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Direct Oral Anticoagulants for Stroke Prevention in Patients with Device-Detected Atrial Fibrillation: A Study-Level Meta-Analysis of the NOAH-AFNET 6 and ARTESiA Trials

Running title: *McIntyre et al.; DOACs in Patients with Device-Detected AF*

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Abstract

Background: Device-detected atrial fibrillation (AF) (also known as subclinical AF or atrial high-rate episodes) is a common finding in patients with an implanted cardiac rhythm device and is associated with an increased risk of ischemic stroke. Whether oral anticoagulation is effective and safe in this patient population is unclear.

Methods: We performed a systematic review of MEDLINE and Embase for randomized trials comparing oral anticoagulation to antiplatelet or no antithrombotic therapy in adults with device-detected AF recorded by a pacemaker, implantable cardioverter-defibrillator, cardiac resynchronization therapy device or implanted cardiac monitor. We used random-effects models for meta-analysis and rated the quality of evidence using the GRADE framework. The review was pre-registered (PROSPERO CRD42023463212).

Results: From 785 unique citations, we identified two randomized trials with relevant clinical outcome data; NOAH-AFNET 6 (2,536 participants) evaluated edoxaban and ARTESiA (4,012 participants) evaluated apixaban. Meta-analysis demonstrated that oral anticoagulation with these agents reduced ischemic stroke (relative risk [RR] 0.68, 95% confidence interval [CI] 0.50-0.92; high-quality evidence). The results from the two trials were consistent (I^2 statistic for heterogeneity=0%). Oral anticoagulation also reduced a composite of cardiovascular death, all-cause stroke, peripheral arterial embolism, myocardial infarction or pulmonary embolism (RR 0.85, 95% CI 0.73-1.00, I^2=0%; moderate-quality evidence). There was no reduction in cardiovascular death (RR 0.95, 95% CI 0.76-1.17, I^2=0%; moderate-quality evidence) or all-cause mortality (RR 1.08, 95% CI 0.96-1.21 I^2=0%; moderate-quality evidence). Oral anticoagulation increased major bleeding (RR 1.62, 95% CI 1.05-2.5 I^2=61%; high-quality evidence).

Conclusions: The results of the NOAH-AFNET 6 and ARTESiA trials are consistent with each other. Meta-analysis of these two large randomized trials provides high-quality evidence that oral anticoagulation with edoxaban or apixaban reduces the risk of stroke in patients with device-detected AF and increases the risk of major bleeding.

Key Words: subclinical atrial fibrillation, SCAF, atrial high rate episodes, AHRE, DOACs, pacemaker

Non-standard Acronyms and Abbreviations

AF: Atrial Fibrillation
AHRE: atrial high-rate episodes
ASA: acetylsalicylic acid
CI: Confidence Interval
ARTESiA: Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation
NOAH-AFNET 6: Non–vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes
RR: Relative Risk
SCAF: subclinical atrial fibrillation

Clinical Perspective

What is new?

- A systematic review of the literature found two randomized trials comparing oral anticoagulation to antiplatelet or no antithrombotic therapy in adult patients with device-detected atrial fibrillation (AF) detected by a pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy device or an implanted cardiac monitor: NOAH-AFNET 6 and ARTESiA.
- Meta-analysis of NOAH-AFNET 6 and ARTESiA found that oral anticoagulation with edoxaban or apixaban reduces the relative risk of stroke by approximately 32% and increases the relative risk of major bleeding by approximately 62%.

What are the clinical implications?

- These findings support the consideration of oral anticoagulation for patients with device-detected AF through a shared decision-making process that considers treatment effects, estimated event rates, anticipated severity of stroke and/or bleeding, and patient values and preferences.

Introduction

Device-detected atrial fibrillation (AF), also known as subclinical atrial fibrillation (SCAF) or atrial high-rate episodes (AHRE), is a common finding in patients with a pacemaker, defibrillator or implanted cardiac monitor.[1,2] Device-detected AF is associated with an increased risk of ischemic stroke, although this risk is lower than in similar patients with "clinical" AF documented by surface ECG. Patients with implanted devices are often elderly, and have a high burden of stroke risk factors. These elderly patients may also have a higher risk of major bleeding, potentially impacting the risk-to-benefit ratio of treatment with oral anticoagulation. Oral anticoagulation with warfarin or the direct oral anticoagulants (DOACs; dabigatran, apixaban, rivaroxaban, edoxaban) has shown to be effective and safe for patients with ECG-documented AF.[3] However, whether oral anticoagulation is effective and safe in patients with device-detected AF is unknown.

Two large randomized trials have tested the efficacy and safety of DOACs in patients with device-detected AF. The Non–vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial randomized participants to edoxaban or comparator (acetylsalicylic acid (ASA) or placebo according to clinical indication).[4] The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial randomized participants to apixaban or ASA.[5] NOAH-AFNET 6 was stopped prematurely due to safety concerns and an informal trend towards futility. The trial reported no significant difference in the primary efficacy endpoint of a composite of stroke, systemic embolism (including myocardial infarction, pulmonary embolism or systemic arterial embolism) or cardiovascular death between the two groups. There were numerically fewer thrombotic events in patients randomized to edoxaban.[6] ARTESiA reported

that apixaban significantly reduced the risk of the primary efficacy endpoint of ischemic stroke or systemic embolism.[7] There was a higher rate of major bleeding in patients randomized to anticoagulation in both trials. The rate of stroke was lower than anticipated in both trials.[4,5]

The objective of this study-level meta-analysis was to assess the efficacy and safety of oral anticoagulation in patients with device-detected AF by systematically reviewing, synthesizing and appraising published randomized trials.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files.

We registered the protocol with PROSPERO (CRD42023463212). **Supplement 1** lists the differences between the registered protocol and the final manuscript.

Eligibility criteria

We searched for randomized trials comparing oral anticoagulation to antiplatelet or no antithrombotic therapy in adult patients with device-detected AF (SCAF / AHRE) detected by a pacemaker, implantable cardioverter defibrillator, cardiac resynchronization therapy device or an implanted cardiac monitor.

We excluded studies of patients with a history of ECG-diagnosed AF and studies performed exclusively in a population with cryptogenic stroke or embolic stroke of undetermined source (ESUS). We excluded studies evaluating vitamin K antagonists. We excluded studies that used device-detected AF monitoring to initiate and withhold oral anticoagulation. We did not place any restrictions on language or publication status.

Search methods

We searched MEDLINE and Embase from 1996 to September 2023. We used a mix of keywords and medical subject headings designed to capture concepts of SCAF/AHRE and oral anticoagulation. We used a validated filter for randomized trials.[8] Our search strategy appears in **Supplement 2**.

Selection of studies

We performed study selection using Covidence Systematic review software (Veritas Health Innovation, Melbourne, Australia). Independently and in duplicate, two reviewers screened titles and abstracts and retrieved full-text reports for all items deemed potentially relevant by either reviewer. Subsequently, two authors independently compared full-text reports against our eligibility criteria. We resolved any disagreements through discussion.

Outcomes

We chose ischemic stroke as our primary outcome (including strokes adjudicated as being of unspecified etiology); prevention of this outcome is the primary goal of anticoagulation treatment in patients with device-detected AF. The most important secondary outcome was a composite of all-cause stroke, systemic embolism (including peripheral arterial embolism, myocardial infarction and pulmonary embolism) and cardiovascular death. Other efficacy outcomes included all-cause stroke (ischemic, hemorrhagic or unspecified); a composite of ischemic stroke or systemic embolism; cardiovascular death and all-cause mortality. Major bleeding according to the International Society for Thrombosis and Hemostasis (ISTH) criteria was our primary safety outcome, as is the case in most large trials of long-term anticoagulation.[9] Other bleeding outcomes included fatal bleeding and a composite of fatal bleeding and all-cause mortality. We accepted study authors' definitions for clinical outcomes.

Data extraction

We abstracted descriptive data (*e.g.,* patient population, intervention, comparator) from all selected studies. Two reviewers independently and in duplicate extracted the data using pre-designed data collection forms. We resolved any disagreements through discussion.

Risk of bias

We assessed the risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool.[10] We independently assessed the risk of bias as 'low', 'high' or 'some concerns' in five domains: randomization process, deviations from intended interventions, missing outcome data, bias in measurement of the outcome, and selection of the reported result. We considered the overall risk of bias for each study as 'low' if all risk of bias domains were ranked 'low', as 'some concerns' if at least one domain was ranked as 'unclear' without any domains ranked as 'high', and as 'high' if one or more domains were ranked as 'high' risk of bias.

Statistical analysis

We used the number of participants at risk and with an event in each trial to calculate relative risks (RR) with accompanying 95% confidence intervals (CI). We pooled data using DataParty (dataparty.ca), employing random-effects models with Mantel−Haenszel weighting. We assessed clinical and methodological heterogeneity based on study characteristics. We measured statistical heterogeneity using the I^2 statistic. We considered an I^2 greater than 50% as showing substantial heterogeneity. We aimed to conduct analyses for efficacy outcomes in the intention-to-treat population or the modified intention-to-treat population (defined as all the participants who had undergone randomization and received at least one dose of study drug). We aimed to conduct analyses on bleeding outcomes in the on-treatment population (participants who were taking study drug at the time of the event). We considered a P-value <0.05 (two-sided) to be statistically significant.

We calculated absolute risk reductions for the primary efficacy and bleeding outcomes by multiplying baseline event rates by the pooled RR and it's 95% CI. For ischemic stroke we explored two different baseline absolute risks: i) trial-based, using the annual-event rate in the ASA/placebo arm from the intention to treat populations of the two trials (*i.e.* 1.0%) and ii) literature-based, using an annual event rate of 1.9% from a meta-analysis of observational studies[11]. For major bleeding, we used the annual event rate in the ASA/placebo arm from the intention to treat populations of the two trials (*i.e.* 1.1%).

Quality assessment

We assessed the quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[12] We appraised our confidence in the estimate of effects by considering risk of bias in individual studies, directness of the evidence, precision of effect estimates for individual clinical outcomes, heterogeneity of the data and potential for publication bias.

Institutional research ethics board approval was not required for this study.

Results

Selection of included studies

From 785 unique citations, we identified 2 randomized trials that met our eligibility criteria: NOAH-AFNET 6 (2,536 participants) and ARTESiA (4,012 participants).[6] **Supplement 3** outlines the study selection process. **Table 1** outlines the characteristics of the trials with further details in **Supplement 4**. **Supplement 5** lists which outcomes were extracted from the published papers and which were generated from unpublished data.

Relevant excluded studies

We found one small trial with 48 participants, published as an abstract only.[13] No participants in the study had a stroke. This trial also reported that 2 patients died from gastrointestinal bleeding and one additional patient had non-fatal major bleeding. However, the group allocation of these participants was not clear. Accordingly, we did not pool any data from this study.

Our search also identified the Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk (IMPACT) randomized trial.[14] In the intervention arm of this trial, participants were continuously monitored and oral anticoagulation was started and stopped based on the presence or absence of arrhythmias. In accordance with our protocol, we excluded this trial because it did not use continuous oral anticoagulation and because oral anticoagulation was predominantly done with warfarin.

Risk of bias assessment

We outline our judgments about the risk of bias in individual trials in **Supplement 6**. We rated all domains in the NOAH-AFNET 6 and ARTESiA trials as being at low risk of bias.

Ischemic stroke

In the modified intention-to-treat population in NOAH-AFNET 6, the annual rates of ischemic stroke on ASA/Placebo and edoxaban were 1.1% and 0.9%, respectively. In the intention-to-treat population in ARTESiA, the annual rates of ischemic stroke on ASA and apixaban were 1.0% and 0.6%, respectively. Meta-analysis of NOAH-AFNET 6 and ARTESiA found a significant reduction in ischemic stroke with oral anticoagulation (RR 0.68, 95% CI 0.5-0.92, I^2=0%, **Figure 1**). Estimated absolute risk reductions for ischemic stroke were 3 fewer ischemic strokes per thousand patient years (95% CI 5 fewer to 1 fewer) using the trial-based estimate and 6 fewer ischemic strokes per thousand patient years (95% CI 10 fewer to 2 fewer) using the baseline

estimate from a meta-analysis of observational studies. We judged the evidence for ischemic stroke reduction to be high-quality according to the GRADE framework (**Supplement 7**).

Other efficacy outcomes

Meta-analysis of NOAH-AFNET 6 and ARTESiA found a reduction in a composite of ischemic stroke or systemic embolism with oral anticoagulation (RR 0.63, 95% CI 0.47-0.84, I^2=0%, **Figure 2**). We judged the evidence for this outcome as high-quality (**Supplement 7**). Meta-analysis also found a reduction in a composite of all-cause stroke, peripheral arterial embolism, myocardial infarction, pulmonary embolism or cardiovascular death with oral anticoagulation (RR 0.85, 95% CI 0.73-0.99, I^2=0%). We judged the evidence for this outcome to be moderate-quality according to the GRADE framework, owing to imprecision (**Supplement 7**). Meta-analysis found a reduction in a composite of ischemic stroke or systemic embolism (RR 0.63, 95% CI 0.47-0.84, I^2=0%), all-cause stroke (RR 0.68, 95% CI 0.51-0.9, I^2=0%) and a composite of all-cause stroke or systemic embolism with oral anticoagulation (RR 0.65, 95% CI 0.49-0.86, I^2 = 0%). We judged the evidence for these outcomes as high-quality (**Supplement 7**). Meta-analysis found no reduction in cardiovascular death (RR 0.95, 95% CI 0.76-1.17, I^2=0%) or all-cause mortality with oral anticoagulation (RR 1.08, 95% CI 0.96-1.21, I^2=0%). We judged the evidence for these outcomes to be moderate-quality according to the GRADE framework, owing to imprecision (**Supplement 7**).

Bleeding Outcomes

In the on-treatment population in ARTESiA, the annual rates of major bleeding on ASA and apixaban were 1.0% and 1.7%, respectively, whereas in the intention-to-treat population these numbers were 1.1% and 1.5%, respectively. Because on-treatment major bleeding was not available for the NOAH-AFNET 6 trial, we assessed major bleeding primarily with the intention-

to-treat populations. Meta-analysis of NOAH-AFNET 6 and ARTESiA found an increase in major bleeding with oral anticoagulation (RR 1.62, 95% CI 1.05-2.5 $I^2 = 61\%$). Meta-analysis found that oral anticoagulation increased the risk of a composite of all-cause mortality or major bleeding (RR 1.16, 95% CI 1.0-1.35, $I^2=35\%$). However, meta-analysis found no difference in fatal bleeding (RR 0.79, 95% CI 0.37-1.69, $I^2=0\%$). Findings were consistent when we meta-analysed modified intention to treat numbers from NOAH AFNET 6 with on treatment numbers from ARTESiA (**Supplement 8**). The estimated absolute risk increase for major bleeding was 7 more major bleeds per thousand patient years (95% CI 1 more to 17 more). We judged the quality of evidence for major bleeding to be high, while we judged the evidence for both fatal bleeding and a composite of all cause mortality or major bleeding as moderate-quality due to imprecision (**Supplement 7**).

Discussion

This up-to-date and comprehensive systematic review and meta-analysis found that the effects of oral anticoagulation with edoxaban or apixaban in patients with device-detected AF were consistent in two large outcome trials. There was no detectable heterogeneity in the results of NOAH-AFNET 6 and ARTESiA. Oral anticoagulation with edoxaban or apixaban reduces the risk of ischemic stroke by approximately one-third and increases major bleeding by roughly double. There was no reduction of cardiovascular death or all-cause mortality with oral anticoagulation. Our analysis of the efficacy and safety outcomes of the two trials demonstrates the consistency of their findings.

This meta-analysis demonstrated the superiority of oral anticoagulation for efficacy across several complementary outcomes. NOAH-AFNET 6 used a composite of cardiovascular death, stroke, myocardial infarction, pulmonary embolism or systemic arterial embolism, while ARTESiA used a composite of stroke or systemic embolism. While the majority of deaths in patients with AF are cardiovascular, fewer than 10% of all deaths in this population are attributable to stroke. [15-17] Most deaths in AF patients occur due to underlying cardiovascular disease, heart failure or sudden death, with a risk of stroke in this population of about 1% per year. [15,16,18] Even a substantial reduction in stroke would not be expected to result in a measurable decrease in the risk of death. Accordingly, this meta-analysis found a 32% decrease in the risk of ischemic stroke and a smaller 15% reduction in the composite of stroke, systemic embolism and cardiovascular death. The relative reduction in ischemic stroke as compared to ASA/placebo is similar to the reduction seen with warfarin versus antiplatelet therapy and somewhat smaller than that seen with apixaban versus ASA in patients with ECG-diagnosed AF, although confidence intervals overlap.[19,20] Thus the magnitude of the relative risk of stroke reduction with anticoagulation in device-detected and in clinical AF appear to be congruent.

The observed rates of stroke without anticoagulation were lower than anticipated.[4,5] Reasons for the relatively low stroke rates could include cross-over to open-label anticoagulation when AF was documented by surface ECG, characteristics of enrolled patients not captured by aggregated clinical risk factors, improved treatment of concomitant cardiovascular diseases, temporal trends in cardiovascular event rates, and the relatively low baseline arrhythmia burden in both trials (average duration of the longest episode 1.5 hours and 2.8 hours during long-term rhythm monitoring with implanted devices).[21,22]

Not surprisingly, edoxaban and apixaban increased the risk of major bleeding. The omission of aspirin in nearly half of the patients randomized to no anticoagulation in NOAH-AFNET 6 and its early termination after 184 of 220 planned primary events may have led to a slightly higher estimate for excess major bleeding.[23] The annual risk of bleeding without anticoagulation (no therapy or ASA) in this population was approximately 1.0%, which is comparable to the rate of bleeding observed in ASA treated patients with ECG-documented AF in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) Trial (1.2%).[19] Crude rates of bleeding in patients taking edoxaban and apixaban were lower in NOAH-AFNET 6 and ARTESiA than in the pivotal trials for these agents, possibly due to improved management of modifiable risk factors for bleeding.[24,25] Fatal bleeding events in NOAH-AFNET 6, ARTESiA and this meta-analysis were too infrequent to draw any meaningful conclusions.

The primary results of NOAH-AFNET 6 and ARTESiA, and this meta-analysis, show consistent findings: Anticoagulation with edoxaban or apixaban reduces ischemic stroke and results in an expected increase in major bleeding in patients with device-detected AF and stroke risk factors. The overall stroke rate without anticoagulation was approximately 1% per year in both trials. When deciding whether to prescribe anticoagulants for patients with device-detected AF, physicians need to take all of these factors into consideration, along with anticipated event severity and patient values and preferences. Further analyses of trial data sets may identify subgroups of patients with a high risk of stroke who might derive the most relative from oral anticoagulation. Moreover, additional tools may be needed to identify patients with device-detected AF who are at highest absolute risk of stroke.

This systematic review and meta-analysis has important limitations. First, there were differences in the study populations and the comparator to oral anticoagulation between NOAH-AFNET 6 and ARTESiA. Second, the two studies used different primary efficacy outcomes. However, we found no evidence of statistical heterogeneity for any of the studied efficacy outcomes. Third, aside from mortality and fatal bleeding, there are no data in this meta-analysis that can be used to assess the severity of strokes and major bleeding events, to help build granular risk-benefit profiles. Additional methods are needed to identify the subset of patients with device-detected AF who might benefit the most from oral anticoagulation. Fourth, there may be subgroups of patients with device-detected AF who respond differently to oral anticoagulation, and most of these cannot be properly explored with study level meta-analysis. Fifth, both trials enrolled a predominantly white population. Effects in other ethnicities could be different. Sixth, the findings of this meta-analysis are consistent between two DOACs. While there may be pharmacological reasons to believe that the effects are a class effect of oral anticoagulation, this analysis does not contain data on the factor Xa inhibitor rivaroxaban, the direct thrombin inhibitor dabigatran, nor vitamin K antagonists such as warfarin. Finally, the strength of randomized trials (and meta-analysis thereof) is in the estimation of treatment effects (*e.g.* relative risk) and not absolute risk.[26] Although event rates were consistent in both trials, estimation of baseline absolute risk should be drawn from various sources, including from outside the trials in the meta-analysis.[11] Moreover, the individual baseline risk is variable in each study population. Evaluation of the trials' data sets on an individual level may identify additional factors associated with efficacy and safety of anticoagulation therapy in patients with device-detected AF.

Conclusion

The results of the NOAH-AFNET 6 and ARTESiA trials are consistent with each other. Meta-analysis of these two large randomized trials provides high-quality evidence that oral anticoagulation with edoxaban or apixaban reduces the risk of stroke in patients with device-detected AF and increases the risk of major bleeding.

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None

Disclosures

All authors are either NOAH-AFNET 6 or ARTESiA investigators.

Supplemental Materials

Supplements 1-8

Supplemental Figure 1-2

Supplemental Tables 1-4

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Table 1. Characteristics of Included Studies.

	NOAH-AFNET 6	ARTESiA
N	2,536	4,012
Intervention	Edoxaban	Apixaban
Comparator	ASA/placebo	ASA
Trial Registration (ClinicalTrials.gov identifier)	NCT02618577	NCT01938248
Age years (mean ± SD)	77.5 ± 6.7	76.8 ± 7.6
Female Sex	37.4%	36.1%
CHA_2DS_2-VASc score (median, IQR/mean±SD)	4 (3–5)	3.9 ± 1.1
Hypertension	86.9%	81.5%
Diabetes mellitus	26.9%	29.1%
Heart failure	27.4%	28.3%
Prior stroke, systemic Embolism or TIA	10.0%	9.0%
Creatinine clearance (mL/min, mean ± SD)	66.0 ± 23.4	71.4 ± 28.7
Received reduced-dose DOAC (study drug)	28.7%	10.4%
Received ASA (study drug)	53.9%	100%
Race/ethnicity*	Not systematically recorded (primarily European/Caucasian)	European/Caucasian 94.1% Black African 2.1% Native Latin 0.4% South Asian 0.3% Native North American/Pacific 0.5% Other 2.6%
Device type Pacemaker ICD CRT-ICD or CRT pacemaker ICM	 81.7% 7.4% 9.9% 1.0%	 69.4% 13.8% 11.5% 5.2%
Duration of device-detected AF prior to enrollment † (median, IQR)	2.8 hours (0.8–9.4)	1.5 hours (0.2-5.0)
Median number of device-detected AF episodes prior to enrollment	2.8	NR
Follow-Up	Median 1.8 years	Mean 3.5 ± 1.8 years
Incidence of clinical AF ‡	9% per patient-year	6.3% per patient-year

Abbreviations: AF atrial fibrillation, ASA acetylsalicylic acid, CRT cardiac resynchronization therapy, DOAC direct oral anticoagulation, ICD implantable cardioverter defibrillator, ICM implantable cardiac monitor, NR Not Reported SD: Standard Deviation, TIA: Transient Ischemic Attack,

* Data are for apixaban group and are similar to ASA group

†For NOAH-AFNET 6 and ARTESiA, this is the longest episode prior to enrolment

‡NOAH-AFNET 6 definition includes detection by surface ECG, ARTESiA definition includes detection by surface ECG and/or device-detected AF >24 hours

Figure Legends

Figure 1. Risk of Ischemic Stroke.

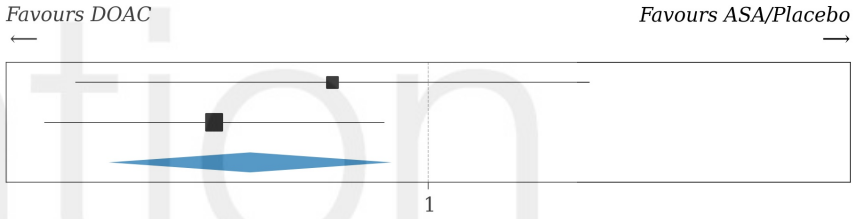
Figure 2. Risk of Other Efficacy Outcomes.

Figure 3. Risk of Bleeding Outcomes.

Ischemic Stroke

Study	DOAC	(%)	ASA/Placebo	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	22/1,270	(1.7%)	27/1,266	(2.1%)	30.4%	0.81 [0.47, 1.42]
ARTESiA	45/2,015	(2.2%)	71/1,997	(3.6%)	69.6%	0.63 [0.43, 0.91]
Pooled Estimate	67/3,285	(2.0%)	98/3,263	(3.0%)	I^2: 0%	0.68 [0.5, 0.92]

Mantel-Haenszel, DerSimonian-Laird Random Effects
p=0.01, z=2.47
τ^2=0.00
RR: Risk Ratio
CI: Confidence Interval

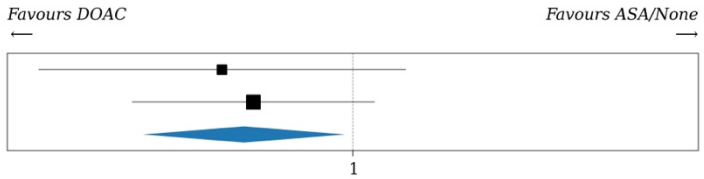


Composite of All-cause Stroke, Peripheral Arterial Embolism, Myocardial Infarction, Pulmonary Embolism or Cardiovascular Death

Study	DOAC	(%)	ASA/None	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	83/1,270	(6.5%)	101/1,266	(8.0%)	30.4%	0.82 [0.62, 1.08]
ARTESiA	189/2,015	(9.4%)	218/1,997	(10.9%)	69.6%	0.86 [0.71, 1.03]
Pooled Estimate	272/3,285	(8.3%)	319/3,263	(9.8%)	I^2: 0%	0.85 [0.73, 0.99]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.03, z=2.11, τ²=0.00*

RR: Risk Ratio, CI: Confidence Interval

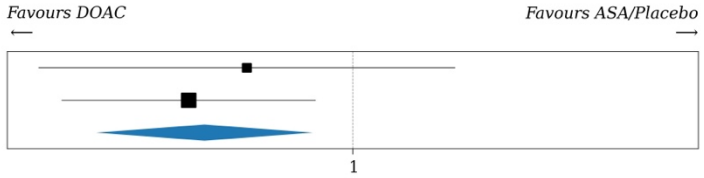


All-cause Stroke

Study	DOAC	(%)	ASA/Placebo	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	22/1,270	(1.7%)	29/1,266	(2.3%)	27.1%	0.76 [0.44, 1.31]
ARTESiA	55/2,015	(2.7%)	84/1,997	(4.2%)	72.9%	0.65 [0.46, 0.91]
Pooled Estimate	77/3,285	(2.3%)	113/3,263	(3.5%)	I^2: 0%	0.68 [0.51, 0.9]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.01, z=2.68, τ²=0.00*

RR: Risk Ratio, CI: Confidence Interval

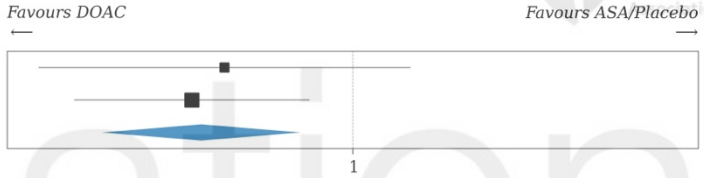


All-cause Stroke or Systemic Embolism

Study	DOAC	(%)	ASA/Placebo	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	23/1,270	(1.8%)	33/1,266	(2.6%)	28.5%	0.69 [0.41, 1.18]
ARTESiA	55/2,015	(2.7%)	86/1,997	(4.3%)	71.5%	0.63 [0.45, 0.88]
Pooled Estimate	78/3,285	(2.4%)	119/3,263	(3.6%)	I^2: 0%	0.65 [0.49, 0.86]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.00, z=2.99, τ²=0.00*

RR: Risk Ratio, CI: Confidence Interval

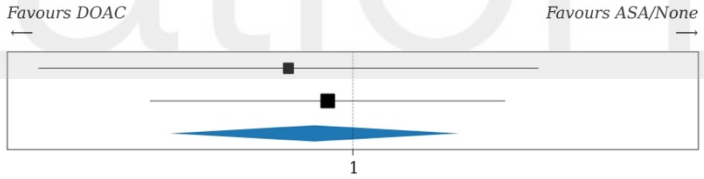


Cardiovascular Death

Study	DOAC	(%)	ASA/None	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	52/1,270	(4.1%)	57/1,266	(4.5%)	33.6%	0.91 [0.63, 1.31]
ARTESiA	105/2,015	(5.2%)	108/1,997	(5.4%)	66.4%	0.96 [0.74, 1.25]
Pooled Estimate	157/3,285	(4.8%)	165/3,263	(5.1%)	I^2: 0%	0.95 [0.76, 1.17]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.60, z=0.52, τ²=0.00*

RR: Risk Ratio, CI: Confidence Interval

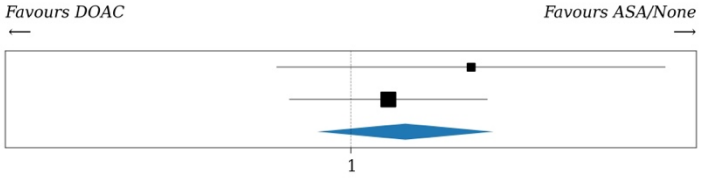


All-cause Mortality

Study	DOAC	(%)	ASA/None	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	111/1,270	(8.7%)	94/1,266	(7.4%)	20.6%	1.18 [0.9, 1.53]
ARTESiA	362/2,015	(18.0%)	341/1,997	(17.1%)	79.4%	1.05 [0.92, 1.2]
Pooled Estimate	473/3,285	(14.4%)	435/3,263	(13.3%)	I^2: 0%	1.08 [0.96, 1.21]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.23, z=1.21, τ²=0.00*

RR: Risk Ratio, CI: Confidence Interval

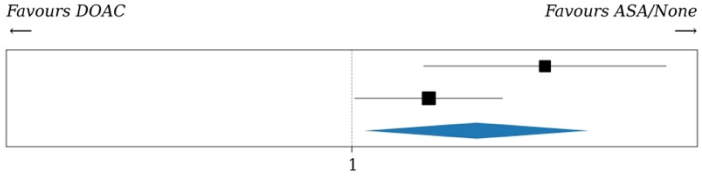


Major Bleeding

Study	DOAC	(%)	ASA/None	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	53/1,270	(4.2%)	25/1,266	(2.0%)	41.1%	2.11 [1.32, 3.38]
ARTESiA	106/2,015	(5.3%)	78/1,997	(3.9%)	58.9%	1.35 [1.01, 1.79]
Pooled Estimate	159/3,285	(4.8%)	103/3,263	(3.2%)	I^2: 61%	1.62 [1.05, 2.5]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.03, z=2.18, τ^2=0.06*

RR: Risk Ratio
CI: Confidence Interval

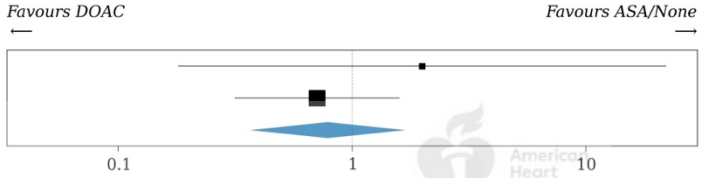


Fatal Bleeding

Study	DOAC	(%)	ASA/None	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	2/1,270	(0.2%)	1/1,266	(0.1%)	10.2%	1.99 [0.18, 21.96]
ARTESiA	10/2,015	(0.5%)	14/1,997	(0.7%)	89.8%	0.71 [0.32, 1.59]
Pooled Estimate	12/3,285	(0.4%)	15/3,263	(0.5%)	I^2: 0%	0.79 [0.37, 1.69]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.54, z=0.61, τ^2=0.00*

RR: Risk Ratio
CI: Confidence Interval



All-cause Mortality or Major Bleeding

Study	DOAC	(%)	ASA/None	(%)	Weight	RR [95% CI]
NOAH-AFNET 6	149/1,270	(11.7%)	114/1,266	(9.0%)	31.9%	1.3 [1.03, 1.64]
ARTESiA	431/2,015	(21.4%)	387/1,997	(19.4%)	68.1%	1.1 [0.98, 1.25]
Pooled Estimate	580/3,285	(17.7%)	501/3,263	(15.4%)	I^2: 35%	1.16 [1.0, 1.35]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.05, z=1.96, τ^2=0.00*

RR: Risk Ratio
CI: Confidence Interval