembolic events: OR 1.00, 95% CI [0.77 to 1.29]; P=0.98; I^2=25%. ICrH: OR 0.79, 95% CI [0.49 to 1.28]; P=0.34; I^2=0%. Mortality: OR 0.88, 95% CI [0.73 to 1.06]; P=0.17; I^2=0%) for European patients. NOAC treatment was also associated with decreased risks of thromboembolic events(OR 0.74, 95% CI [0.55 to 1.00]; P=0.05; I^2=92%) for patients in North America. Meta-analyses weren't conducted in North America on ICrH and mortality because the data is not available or not sufficient for meta-analysis (no study on ICrH and only one study on mortality). Results are shown in Fig. 6.

Risk of Bias Assessment

Risk of bias was generally low in all studies. Among the 15 studies low risk of bias was assigned to scale items ranging from 7 out of 9 to 9 out of 9 items. All 16 studies had low risk for ascertainment of exposure and assessment of outcome. One study scored 9, five studies scored 8 and the remaining nine studies scored 7. Low risk of bias of blinding outcome assessments were presented on all the RCTs except one. One study showed high risk of bias on blinding of participants, while the remaining 5 studies presented low risk of bias. In total, one study was of very high-quality with low risk of bias in 6 items and one study was of low-quality with low risk of bias in only 3 items. The other 4 studies showed showed low risk of bias in 5 items. The overall risk of bias assessment for all included Supplementary Table 3, Figs 1 and 2.

Discussion

In the present meta-analysis, the pooled estimates of observational data revealed that NOAC use was associated with reduced risks of thromboembolic events, ICrH and all-cause mortality in patients AF patients with previous stroke. The benefits of reduction in thromboembolic events were more pronounced in patients with previous ICrH than those with previous IS after receiving NOACs. NOAC therapy significantly reduced the risk of thromboembolic events at <=1 year follow-up but not at > 1 year. The risks of ICrH and mortality did not differ by follow-up time. Analysing the RCT data, only patients with previous IS were included in the pooled estimates. The pooled odd ratios demonstrated that NOAC therapy was associated with significant reduction in thromboembolic events, incident ICrH and all-cause mortality. The reduced risks of ICrH and mortality were observed at both <=1 year and >1 year follow-up, which is similar to that in the pooled analyses of observationl studies. In contrast to the results from observational data, the significant reduction in thromboembolic events was only observed at follow-up >1 year. Meta-analysis by geographic locations showed that the benefits of NOAC over warfarin were presented in Asian and American patients, while in European patients the efficacy was not significant.

Both pooled estimates of RCT data and observational studies found that NOACs are more effective than warfarin in preventing thromboembolic events and ICrH, which is consistent with current guidelines that NOAC is superior to warfarin in patients with AF and previous IS (8-9). The net benefits of NOACs in combination with the fact that international normalised ratio(INR) monitor, dose adjustment, and dietary restrictions are required for warfarin have made NOACs a better choice for stroke prevention in AF patients with previous IS. However, regarding the use of

NOACs in patients previous ICrH, there is no completed phase 3 RCT to prove its efficacy and safety. Currently, therefore, meta-analysis of observational studies provides the best evidence. Our review found that NOACs use was associated with a significantly decreased risk of thromboembolic events, recurrent ICH and mortality. Most of previous meta-analyses investigated the safety and efficacy of restarting OAC therapy after ICrH with only warfarin used in most included studies (10-11). As NOACs become more widely available, research comparing NOAC and warfarin in patients with AF and previous ICrH is warranted to guide clinical practice. Recently, one review compared the effect of NOACs versus warfarin on recurrent ICH in AF patients with a history of ICrH only included 3 observational studies with 8711 participants (3). In the present study, we updated the previous reviews with more studies and more patients included. Additionally, subgroup analyses by follow-up time and geographic locations were performed.

The benefits in reducing the risks of recurrent ICrH and all-cause mortality did not differ by follow-up time in both pooled analyses of RCT data and observational data. However, the reduction in thromboembolic events was only observed at <=1 year follow-up in observational data while in RCT data,this reduction was only seen at >1 year follow-up. In RCT data, only two studies(14,15) with a total of about 100 events were included in the pooled analysis at follow-up <1 year, which was not sufficiently powered to evaluate the efficacy. Moreover, in one(15) out of these two studies, most of the recurrent ischemic lesions were asymptomatic ones on results of MRI within 4 weeks after first stroke, which may not be captured in population-based observational studies. In the pooled analysis of observational studies, the superior efficacy of NOACs was only observed at follow-up <1 year. Possible reasons include heterogeneity in stroke severity, variation in initial timing of OAC and the possibility that high mortality rates in the warfarin group might have concealed the occurrence of the thromboembolic events. Although the benefits in reduction of thromboembolic events in subgroup analysis by follow-up period showed conflict results, it also suggest a clear trend of an appealing effectiveness profile for NOACs in comparison with warfarin in the present study. In addition, we should note these findings were from a combination of observational studies included AF patients with previous ICrH and previous IS, while the results from RCT data only included AF patients with previous IS. A recent meta-analysis(pooled analysis of a combination of observational and RCT data) comparing OAC (NOAC, warfarin,etc) and no therapy in AF patients who survived an ICrH found the superior performance of OAC in reducing thromboembolic events was only observed at <=1year follow-up(3). Moreover, most of the included studies in that review(3) were observational. In the present study, the number of observation studies on AF patients with previous ICrH is not large enough to stratify the studies by follow-up and no phase 3 RCT on patients with ICrH. Therefore, further studies focus on AF patients survived an ICrH are warranted.

It is interesting that NOAC-associated reduced risks in thromboembolic events, ICrH and all-cause mortality were shown in Asian patients, but these benefits were not statistically significant in European patients. According to previous literature, risk of warfarin-related ICrH is higher in the Asian population compared with non-Asians and NOACs seem to have a greater relative risk reduction of ICH in the Asian population than in non-Asians(35-36). This may partially account for the pronounced benefits of NOAC over warfarin in Asian patients. Another explanation may be the small number of ICrH cases in European patients, which result in limited statistical power to achieve significant. To the best of our knowledge, this is the first meta-analysis comparing the effectiveness and safety of NOAC in AF patients with a prior history of ICH and a history of IS. It is interesting that the benefits of NOACs were more pronounced in patients with previous IrCH versus those with IS. ICrH survivors are at a high risk of not only sustaining haemorrhage but also experiencing further ischemic stroke. Moreover, the risk of recurrent ischemic stroke is even higher in patients with AF and a history of ICrH compared with those without ICrH (9). NOACs showed better efficacy in anticoagulation and superior safety while reducing ICrH risk by 50%, compared with warfarin (6,7) Therefore, patients with previous ICrH, who may be more prone to have recurrent any stroke than patients with IS, would have more benefits with the treatment of NOACs.

Current recommendations to inform optimal timing of anticoagulation after both IS and ICrH are based on expert consensus. European Society of Cardiology (ESC) for the management of AF in patients who suffer a moderate-to-severe ischaemic stroke recommended that anticoagulation treatment should be interrupted for 3–12 days to allow a multidisciplinary assessment of acute stroke and bleeding risk(37). For AF patients after ICrH, the optimal timing of anticoagulation should be delayed beyond the acute phase, probably for at least 4 weeks(37). In the present study, we found only one study out of six ICrH studies reported the initiation time of NOAC (within 90 days after ICrH). To guide

optimal timing of OAC initiation after an ICrH in patients with AF, well-designed randomized controlled trials are warranted.

Strength and limitations

The key limitation of this review is that only observational cohort studies were included in the pooled estimates of comparing NOAC versus warfarin in AF patients with a history of ICrH. The clinical and methodological heterogeneity in non-randomized studies limits the results to general population. For example, differences in timing and dosage of re(initiation) of OAC therapy may result from factors associated with future bleeding risk such as age, stroke severity or size of the haematoma. These specific factors are instances of confoundings by indication in observational studies, in which patients at higher perceived risks may be less likely to be restarted on NOAC or warfarin.Several onging phase 3 RCTs comparing the efficacy and safety of NOAC versus warfarin for stroke prevention in patients with AF who survived an ICrH(38-40). will be critical to to better understand the benefits of NOACs in this patient population. Second, there was selection bias of individual studies in that some included only patients with intraparenchymal haemorrhage while others reported on both intracerebral and other types of ICH combined. Intracerebral haemorrhage is reported to be associated with a higher risk of thrombotic events than subarachnoid haemorrhage(SAH), while recurrence of SAH is considered rare (41). Third, the number of studies on AF patients with previous ICrH is not large enough to stratify the studies by follow-up. In addition, information on blood pressure control was not available, which is an important factor for ICH recurrence (42). A strength of our study is the inclusion of more studies for meta-analysis. The greater number of included studies enabled us to undertake more subgroup analyses than previous studies. All the systematic reviews identified were hand-searched for relevant studies, which decreased the number of missed studies.

Conclusion

Meta-analysis of observational studies evaluating the effectiveness and safety of NOACs suggests that compared with warfarin, NOACs are associated with lower risks of thromboembolic events, recurrent ICH, and all-cause mortality in both AF patients with a history of ischemic stroke and patients with previous ICH. Moreover, the benefits of reduction in thromboembolic events were more pronounced in patients with previous ICrH than those with previous IS after receiving NOACs. The pooled analysis of RCT data also demonstrated the superior efficacy and safety of NOACs to warfarin in AF patients with previous IS. However, no completed phase 3 RCT assessing the benefits of NOAC in AF patients with previous ICH. Because of the limitations of observational studies further evidence from RCTs is warranted to better guide clinicians in making informed decisions.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Minglei Shi, Conceptualization, Data Curation, Formal analysis, Writing – original draft; Lu Liu, Conceptualization, Funding acquisition, Writing – review & editing; Hatem Wafa, Funding acquisition, Data Curation; Vasa Curcin, Conceptualization, Supervision, Writing – review & editing and Yanzhong Wang, Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Figure Legends

Fig. 1: PRISMA flow diagram depicting the selection of included studies.

Fig. 2 Meta-analysis of RCT data: Forest plot depicting the risks of unfavorable outcomes (thromboembolic events, incident ICrH and mortality) in patients with AF and previous IS receiving NOAC versus warfarin

Fig. 3 Meta-analysis of RCT data: Forest plot depicting the risks of unfavorable outcomes (thromboembolic events, incident ICrH and mortality) in patients with AF and previous IS receiving NOAC versus warfarin by follow-up periods

Fig. 4 Meta-analysis of observational data: Forest plot depicting the risks of unfavorable outcomes (thromboembolic events, incident ICrH and mortality) in patients with AF and previous stroke receiving NOAC versus warfarin.

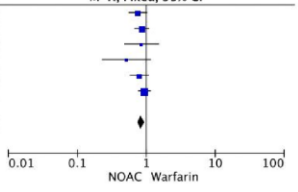
Fig. 5 Meta-analysis of observational data: Forest plot depicting the risks of unfavorable outcomes (thromboembolic events, incident ICrH and mortality) in patients with AF and previous stroke receiving NOAC versus warfarin by follow-up periods

Fig. 6 Meta-analysis of observational data: Forest plot depicting the risks of unfavorable outcomes (thromboembolic events, incident ICrH and mortality) in patients with AF and previous stroke receiving NOAC versus warfarin by geographic locations.

Thromboembolic Events

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE J Donald Easton 2012	73	1694	98	1742	17.4%	0.76 [0.55, 1.03]
ENGAGE AF-TIMI 48 Natalia S. Rost 2016	125	1976	145	1991	25.5%	0.86 [0.67, 1.10]
Keun-Sik Hong 2017	47	95	47	88	4.6%	0.85 [0.48, 1.53]
Norio Tanahashi 2013	9	407	17	405	3.1%	0.52 [0.23, 1.17]
RELY Hans-Christoph Diener 2010	106	2428	65	1195	15.7%	0.79 [0.58, 1.09]
ROCKET AF Graeme J Hankey 2012	179	3754	187	3714	33.7%	0.94 [0.77, 1.17]
Total (95% CI)		**10354**		**9135**	**100.0%**	**0.85 [0.75, 0.96]**
Total events	539		559			

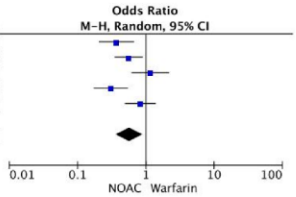
Heterogeneity: $Chi^2 = 3.13$, df = 5 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 2.57 (P = 0.01)



Incident ICrH

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE J Donald Easton(2012)	15	1694	41	1742	19.3%	0.37 [0.20, 0.67]
ENGAGE AF-TIMI 48 Natalia S. Rost(2016)	27	1976	48	1991	21.9%	0.56 [0.35, 0.90]
Keun-Sik Hong 2017	30	95	25	88	18.4%	1.16 [0.62, 2.19]
RELY Hans-Christoph Diener(2010)	19	2428	30	1195	19.6%	0.31 [0.17, 0.55]
ROCKET AF Graeme J Hankey(2012)	26	3754	31	3714	20.8%	0.83 [0.49, 1.40]
Total (95% CI)		**9947**		**8730**	**100.0%**	**0.57 [0.36, 0.90]**
Total events	117		175			

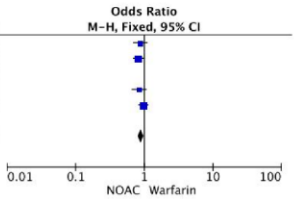
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 13.26$, df = 4 (P = 0.01); $I^2 = 70\%$
Test for overall effect: Z = 2.42 (P = 0.02)



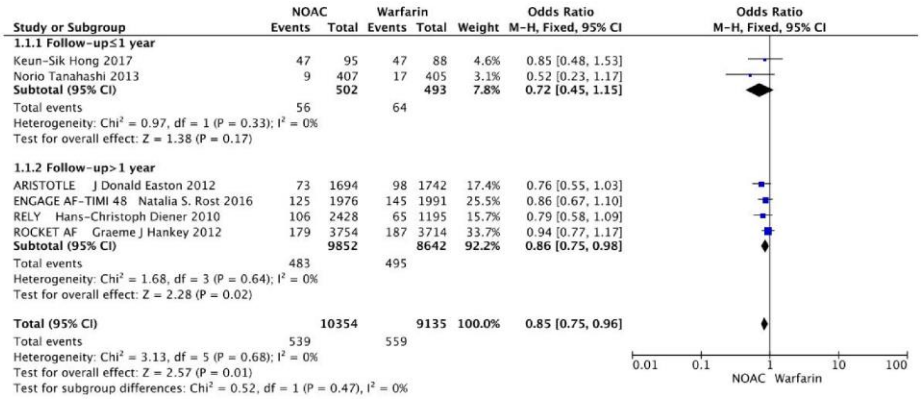
Mortality

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE J Donald Easton 2012	129	1694	150	1742	17.4%	0.87 [0.68, 1.12]
ENGAGE AF-TIMI 48 Natalia S. Rost 2016	231	1976	276	1991	30.9%	0.82 [0.68, 0.99]
Keun-Sik Hong 2017	0	95	0	88		Not estimable
RELY Hans-Christoph Diener 2010	185	2428	107	1195	16.9%	0.84 [0.65, 1.08]
ROCKET AF Graeme J Hankey 2012	288	3754	294	3714	34.8%	0.97 [0.82, 1.14]
Total (95% CI)		**9947**		**8730**	**100.0%**	**0.88 [0.80, 0.98]**
Total events	833		827			

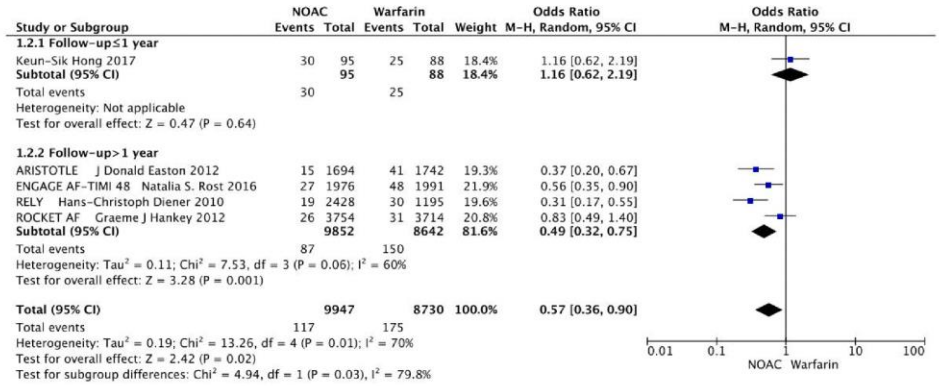
Heterogeneity: $Chi^2 = 1.82$, df = 3 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 2.36 (P = 0.02)



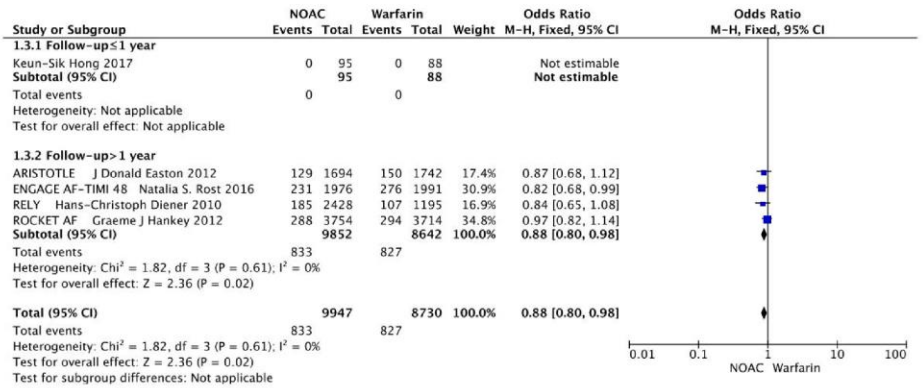
Thromboembolic Events



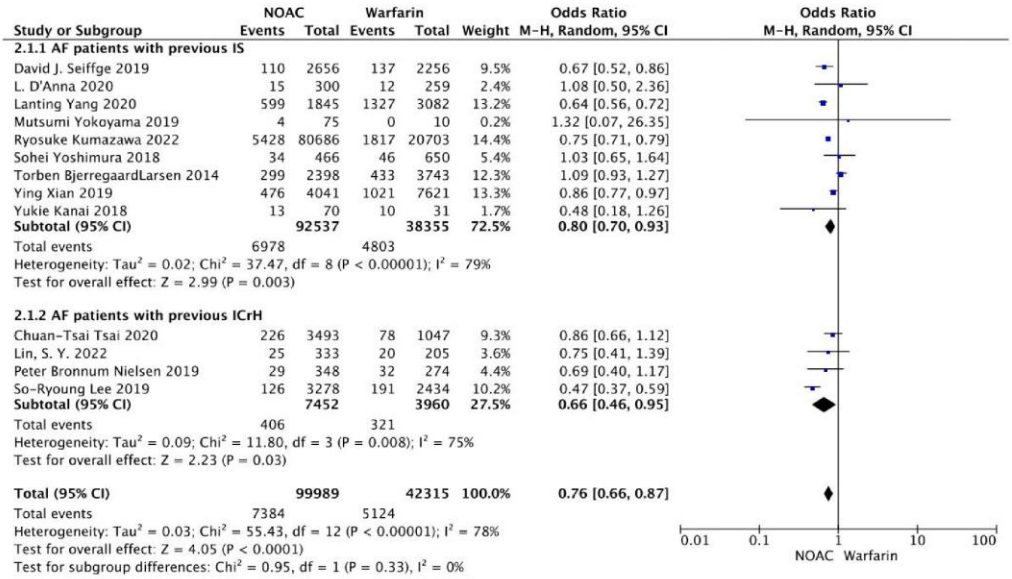
Incident ICrH



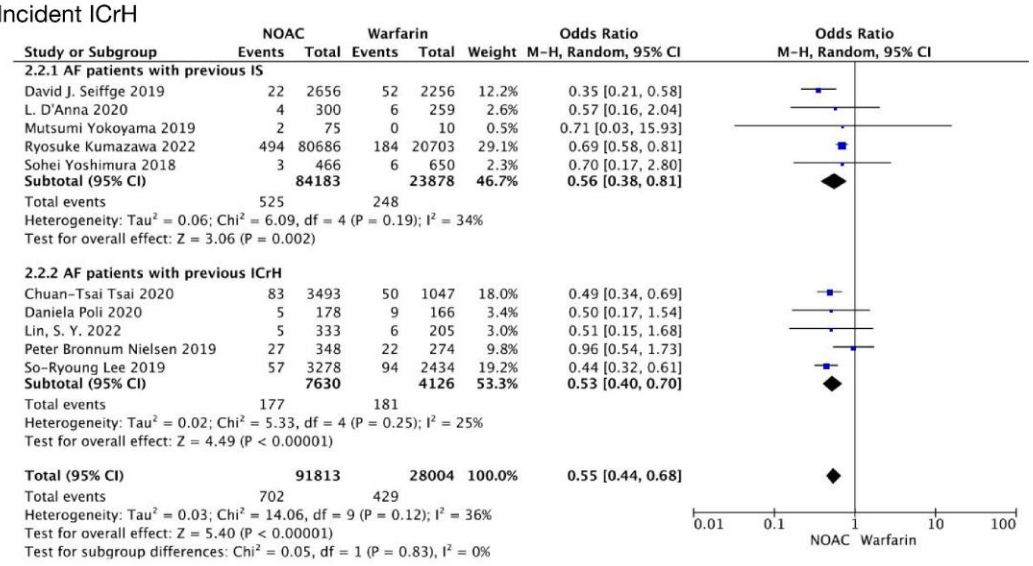
Mortality



Thromboembolic Events



Incident ICrH



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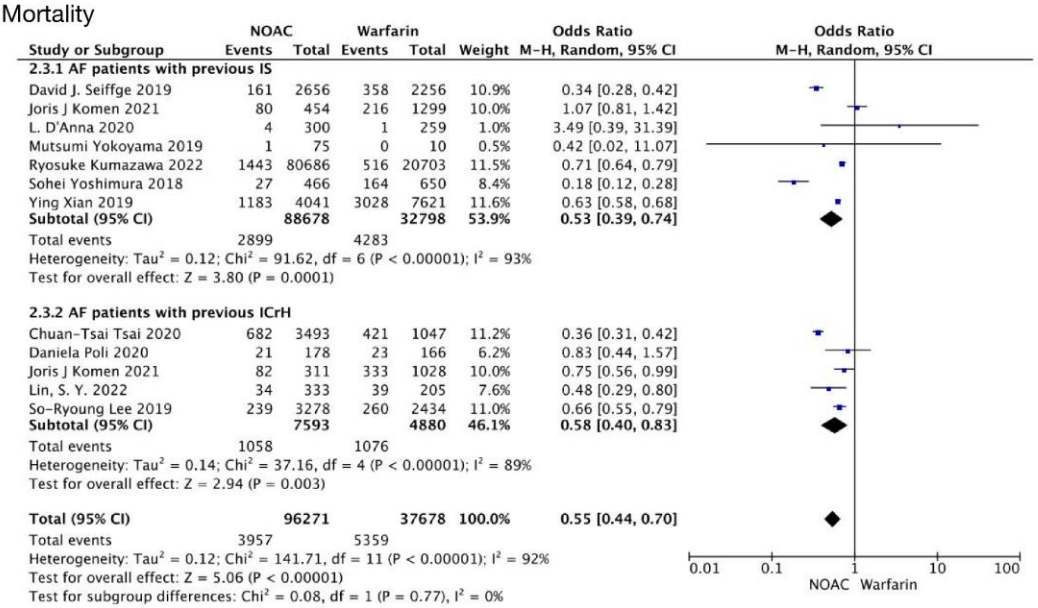
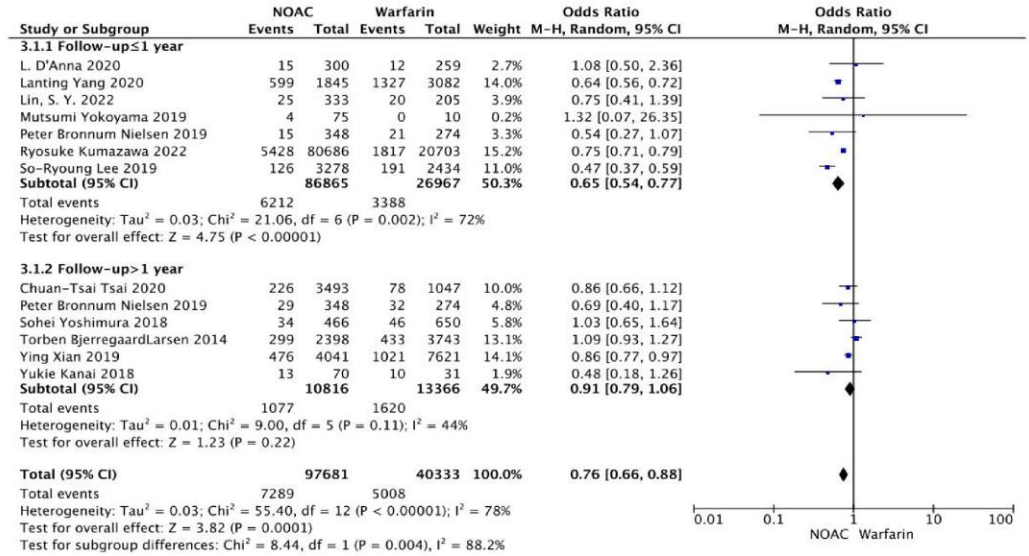
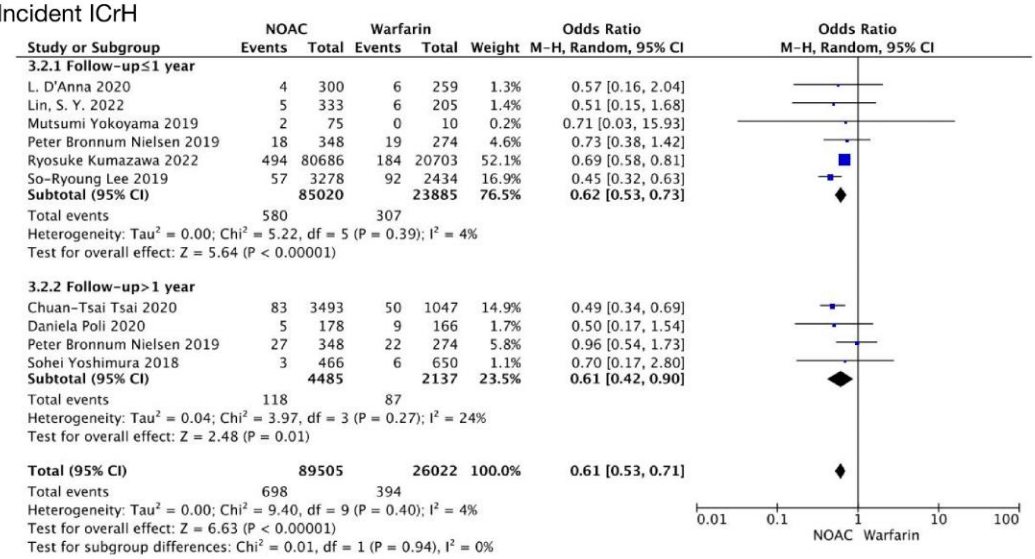


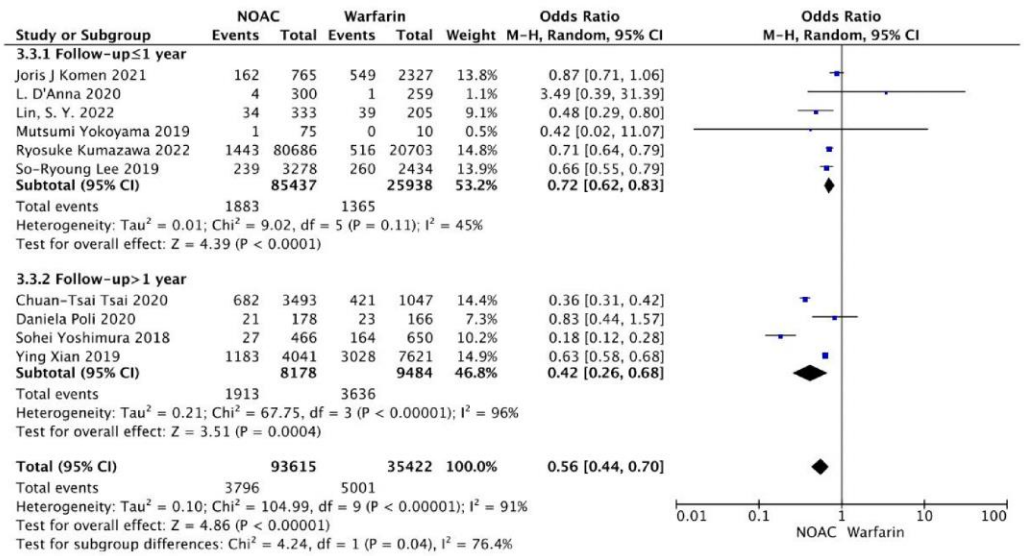
Thromboembolic Events



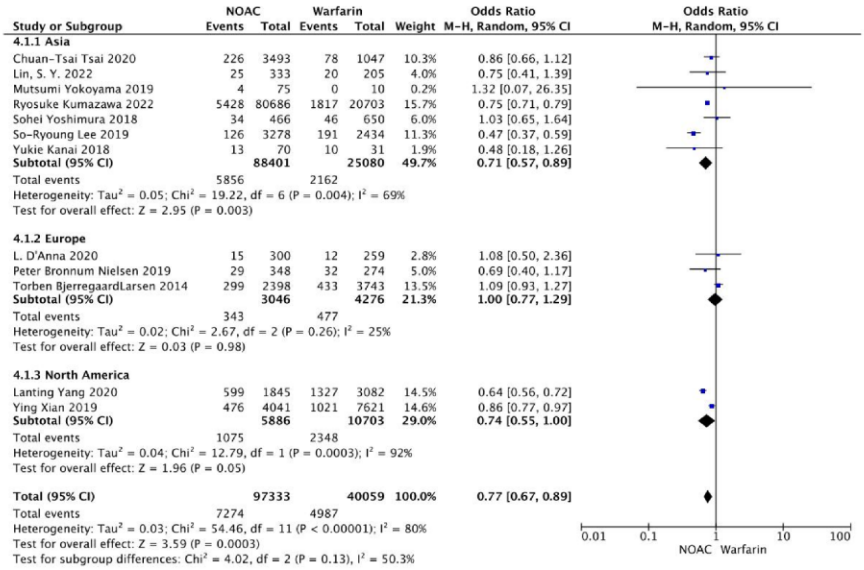
Incident ICrH



Mortality



Thromboembolic Events



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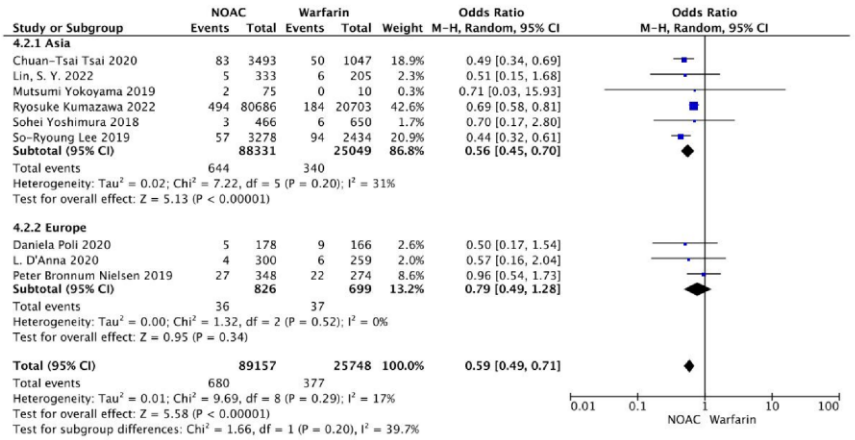

Mortality