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1 **Anticoagulation in device-detected atrial fibrillation with or without vascular disease:**
2 **a combined analysis of the NOAH-AFNET 6 and ARTESiA trials**

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12 **Short Title:** Anticoagulation in patients DDAF with and without vascular disease

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15 **Key words:** atrial fibrillation, device-detected atrial fibrillation, oral anticoagulation, trial, stroke

16 **Abbreviations:**

17	AF	atrial fibrillation
18	ARTESiA	Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-
19		Detected Subclinical Atrial Fibrillation
20	CHA ₂ DS ₂ -VASc	Heart failure, hypertension, age 75 years, diabetes, stroke/systemic
21		embolism, sex, prior vascular disease
22	CI	confidence interval
23	DDAF	Device-detected atrial fibrillation
24	DOAC	direct oral anticoagulant
25	HAS-BLED	uncontrolled hypertension, abnormal renal and/or hepatic function, stroke,
26		bleeding history or predisposition, labile INR, elderly, drugs or excessive
27		alcohol drinking
28	HR	hazard ratio
29	ISTH	International Society on Thrombosis and Haemostasis (ISTH)
30	NOAH	Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High
31		rate episodes
32	RR	risk ratio
33	SD	standard deviation
34	SE	systemic arterial embolism
35	TIA	transient ischemic attack
36		

37 **Abstract (252 words)**

38 **Background and aims.** The optimal antithrombotic therapy in patients with device-detected
 39 atrial fibrillation (DDAF) is unknown. Concomitant vascular disease can modify the benefits and
 40 risks of anticoagulation.

41 **Methods.** These pre-specified analyses of the NOAH-AFNET 6 (n=2534 patients) and ARTESiA
 42 (n=4012 patients) trials compared anticoagulation to no anticoagulation in patients with DDAF
 43 with or without vascular disease, defined as prior stroke/transient ischemic attack, coronary or
 44 peripheral artery disease. Efficacy outcomes were the primary outcomes of both trials, a
 45 composite of stroke, systemic arterial embolism (SE), myocardial infarction, pulmonary

1 embolism or cardiovascular death, and stroke or SE. Safety outcomes were major bleeding or
2 major bleeding and death.

3 **Results.** In patients with vascular disease (NOAH-AFNET 6 56%, ARTESiA 46.0%), stroke,
4 myocardial infarction, systemic or pulmonary embolism, or cardiovascular death occurred at
5 3.9%/patient-year with and 5.0%/patient-year without anticoagulation (NOAH-AFNET 6), and
6 3.2%/patient-year with and 4.4%/patient-year without anticoagulation (ARTESiA). Without
7 vascular disease, outcomes were equal with and without anticoagulation (NOAH-AFNET 6
8 2.7%/patient-year, ARTESiA 2.3%/patient-year in both randomised groups). Meta-analysis found
9 consistent results across both trials ($I^2_{\text{heterogeneity}}=6\%$) with a trend for interaction with randomised
10 therapy ($p_{\text{interaction}}=0.08$). Stroke/SE behaved similarly. Anticoagulation increased major bleeding
11 in vascular disease patients (edoxaban 2.1%/patient-year, no anticoagulation 1.3%/patient-year;
12 apixaban 1.7%/patient-year; no anticoagulation 1.1%/patient-year; incidence rate ratio 1.55
13 [1.10-2.20]) and without vascular disease (edoxaban 2.2%/patient-year; no anticoagulation
14 0.6%/patient-year; apixaban 1.4%/patient-year; no anticoagulation 1.1%/patient-year, incidence
15 rate ratio 1.93 [0.72-5.20]).

16 **Conclusions.** Patients with DDAF and vascular disease are at higher risk of stroke and
17 cardiovascular events and may derive a greater benefit from anticoagulation than patients with
18 DDAF without vascular disease.

19 20 **Introduction**

21 Device-detected atrial fibrillation (DDAF) is found in 20-30% of older adults with cardiovascular
22 disease, often in patients without ECG-documented atrial fibrillation (AF).^{1, 2} DDAF refers to
23 episodic atrial arrhythmias that resemble AF but are typically short and rare.³ Expert consensus
24 and analogies between DDAF and ECG-documented AF led clinicians to prescribe
25 anticoagulation to patients with DDAF.⁴ Two recent trials compared anticoagulation to no
26 anticoagulation in patients with DDAF and stroke risk factors, but without ECG-documented AF.
27 The NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High
28 Rate Episodes) trial randomized patients with DDAF lasting 6 minutes or longer to
29 anticoagulation with edoxaban or no anticoagulation.⁵ Patients with vascular disease and an
30 indication for acetylsalicylic acid randomized to no anticoagulation received aspirin 100 mg once

1 daily with the study medication, the others received placebo as double dummy. The trial was
2 stopped prematurely due to an expected increase in bleeding combined with a trend towards
3 futility for efficacy. The ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients
4 with Device Detected Subclinical Atrial Fibrillation) trial randomized patients with DDAF lasting 6
5 minutes to 23:59 hours to anticoagulation with apixaban or aspirin 81 mg once daily⁶ and found
6 a stroke risk-reducing effect of anticoagulation compared to aspirin. Both trials consistently found
7 a low rate of stroke without anticoagulation (1.1-1.2% per patient-year), the expected increase in
8 bleeding with anticoagulation, and a small further reduction in stroke with anticoagulation.⁷
9 Many patients with DDAF (56% in NOAH-AFNET 6, 46% in ARTESiA) have vascular disease
10 that creates an indication for antiplatelet therapy, usually aspirin, to prevent thrombo-embolic
11 events including ischemic stroke, myocardial infarction (MI), and systemic arterial embolism
12 (SE).⁸ Aspirin increases the risk of major bleeding compared to no therapy.^{9, 10} This may alter the
13 efficacy and safety of anticoagulation therapy. We therefore performed subgroup analyses of
14 NOAH-AFNET 6 and ARTESiA in patients with and without vascular disease.

16 **Methods**

17 This pre-specified secondary analysis of the NOAH-AFNET 6 trial investigated the effects of
18 vascular disease on the efficacy and safety of anticoagulation therapy compared to no
19 anticoagulation in the NOAH-AFNET 6. Results were validated in a pre-specified secondary
20 analysis of ARTESiA and meta-analysed.

21 **Design of NOAH-AFNET 6 and ARTESiA.** In NOAH-AFNET 6 patients with DDAF, but without
22 ECG-documented AF, aged ≥ 65 years and with a minimum of one additional stroke risk factor
23 were randomized to oral anticoagulation with edoxaban in the dose approved for stroke
24 prevention in AF or to no anticoagulation. In the double-blind, double-dummy design, patients
25 randomized to no anticoagulation received 100 mg aspirin if it was indicated, otherwise they

1 received placebo. Those without an indication for aspirin and all patients randomised to
2 edoxaban took a dummy aspirin tablet. Physician decision could overrule aspirin indications.

3 In ARTESiA patients with DDAF lasting between 6:01 minutes and 23:59 hours were enrolled.
4 Inclusion criteria further comprised an age of at least 55 years and a CHA₂DS₂-VASc (heart
5 failure, hypertension, age 75 years, diabetes, stroke/systemic embolism, sex, prior vascular
6 disease) score of at least 3. A small subset of patients with a CHA₂DS₂-VASc score of 2 were
7 enrolled in the early phase of the trial. Patients with prior stroke or age of at least 75 years or
8 greater could also be enrolled. Randomization allocated patients to apixaban 5 mg twice daily
9 (2.5 mg twice daily if guideline-recommended dose-reduction criteria applied) or aspirin 81 mg
10 daily in a double-blind, double-dummy design. In ARTESiA, open label aspirin on top of the
11 study medication was permitted.

12 In both trials, an ECG was recorded at each study visit (every 6 months). Patients with AF
13 documented on one of these ECGs were switched to open-label anticoagulation. In ARTESiA,
14 patients with DDAF episodes lasting ≥ 24 hours were also switched to open-label anticoagulation
15 therapy. Outcomes were centrally adjudicated by an independent review committee.

16 **Definition of populations.** For this analysis, patients were classified as having vascular disease
17 or not. An indication for aspirin was defined as presence of one of the following features:
18 unstable angina, prior MI, prior coronary artery bypass grafting or percutaneous coronary
19 intervention, prior transient ischemic attack, prior stroke, or established arterial disease. Details
20 of the variables used are provided in the **Supplement**. All patients were followed up until the end
21 of the trial.

22 **Outcomes.** Outcomes of interest were primary composite outcomes for efficacy and safety from
23 the main trials.^{6, 11} The efficacy outcomes were a composite of ischemic stroke (including
24 transient events with matching lesion on cerebral imaging), SE including peripheral and
25 abdominal embolism, MI, pulmonary embolism (PE) or cardiovascular death (including unknown

1 death) and a composite of all-cause stroke or SE (**Figure 1**). Safety outcomes were a composite
2 of major bleeding or death and major bleeding. Major bleeding was defined according to the
3 International Society on Thrombosis and Haemostasis criteria ¹².

4 Both studies were approved by the local Ethics Committees and adhere to inclusiveness.

5 **Statistical analysis.** For the baseline and demographic characteristics categorical data are
6 summarized by numbers and percentages, and continuous data are summarized by mean and
7 standard deviation or median and 1st and 3rd quartiles (interquartile range, IQR) as appropriate.
8 The primary analysis population consisted of all randomized patients receiving at least one dose
9 of the study drug. Patients that had a contraindication to aspirin were excluded from the analysis
10 set, i.e. a modified intention-to-treat population was analysed. For the primary time-to-event
11 analyses, patients were censored when they developed ECG-documented AF, were unblinded,
12 were lost to follow-up, or withdrew consent. All Ukrainian patients were censored on 24 February
13 2022, the day of the Russian invasion. Deaths of unknown cause were classified as
14 cardiovascular deaths in NOAH-AFNET 6, but not in ARTESiA. No imputation was conducted.
15 All analyses are exploratory, and thus no adjustment was made for multiple testing. Sensitivity
16 analysis for the primary efficacy and safety outcomes were conducted for all randomized
17 patients (including contraindications), the per-protocol population, a population that was not
18 censored for AF-onset or unblinding, a population without censoring at discontinuation of the
19 study medication and a grouping based on aspirin dispense. Baseline characteristics were
20 compared between patients with and without vascular disease using test χ^2 for categorical data,
21 t-test for non-skewed continuous data, and Mann-Whitney U test for skewed continuous data.
22 For all time-to-event analyses, cause-specific Cox proportional hazards models using the
23 Breslow method to handle tied failures were conducted with frailty for centres. To examine the
24 impact of patients with vascular disease, the interaction term between treatment and an indicator
25 for vascular disease, and the corresponding main effects were added to the model. The outcome
26 results are reported as group-specific event rates in percentage per patients-years and as

1 estimated cause-specific hazard ratios (HR) with a two-sided 95% confidence interval (CI) and
2 corresponding p-value for the HRs and the interaction between treatment and vascular disease.
3 Cumulative incidence curves are shown using Aalen Johansen estimates that consider
4 competing events. Otherwise, Kaplan-Meier curves are used. Trials were analysed separately and
5 results reported by trial, then in combined analysis.

6 All analyses were conducted with the use of R software version 4.2.3 (R Project for statistical
7 computing, SAS version 9.4).

8
9 **Meta-Analysis.** For meta-analysis, we employed random-effects models with Mantel-Haenszel
10 weighting pooling data using DataParty (dataparty.ca). We calculated incidence rate ratios for
11 each individual study and then pooled these at the study level.

12 Data are at the study level. The combined annualized statistical heterogeneity was assessed by
13 I^2 statistic. Substantial heterogeneity was indicated by an I^2 greater than 50%. We conducted
14 analyses for efficacy outcomes in the intention-to-treat population or the modified intention-to-
15 treat population (defined as all the participants who had undergone randomization and received
16 at least one dose of study drug).

17 18 **Results**

19 **Patient Characteristics.** About half of the patients had vascular disease prior to randomization
20 (N=1363 of 2433, 56.0% in NOAH-AFNET 6, and N=1841 of 4012, 45.9% in ARTESiA). Baseline
21 characteristics differed by vascular disease status (**Table 1**), mainly driven by a higher prevalence
22 of vascular diseases and heart failure in more than one third of patients with vascular disease.
23 Eleven patients in NOAH-AFNET 6 (0.8%) with vascular disease did not receive aspirin based on
24 contraindications by investigator decision. In patients without vascular disease, 13 (1.2%) received
25 aspirin based on investigator decisions. In ARTESiA, N=925 patients used open label aspirin in
26 addition to apixaban. Patients with vascular disease also had more often a defibrillator and cardiac

1 resynchronization therapy. There were no relevant differences between randomised treatment
2 groups. The median follow-up duration was 1.8 years in both groups in NOAH-AFNET 6, it was
3 3.4 years in the vascular disease group and 3.6 years without vascular disease in ARTESiA.

4 **Primary outcome by vascular disease status.** *Stroke, systemic arterial embolism, myocardial*
5 *infarction, pulmonary embolism or cardiovascular death.* In the 1363 patients with vascular
6 disease enrolled in NOAH-AFNET 6, the primary outcome occurred in 53 events/1367 patient-
7 years with anticoagulation (3.9%/patient-year) and in 66/1322 patient-years with placebo
8 (5.0%/patient-year, HR 0.78, 95% CI 0.54-1.12, **Figure 2, Table 2**). The primary outcome
9 occurred less frequently in patients without vascular disease and at an equal incidence rate in
10 both randomized treatment (anticoagulation 30/1109 patient-years with event (2.7%/patient-year),
11 placebo 30/1091 patient-years with event (2.7%/patient-year, HR 1.00, 95% CI 0.60-1.66).
12 Numerically there appeared to be more events in patients with vascular disease, especially in
13 patients randomized to no anticoagulation. There was no evidence for an interaction between
14 vascular disease status and randomized treatment ($p_{\text{interaction}}=0.41$).

15 In the 1841 patients with vascular disease enrolled in ARTESiA, the composite outcome
16 occurred in 100/3095 patient-years with anticoagulation (3.2%/patient-year) and in 131/2991
17 patient-years without anticoagulation (4.4%/patient-year, HR 0.74, 95% CI 0.57- 0.96, **Figure 2A**).
18 The primary outcome occurred less frequently in patients without vascular disease and at equal
19 rates in both randomized groups (anticoagulation 89/3861 patient-years with event (2.3%/patient-
20 year), aspirin 87/3831 patient-years with event (2.3%/patient-year, HR 1.02, 95% CI 0.76-1.36).
21 In ARTESiA, too, there appeared to be more events in patients with vascular disease, especially
22 in patients randomized to no anticoagulation. There was no evidence for an interaction between
23 vascular disease status and randomized treatment ($p_{\text{interaction}}=0.11$).

24 Meta-analysis showed an incidence rate ratio (IRR) in the vascular disease group for
25 stroke/SE/MI/PE/cardiovascular death of 0.75, 95% confidence interval (CI) 0.61-0.92 as

1 compared to IRR 1.01, 95% CI 0.78-1.30 in the subgroup without vascular disease (**Figure 3**,
2 $p_{\text{interaction}}=0.08$). The results from the trials were consistent (I^2 statistic for heterogeneity=6%).

3 *Stroke or systemic arterial embolism.* In NOAH-AFNET 6, 17 events/1371 patient-years
4 stroke/SE occurred in patients with vascular disease randomized to anticoagulation (1.2%/patient-
5 year) and in 29/1325 patient-years randomized to no anticoagulation containing double-blind
6 double-dummy aspirin (2.2%/patient-year, HR 0.56, 95% CI 0.31-1.02; **Figure 2B**). In patients
7 without vascular disease, the outcome of stroke/SE occurred in 11/1116 patient-years with
8 anticoagulation (1.0%/patient-year) and in 9/1101 patient-years without anticoagulation
9 (0.8%/patient-year, HR 1.20, 95% CI 0.50-2.89, $p_{\text{interaction}}=0.17$).

10 In ARTESiA, 30 stroke/SE events/925 patient-years occurred in patients with vascular
11 disease randomized to apixaban (1.0%/patient-year) and in 54/916 patient-years randomized to
12 aspirin (1.8%/patient-year, HR 0.54, 95% CI 0.34-0.84). In patients without vascular disease, the
13 outcome of stroke/SE occurred in 25/1090 patient-years randomized to anticoagulation
14 (0.6%/patient-year) and in 32/1081 patient-years randomized to aspirin (0.8%/patient-year, HR
15 0.78, 95% CI 0.46- 1.31), $p_{\text{interaction}}=0.29$.

16 In the meta-analysis of stroke/SE the IRR in the vascular disease group was 0.55, 95% CI
17 0.38-0.78; IRR in the no aspirin group 0.87, 95% CI 0.56-1.36; $p_{\text{interaction}}=0.13$ (**Figure 3**). The
18 results from the trials were consistent (I^2 statistic for heterogeneity=8%).

19
20 **Safety outcomes. Major bleeding.** Aalen-Johansen cumulative incidence curves by vascular
21 disease status in the anticoagulation and control groups are shown in **Figure 4A**. Anticoagulation
22 increased major bleeding in vascular disease patients. In patients with vascular disease 2.13%
23 events/patient-year occurred on edoxaban and 1.28%/patient-year on aspirin, 1.71%/patient-year
24 with apixaban vs. 1.14%/patient-year on aspirin (**Table 2**). In patients without vascular disease
25 2.19%/patient-year occurred with anticoagulation vs. 0.64%/patient-year without anticoagulation
26 in NOAH-AFNET 6, 1.38%/patient-year on apixaban and in 1.11%/patient-year on aspirin in

1 ARTESiA. The HR for major bleeding in patients with vascular disease with anticoagulation was
2 1.66 (95% CI 0.91-3.02) in NOAH-AFNET 6. The same HR without vascular disease was 3.47
3 (95% CI 1.49-8.06; $p_{\text{interaction}}=0.16$). The HR for major bleeding with anticoagulation was 1.50 (95%
4 CI 0.98- 2.31) in ARTESiA in the vascular disease group, and HR 1.25, (95% CI 0.83-1.86) in the
5 subgroup without vascular disease ($p_{\text{interaction}}=0.53$). The differences in the safety outcomes major
6 bleeding or death were mainly due to different event rates for International Society on Thrombosis
7 and Haemostasis (ISTH) major bleeding (**Table 2**).

8 Meta-analysis showed an IRR of 1.55 (95% CI 1.10-2.20) with vascular disease and an
9 IRR of 1.93 (95% CI 0.72-5.20, **Figure 5**) without vascular disease.

10 *Major bleeding or death.* There were more safety outcomes (major ISTH bleeding or death)
11 with edoxaban in NOAH-AFNET 6. In patients with vascular disease the difference in the primary
12 safety outcome was less pronounced and not substantially different. There were 90/1360 patient-
13 years of primary safety outcomes with edoxaban (6.6%/patient-year) and 72/1324 patient-years
14 without anticoagulation (5.4%/patient-year, HR 1.23, 95% CI 0.90-1.67, $p_{\text{interaction}}=0.40$, **Figure 4B**,
15 **Table 2**). The increase in major bleeding appeared more pronounced in patients without vascular
16 disease (where the comparator was placebo). There were 56 events/1094 patient-years of primary
17 safety outcomes with edoxaban (5.1%/patient-year) and 37/1097 patient-years with placebo
18 (3.4%/patient-year, HR 1.54, 95% CI 1.02-2.34).

19 In ARTESiA, there were 224 events/3091 patient-years of safety outcome with apixaban
20 (7.25%/patient-year) and 206/3069 patient-years with aspirin (6.7%/patient-year, HR 1.08, 95%
21 CI 0.89-1.30) in patients with vascular disease. In patients without vascular disease, there were
22 207/3836 patient-years of the safety outcome with apixaban (5.4%/patient-year) and 181/3874
23 patient-years on aspirin (4.7%/patient-year, HR 1.15, 95% CI 0.95-1.41), $p_{\text{interaction}}=0.63$).

24 Meta-analysis showed an IRR in the vascular disease group of 1.12, 95% CI 0.95-1.30;
25 IRR in the no vascular disease group 1.25, 95% CI 0.98-1.58 (**Figure 5**).

26

1 **Secondary outcomes according to vascular disease status.** Secondary time to event
2 endpoints adjusted for vascular disease for the other pre-specified secondary outcomes are
3 provided in **Table 3**. No relevant differences were observed.

4 5 6 **Discussion**

7 **Main findings.** This analysis of the two large trials comparing anticoagulation to no
8 anticoagulation in patients with DDAF yields three main new findings: (i) approximately half (46-
9 56%) of the patients with DDAF have concomitant vascular disease with an indication for aspirin
10 therapy; (ii) patients with DDAF and vascular disease are at increased risk of thrombo-embolic
11 events and of major bleeding. In this subgroup, anticoagulation therapy may reduce thrombo-
12 embolic events with a greater magnitude than in patients without vascular disease, though
13 without formal statistical interaction ($p_{\text{interaction}}$ in meta-analysis 0.08). In patients without vascular
14 disease, the effect of anticoagulation on thrombo-embolic events appears small; and (iii)
15 anticoagulation increases major bleeding with and without vascular disease, with a possibility
16 that the increase in bleeding could be more pronounced in patients not receiving aspirin despite
17 a very limited effect on thrombo-embolic events (Structured Graphical Abstract).

18 These data can guide shared clinical decision making on anticoagulation therapy in patients with
19 DDAF. Verification of these findings in additional data sets and analysis is desirable.

20 **Differences in clinical characteristics in patients with DDAF by vascular disease status.**

21 The main feature differentiating patients with DDAF and an indication for aspirin compared to
22 those without an indication for aspirin is the presence of vascular disease (Table 1). Other
23 differences suggest more severe disease: The devices that registered DDAF were more
24 frequently implantable cardioverter-defibrillators or cardiac resynchronization therapy devices,
25 indicating advanced cardiovascular disease. These differences probably explain the higher rate
26 of thrombo-embolic events without anticoagulation in patients with DDAF and vascular disease

1 compared to patients without vascular disease (Figure 2, Table 2). Similarly, a higher thrombo-
2 embolic event rate was observed in secondary analyses of ARTESiA and NOAH-AFNET 6 by
3 CHA₂DS₂VASc score^{13, 14} and in the small group of patients with a prior stroke¹⁵, but in both
4 cases with an increase in major bleeding and death (NOAH-AFNET 6) or in major bleeding
5 (ARTESiA). Several common components of the CHA₂DS₂VASc score do not require antiplatelet
6 therapy, including hypertension, diabetes, and heart failure. These patients were not included in
7 the subgroup studied here, patients with vascular disease. The present findings can help to
8 select the best antithrombotic therapy in patients with DDAF.

9 **DDAF in the context of ECG-diagnosed AF and no AF.** In patients with ECG-documented AF,
10 anticoagulation therapy with direct oral anticoagulants (DOACs) prevents stroke and systemic
11 embolism more effectively than antiplatelet therapy with aspirin¹⁶ or with aspirin and clopidogrel¹⁷
12 with clear signals of reducing all-cause mortality.^{4, 18} DOACs do not prevent strokes in patients
13 with cardiovascular disease without AF, including patients with embolic stroke of unknown
14 source.^{19, 20} Patients with DDAF studied in NOAH-AFNET 6 and ARTESiA sit between these
15 groups, most likely due to their low AF burden.²¹ The signals for a differential effect of
16 anticoagulation found in the current analysis using a simple stratification by vascular disease
17 identifies a potentially helpful marker identifying a group of patients with DDAF in whom
18 anticoagulation may be clinically justified. The signal was consistent using different outcome
19 definitions for efficacy and safety (**Figure 2, Figure 3**).

20 **Thrombo-embolic event rates in patients with DDAF with and without vascular disease**
21 **and effect of anticoagulation.** Anticoagulation with edoxaban or apixaban reduced thrombo-
22 embolic events in patients with DDAF and vascular disease in this analysis. The net benefit of
23 anticoagulation in these patients appears to be due to two factors: First, the rate of thrombo-
24 embolic event (stroke or SE) without anticoagulation were higher in patients with DDAF and
25 vascular disease and anticoagulation appears to reduce the incidence rate. Second, the
26 increment in bleeding may be lower in patients with vascular disease, most likely due to a

1 different comparator therapy (aspirin in patients with vascular disease, no antithrombotic therapy
2 in patients without vascular disease). In contrast, there were few thrombo-embolic events in
3 patients with DDAF without vascular disease, and anticoagulation did not reduce the rate of
4 thrombo-embolic events in these patients. Current guidelines do not recommend OAC in
5 patients with an expected rate of stroke <1%.^{22, 23} In patients with DDAF without vascular
6 disease, the annual risk of stroke or SE was 1%/year (NOAH-AFNET 6) or <1%/year (ARTESiA)
7 without anticoagulation. Taken together, these results suggest that the absence of overt vascular
8 disease may be suitable to identify patients with DDAF and a low thromboembolic risk.
9 Conversely, patients with DDAF and vascular disease treated with aspirin had an annual risk of
10 stroke or SE of 2.2%/patient-year in NOAH-AFNET 6 and of 1.8%/patient-year in ARTESiA.
11 Vascular disease patients appear to be a group in whom anticoagulation can reduce thrombo-
12 embolic events with an acceptable safety profile. These findings are not supported by formal
13 statistical tests for interaction, but can help to support shared decision making on anticoagulation
14 in patients with DDAF as suggested by a recent expert consensus paper.²⁴

15 **Bleeding events in patients with DDAF with and without vascular disease and effect of**
16 **anticoagulation.** The increase in bleeding with anticoagulation in patients with vascular disease
17 was comparable in both trials (1.5-1.7-fold) with few life-threatening bleeds (0.1%/patient-year).⁵
18 ⁶ The inherent increase in bleeding risk with all antithrombotic drugs will be diminished with an
19 active antithrombotic agent such as aspirin as the comparator.^{6,16} In patients without vascular
20 disease, the anticoagulation-induced increment in bleeding appeared to be higher, especially in
21 NOAH-AFNET 6 where the comparator was placebo. This potential signal for heterogeneity is
22 probably, at least in part, attributed to the increased risk of bleeding associated with aspirin
23 therapy found in the ASPREE (Aspirin in Reducing Events in the Elderly) and ASCEND (A Study
24 of Cardiovascular Events in Diabetes) trials.^{10,25}

1

2 **Strengths and limitations.** Strengths of this analysis include use of the two largest data sets
3 enabling a comparison of anticoagulation and no anticoagulation in patients with DDAF, the pre-
4 specified nature of the individual subanalyses, unified definition of outcomes including the
5 primary outcomes of both trials and the consistency of the trends across both data sets in the
6 trial-level meta-analysis. Limitations include the low event rate in both trials resulting in
7 insufficient event numbers to perform robust tests for treatment interaction. Some of incidence
8 curves of the subgroups suggest that the proportional hazards assumption is not always met.
9 This renders the interaction tests specific to the observed follow-up time, limiting the robustness
10 of our findings. Another limitation stems from minor design differences between the two trials,
11 especially the placebo comparator in patients without vascular disease in NOAH-AFNET 6 while
12 these patients received aspirin in ARTESiA. The indication for aspirin was based on guidelines
13 in both trials, but the variables for defining aspirin indication differed marginally (**Supplementary**
14 **Material**). A small proportion of patients in NOAH-AFNET 6 received aspirin outside the study
15 definition of aspirin indication (1.5%) in the no vascular disease. In ARTESiA some patients
16 received non-prescribed combination therapy of aspirin and DOAC. Such a treatment is not
17 recommended for routine use. It may have diluted the results of current study. However, the
18 effect probably is minor. The trends in both studies are comparable and no relevant
19 heterogeneity was observed for the efficacy outcome which lends credibility to this pre-specified
20 subgroup analysis. An individual patient-level meta-analysis is beyond the scope and abilities of
21 this paper, but may be able to overcome some of the methodological limitations of this analysis
22 and help to better define patients with DDAF who are most likely to benefit from oral
23 anticoagulation. Both NOAH-AFNET 6 and ARTESiA evaluated factors Xa antagonists as
24 anticoagulants in patients with DDAF. Whether novel anticoagulants that target factor XI/XIa
25 have more favourable effects in patients with DDAF needs to be tested, depending on their

1 efficacy in patients with AF.^{26,27} Additional analyses including an individual patient data meta-
2 analysis may be useful to replicate the present finding.

3
4 **Conclusions**
5 Approximately half of the patients with DDAF studied in the NOAH-AFNET 6 and ARTESiA trials
6 have concomitant vascular disease with an established indication for aspirin. In this subgroup,
7 anticoagulation therapy appears to reduce thrombo-embolic events with a greater magnitude
8 than in patients without vascular disease, though without formal statistical interaction. These
9 data can guide shared clinical decision making on anticoagulation therapy in patients with
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 18
 19

20 Figure legends

21 **Figure 1. CONSORT flow chart of this secondary pre-specified sub-analysis.** Shown is the
 22 analysis population in the intention to treat analysis for patients with and without vascular
 23 disease at baseline. The number of efficacy and safety outcomes used in this analysis are
 24 shown.

25
 26 **Figure 2.** Aalen-Johansen cumulative incidence curves considering death as a competing event
 27 in the groups with and without vascular disease for the effect of anticoagulation versus
 28 aspirin/placebo (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status. Orange and
 29 blue curves are NOAH-AFNET 6 data with (orange) and without (blue) anticoagulation, red and
 30 black curves ARTESiA data with (black) and without (red) anticoagulation.

- 31 A) Composite of stroke, systemic arterial embolism, myocardial infarction, pulmonary
 32 embolism and cardiovascular death in patients with vascular disease (left panel) and in
 33 patients without vascular disease (right panel, shaded curves)
 34 B) Stroke and systemic arterial embolism in patients with vascular disease (left panel) and
 35 in patients without vascular disease (right panel, shaded curves)
 36

37 **Figure 3.** Random-effects meta-analysis for the effects of anticoagulation versus aspirin/placebo
 38 (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status A) for the combined outcome
 39 of stroke, systemic arterial embolism, myocardial infarction, pulmonary embolism and
 40 cardiovascular death, $p_{\text{interaction}}=0.08$ and B) for the combined outcome of stroke and systemic
 41 arterial embolism. Incidence rate ratios were combined, $p_{\text{interaction}}=0.13$.

42
 43 **Figure 4.** Cumulative incidence of the safety outcome major bleeding shown as Aalen-Johansen
 44 cumulative incidence curves considering death as a competing event for the effect of
 45 anticoagulation versus aspirin/placebo (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular
 46 disease status. Orange and blue curves are NOAH-AFNET 6 data with (orange) and without

1 (blue) anticoagulation, red and black curves ARTESiA data with (black) and without (red)
2 anticoagulation.

3 A) Major bleeding in patients with vascular disease (left panel) and in patients without
4 vascular disease (right panel, shaded curves)

5 B) Major bleeding or death in patients with vascular disease (left panel) and in patients
6 without vascular disease (right panel, shaded curves)
7

8 **Figure 5.** Random-effects meta-analysis for the effects of anticoagulation versus aspirin/placebo
9 (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status A) for the safety outcome of
10 major bleeding and B) for the combined safety outcome of major bleeding and death. Incidence
11 rate ratios were combined.

12

13

14 **Figure legend graphical abstract**

15 Summary of findings in the NOAH-AFNET 6 and ARTESiA sub-analysis and meta-analysis in
16 patients with and without vascular disease.

17 Orange and blue curves are NOAH-AFNET 6 data with (orange) and without (blue)
18 anticoagulation, red and black curves ARTESiA data with (black) and without (red)
19 anticoagulation.

20 Abbreviations: CV, cardiovascular; DDAF, device-detected atrial fibrillation; DOAC, direct oral
21 anticoagulant; MI, myocardial infarction; OAC, oral anticoagulation; PE, pulmonary embolism;
22 SE, systemic arterial embolism; TIA, transient ischemic attack.

23

24

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26

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- 12
- 13
- 14
- 15

1 **Table 1.** Demographics and baseline characteristics of the study sample by vascular disease status

Variable	NOAH-AFNET 6			ARTESiA		
	Without vascular disease N=1070	With vascular disease N=1363	Total N=2433	Without vascular disease N=2171	With vascular disease N=1841	Total N=4012
Age, years	77.3±6.6	77.7±6.7	77.5±6.7	78.0±6.9	75.4±8.1	76.8±7.6
Male sex, N (%)	604 (56.4)	950 (69.7)	1554 (63.9)	1135 (52.3)	1430 (77.7)	2565 (63.9)
Body mass index, kg/m ²	28.5±4.9	28.3±4.6	28.4±4.8	28.7±5.8	29.0±5.8	28.8±5.8
Arterial hypertension	914 (85.4)	1196 (87.7)	2110 (86.7)	1712 (78.9)	1557(84.6)	3269 (81.5)
<i>Type of implanted device</i>						
Pacemaker, N (%)	930 (86.9)	1049 (77.0)	1979 (81.3)	1738 (80.1)	1046 (56.8)	2784 (69.4)
Cardiac resynchronization therapy pacemaker, N (%)	35 (3.3)	36 (2.6)	71 (2.9)	147 (6.8)	220 (12.0)	367 (9.1)
Implantable cardioverter-defibrillator, N (%)	39 (3.6)	145 (10.6)	184 (7.6)	136 (6.3)	418 (22.7)	554 (13.8)
Defibrillator with cardiac resynchronization therapy , N (%)	54 (5.0)	122 (9.0)	176 (7.2)	47 (2.2)	51 (2.8)	98 (2.4)
Implantable cardiac monitor, N (%)	12 (1.1)	11 (0.8)	23 (0.9)	103 (4.7)	106 (5.8)	209 (5.2)
CHA ₂ DS ₂ -VASc score	3.5±1.0	4.3±1.3	4.0±1.3	3.5±0.8	4.5±1.2	3.9±1.1
Diabetes mellitus, N (%)	225 (21.0)	443 (32.5)	668 (27.5)	573 (26.4)	594 (32.3)	1167 (29.1)

Variable	NOAH-AFNET 6			ARTESiA		
	Without vascular disease N=1070	With vascular disease N=1363	Total N=2433	Without vascular disease N=2171	With vascular disease N=1841	Total N=4012
Indication for aspirin for prevention of stroke or ischemic attack	0 (0.0)	445 (32.6)*	445 (18.3)			
Prior stroke or transient ischemic attack, N (%)				0 (0.0)	346 (18.8)	346 (8.6)
History of heart failure, N (%)	208 (19.4)	466 (34.2)	674 (27.7)	429 (19.8)	708 (38.5)	1137 (28.3)
History of myocardial infarction, N (%)	0 (0.0)	353 (25.9)	353 (14.5)	0 (0.0)	753 (40.9)	753 (18.8)
Prior coronary artery bypass surgery or percutaneous coronary intervention, N (%)	0 (0.0)	502 (36.8)	502 (20.6)			
Other indications for aspirin [#]	0 (0.0)	175 (12.8)	175 (7.5)	0 (0.0)	334 (18.1)	334 (8.3)
Modified HAS-BLED Score	2.7±0.6	3.8±0.6	3.3±0.8	2.3±0.8	2.8±0.8	2.5±0.8

1 Data are number (%) or mean±standard deviation unless indicated otherwise. *Includes prior stroke or TIA (n=209). #Mainly peripheral
2 artery disease but also various other indications.
3 Abbreviations: CHA₂DS₂-VASc, heart failure, hypertension, age 75 years, diabetes, stroke/systemic embolism, sex, prior vascular
4 disease; HAS-BLED, uncontrolled hypertension, abnormal renal and/or hepatic function, stroke, bleeding history or predisposition, labile
5 INR, elderly, drugs or excessive alcohol drinking.

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1 **Table 2.** Time to event outcomes by vascular disease status in NOAH-AFNET 6 and ARTESiA.

NOAH-AFNET 6						
Endpoint	Vascular disease	Edoxaban	Placebo	Edoxaban vs. Placebo		
		Events/PY (incidence per PY %)	Events/PY (incidence per PY %)	Hazard ratio (95% CI)	P-value	P _{interaction}
Primary NOAH (ischemic Stroke, SE, myocardial infarction, pulmonary embolism, cardiovascular death)	No	30/1109 (2.7)	30/1091 (2.7)	1.00 (0.60-1.66)	0.99	0.41
	Yes	53/1367 (3.9)	66/1322 (5.0)	0.78 (0.54,1.12)	0.17	
Primary Artesia (Stroke or SE)	No	11/1116 (0.99)	9/1101 (0.82)	1.20 (0.50-2.89)	0.69	0.17
	Yes	17/1371 (1.24)	29/1325 (2.19)	0.56 (0.31-1.02)	0.059	
Major bleeding	No	24/1094 (2.19)	7/1097 (0.64)	3.47 (1.49-8.06)	0.004	0.16
	Yes	29/1360 (2.13)	17/1324 (1.28)	1.66 (0.91-3.02)	0.10	
Major bleeding or death	No	56/1094 (5.12)	37/1097 (3.37)	1.54 (1.02-2.34)	0.042	0.40
	Yes	90/1360 (6.62)	72/1324 (5.44)	1.23 (0.90-1.67)	0.20	
ARTESiA						
Endpoint	Vascular disease	Apixaban	Aspirin	Apixaban vs. aspirin		
		Events/PY (incidence per PY %)	Events/PY (incidence per PY %)	Hazard ratio (95% CI)	P-value	P _{interaction}

Primary NOAH (Stroke, SE, myocardial infarction, pulmonary embolism, cardiovascular death)*	No	89/3861 (2.31)	87/3831 (2.27)	1.02 (0.76-1.36)	0.92	0.11
	Yes	100/3095 (3.23)	131/2991 (4.38)	0.74 (0.57-0.96)	0.021	
Primary Artesia (Stroke or SE)	No	25/3919 (0.64)	32/3888 (0.82)	0.78 (0.46-1.31)	0.35	0.29
	Yes	30/3140 (0.96)	54/3030 (1.78)	0.54 (0.34-0.84)	0.006	
Major bleeding	No	53/3836 (1.38)	43/3874 (1.11)	1.25 (0.83-1.86)	0.285	0.53
	Yes	53/3091 (1.71)	35/3069 (1.14)	1.50 (0.98-2.31)	0.061	
Major bleeding or death	No	207/3836 (5.40)	181/3874 (4.67)	1.15 (0.95-1.41)	0.16	0.63
	Yes	224/3091 (7.25)	206/3069 (6.71)	1.08 (0.89-1.30)	0.43	

1 Abbreviations: CI, confidence interval; SE, systemic arterial embolism; PY, patient-year.

2 *The primary outcome contains ischemic and unknown stroke.

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1 **Table 3.** Secondary time to event outcomes by vascular disease status in NOAH-AFNET 6 and ARTESiA.

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NOAH-AFNET 6						
Endpoint	Vascular disease	Edoxaban Events/PY (incidence per PY %)	Placebo Events/PY (incidence per PY %)	Edoxaban vs. Placebo Hazard ratio (95% CI)	P-value	P _{interaction}
All-cause stroke	No	11/1116 (0.99)	9/1101 (0.82)	1.20 (0.50-2.89)	0.69	0.24
	Yes	16/1374 (1.16)	25/1329 (1.88)	0.61 (0.33-1.15)	0.13	
Ischemic stroke	No	9/1118 (0.81)	8/1103 (0.73)	-	-	-
	Yes	13/1375 (0.95)	17/1334 (1.27)	-	-	-
Haemorrhagic stroke	No	2/1130 (0.18)	0/1110 (0.00)	-	-	-
	Yes	4/1393 (0.29)	7/1341 (0.52)	-	-	-
Unknown stroke	No	0/1122 (0.00)	1/1109 (0.09)	-	-	-
	Yes	0/1394 (0.00)	1/1340 (0.07)	-	-	-
Systemic embolism	No	0/1390 (0.00)	0/1338 (0.00)	-	-	-
	Yes	1/1122 (0.09)	4/1110 (0.36)	-	-	-
Myocardial infarction	No	2/1389 (0.14)	6/1336 (0.45)	-	-	-
	Yes	8/1120 (0.71)	9/1100 (0.82)	-	-	-
Pulmonary embolism	No	3/1394 (0.22)	4/1341 (0.30)	-	-	-
	Yes	0/1115 (0.00)	5/1104 (0.45)	-	-	-
Cardiovascular death	No	19/1122 (1.69)	18/1110 (1.62)	1.07 (0.56-2.04)	0.84	0.61
	Yes	33/1394 (2.37)	37/1342 (2.76)	0.86 (0.54-1.38)	0.53	
All-cause death	No	39/1122 (3.48)	31/1110 (2.79)	1.26 (0.79-2.02)	0.34	0.79
	Yes	69/1394 (4.95)	58/1342 (4.32)	1.15 (0.81-1.63)	0.43	

ARTESiA

Endpoint	Vascular disease	Events/PY (incidence per PY %)		Apixaban vs. aspirin		
		Apixaban	Aspirin	Hazard ratio (95% CI)	P value	P _{interaction}
All-cause stroke	No	25/3919 (0.64)	32/3888 (0.82)	0.78 (0.46-1.31)	0.35	0.34
	Yes	30/3140 (0.96)	52/3032 (1.72)	0.56 (0.36-0.87)	0.011	
Ischemic stroke	No	18/3923 (0.46)	27/3893 (0.69)	0.59 (0.37-0.96)	0.033	0.77
	Yes	27/3140 (0.86)	44/3035 (1.45)	0.67 (0.37-1.21)	0.18	
Haemorrhagic stroke	No	7/3960 (0.18)	6/3942 (0.15)	1.17 (0.39-3.48)	0.78	0.24
	Yes	3/3194 (0.09)	7/3117 (0.22)	0.41 (0.11-1.60)	0.20	
Unknown stroke	No	1/3964 (0.03)	0/3947 (0.0)	-	-	-
	Yes	1/3195 (0.03)	1/3123 (0.03)	-	-	
Systemic embolism	No	0/3964 (0.0)	0/3947 (0.0)	-	-	-
	Yes	0/3195 (0.0)	2/3122 (0.06)	-	-	
Myocardial infarction	No	19/3913 (0.49)	15/3915 (0.38)	1.27 (0.64-2.50)	0.49	0.175
	Yes	18/3150 (0.57)	26/3084 (0.84)	0.68 (0.37-1.24)	0.20	
Pulmonary embolism	No	6/3957 (0.15)	11/3921 (0.28)	0.54 (0.20-1.46)	0.23	0.48
	Yes	9/3190 (0.28)	10/3114 (0.32)	0.88 (0.36-2.16)	0.77	
Cardiovascular death	No	45/3964 (1.14)	41/3947 (1.04)	1.09 (0.71-1.67)	0.685	0.42
	Yes	60/3195 (1.88)	67/3124 (2.14)	0.87 (0.62-1.23)	0.44	
All-cause death	No	171/3964 (4.31)	153/3947 (3.88)	1.11 (0.89-1.38)	0.34	
	Yes	191/3195 (5.98)	188/3124 (6.02)	0.99 (0.81-1.21)	0.92	

Abbreviations: CI, confidence interval; PY, patient-year

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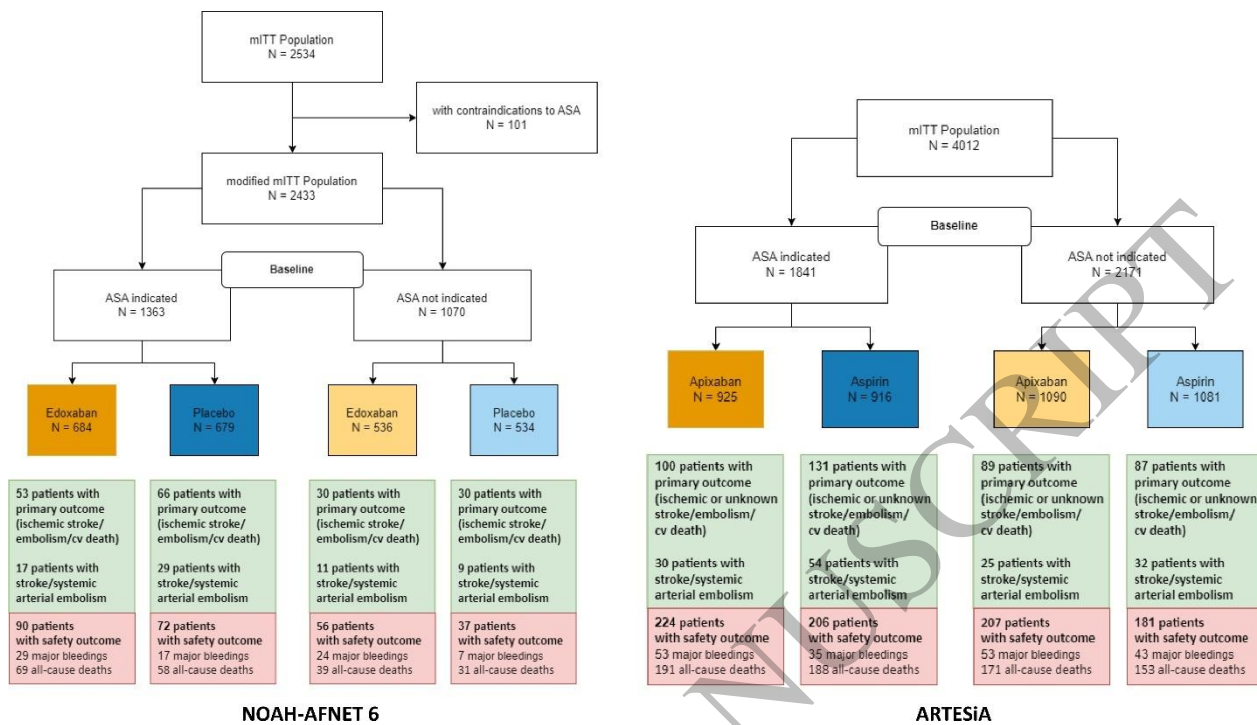


Figure 1
324x183 mm (DPI)

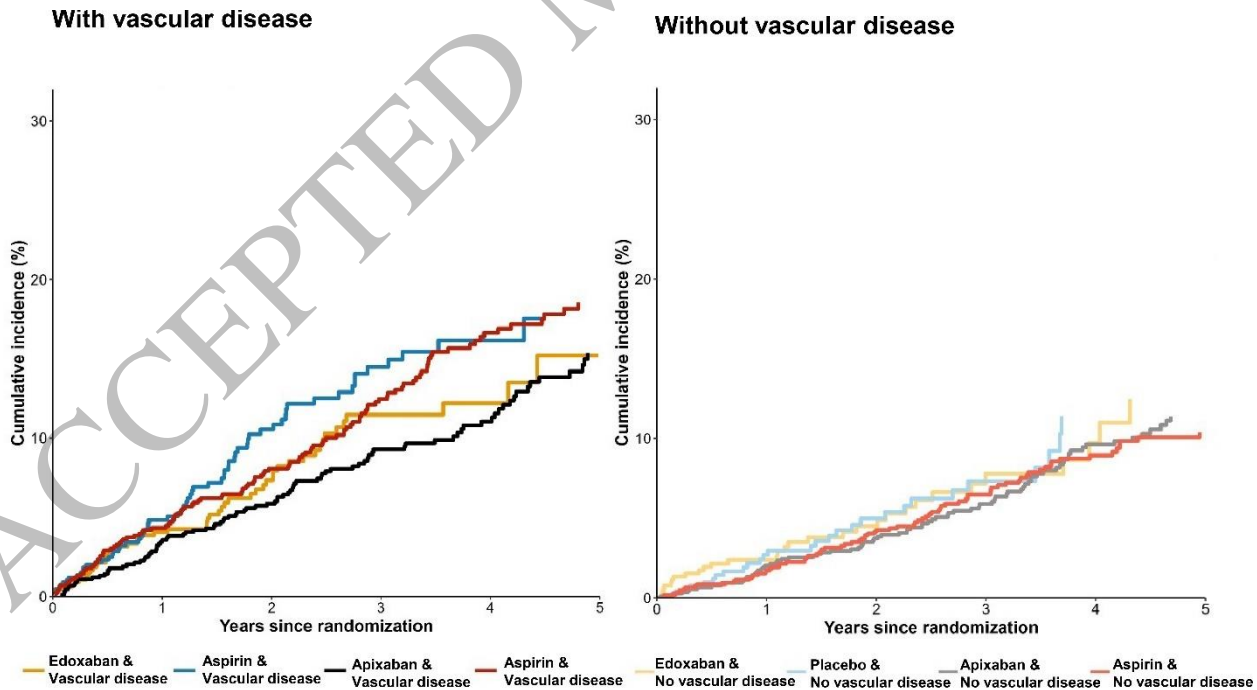


Figure 2A
319x174 mm (DPI)

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With vascular disease

Without vascular disease

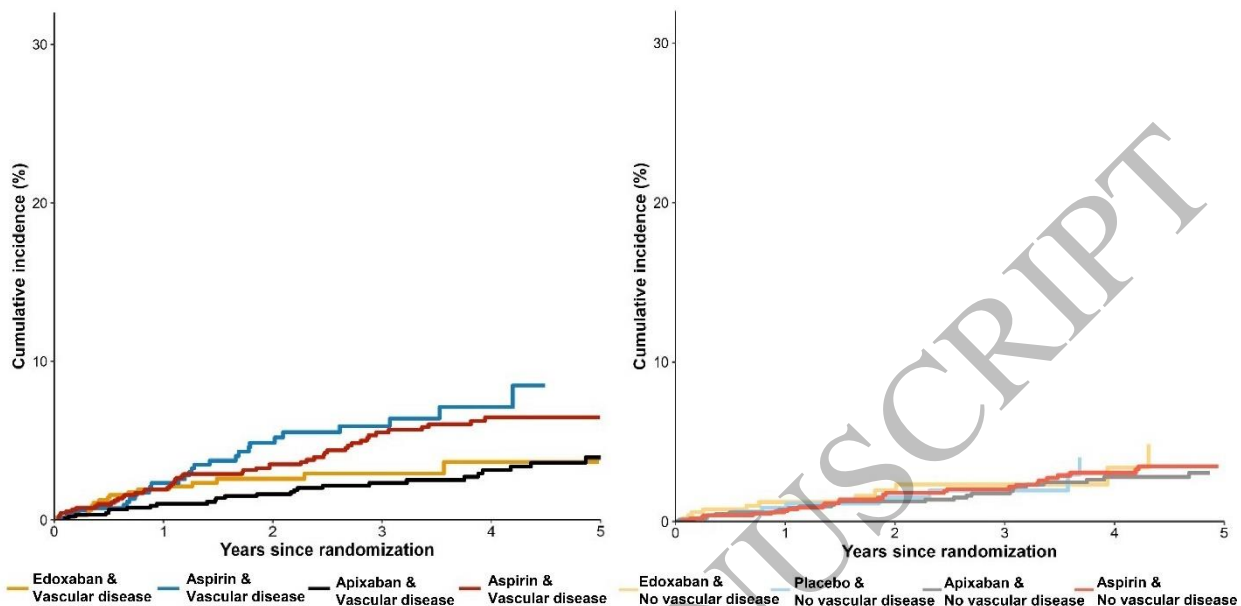


Figure 2B
319x171 mm (DPI)

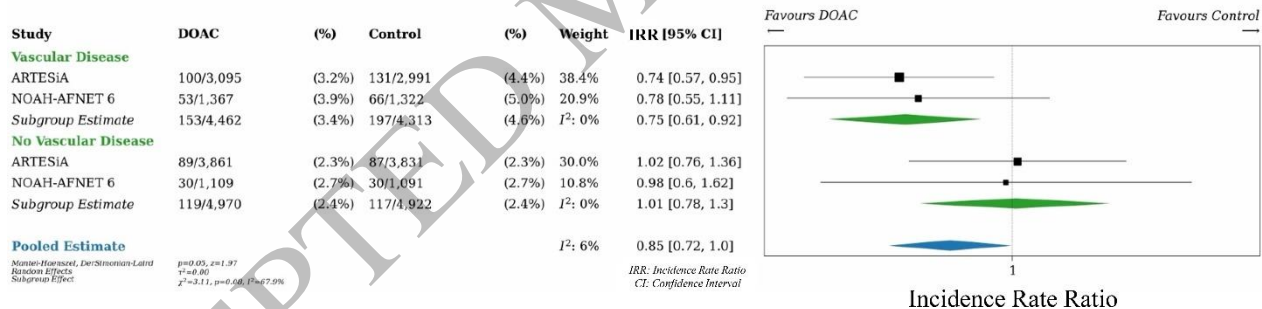


Figure 3A
319x79 mm (DPI)

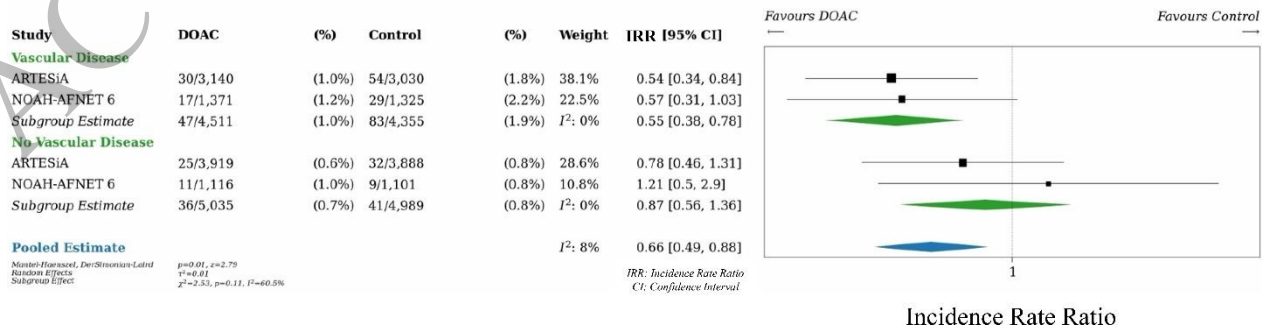


Figure 3B
317x82 mm (DPI)

With vascular disease

Without vascular disease

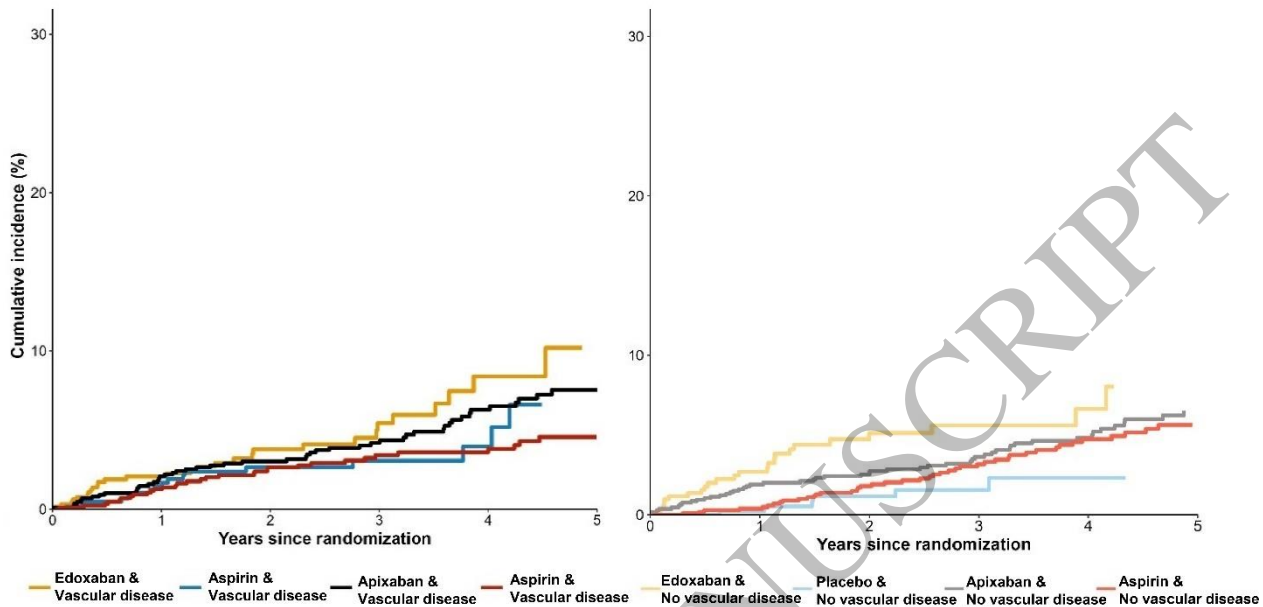


Figure 4A
319x174 mm (DPI)

With vascular disease

Without vascular disease

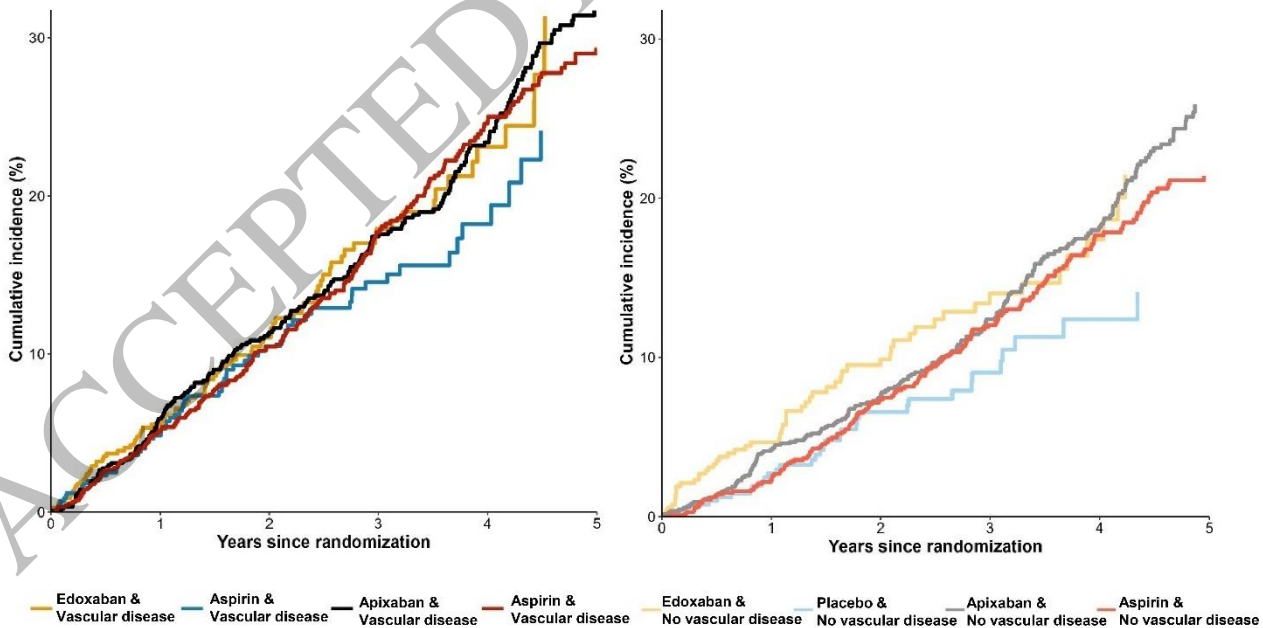


Figure 4B
319x174 mm (DPI)

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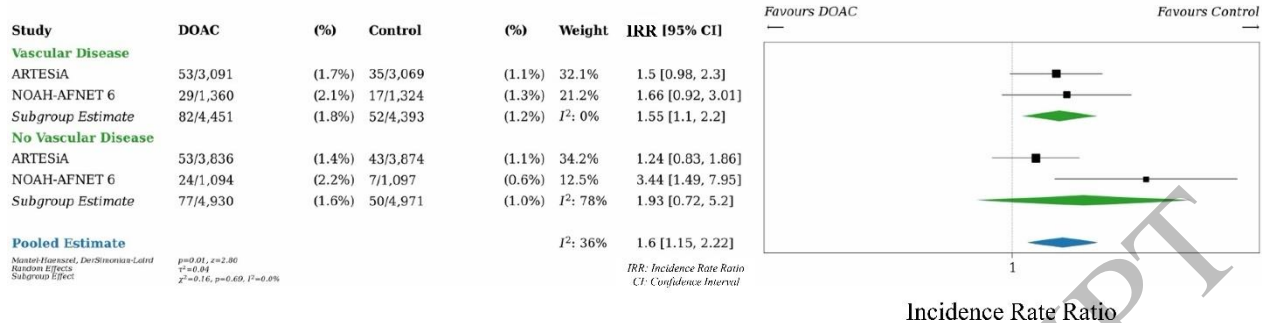


Figure 5A
317x81 mm (DPI)

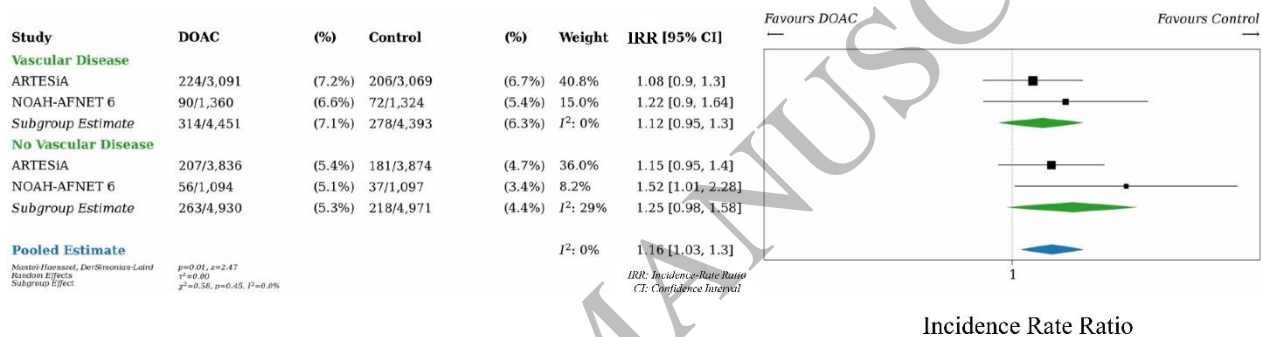


Figure 5B
317x83 mm (DPI)

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1 **Graphical Abstract**

2 **Key Question**

3 Does vascular disease with an established indication for aspirin affect the efficacy and safety of
 4 oral anticoagulation in patients with device-detected atrial fibrillation (DDAF)?

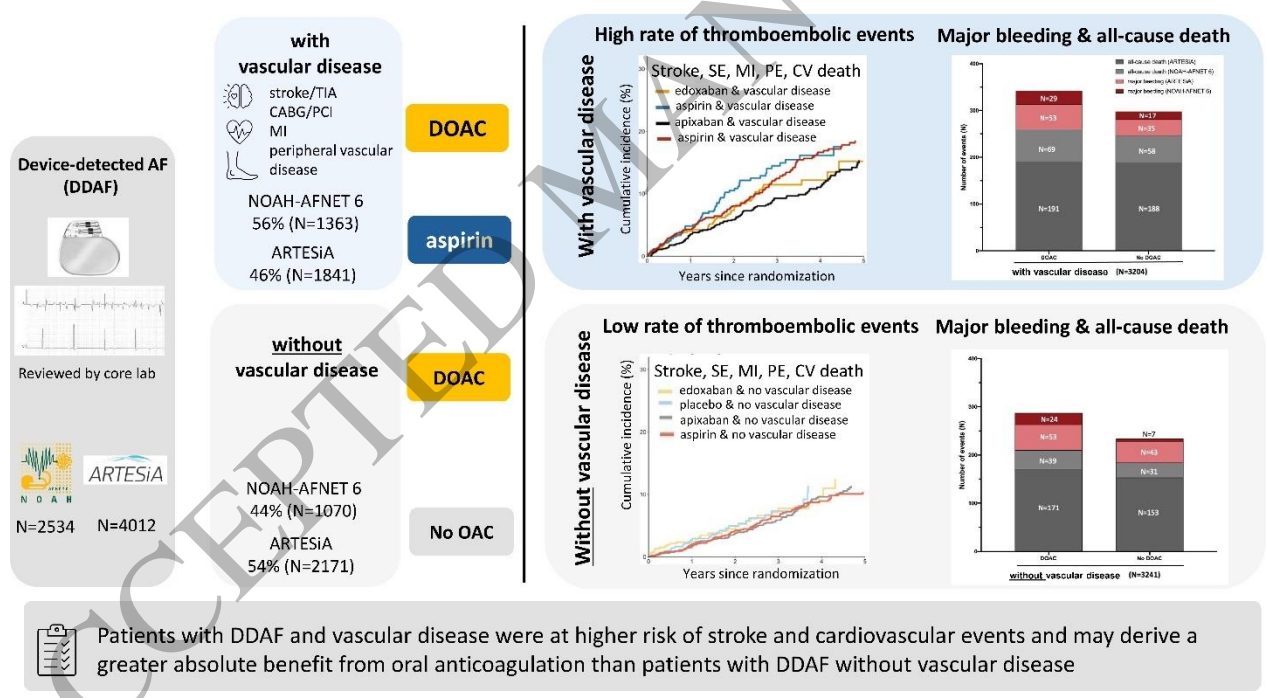
5 **Key Finding**

6 Patients with DDAF and vascular disease were at higher risk of stroke and cardiovascular
 7 events and may derive a greater absolute benefit from oral anticoagulation than patients with
 8 DDAF without vascular disease.

9 **Take Home Message**

10 Based on prespecified subanalyses of the NOAH-AFNET 6 and ARTESiA trials, anticoagulation
 11 with a direct oral anticoagulant may be preferable to therapy with aspirin in patients with DDAF
 12 and vascular disease. No antithrombotic therapy may be the preferred treatment in patients with
 13 DDAF without vascular disease.

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Graphical Abstract
 332x179 mm (DPI)