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

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

Total word count of the text body: 3653 words

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

Abbreviations:

AF	atrial fibrillation
ARTESiA	Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Subclinical Atrial Fibrillation
CHA_2DS_2-VASc	Heart failure, hypertension, age 75 years, diabetes, stroke/systemic embolism, sex, prior vascular disease
CI	confidence interval
DDAF	Device-detected atrial fibrillation
DOAC	direct oral anticoagulant
HAS-BLED	uncontrolled hypertension, abnormal renal and/or hepatic function, stroke, bleeding history or predisposition, labile INR, elderly, drugs or excessive alcohol drinking
HR	hazard ratio
ISTH	International Society on Thrombosis and Haemostasis (ISTH)
NOAH	Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes
RR	risk ratio
SD	standard deviation
SE	systemic arterial embolism
TIA	transient ischemic attack

Abstract (252 words)

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

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

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

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

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

Introduction

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

daily with the study medication, the others received placebo as double dummy. The trial was stopped prematurely due to an expected increase in bleeding combined with a trend towards futility for efficacy. The ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device Detected Subclinical Atrial Fibrillation) trial randomized patients with DDAF lasting 6 minutes to 23:59 hours to anticoagulation with apixaban or aspirin 81 mg once daily[6] and found a stroke risk-reducing effect of anticoagulation compared to aspirin. Both trials consistently found a low rate of stroke without anticoagulation (1.1-1.2% per patient-year), the expected increase in bleeding with anticoagulation, and a small further reduction in stroke with anticoagulation.[7]

Many patients with DDAF (56% in NOAH-AFNET 6, 46% in ARTESiA) have vascular disease that creates an indication for antiplatelet therapy, usually aspirin, to prevent thrombo-embolic events including ischemic stroke, myocardial infarction (MI), and systemic arterial embolism (SE).[8] Aspirin increases the risk of major bleeding compared to no therapy.[9, 10] This may alter the efficacy and safety of anticoagulation therapy. We therefore performed subgroup analyses of NOAH-AFNET 6 and ARTESiA in patients with and without vascular disease.

Methods

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

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

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

In ARTESiA patients with DDAF lasting between 6:01 minutes and 23:59 hours were enrolled. Inclusion criteria further comprised an age of at least 55 years and a CHA_2DS_2-VASc (heart failure, hypertension, age 75 years, diabetes, stroke/systemic embolism, sex, prior vascular disease) score of at least 3. A small subset of patients with a CHA_2DS_2-VASc score of 2 were enrolled in the early phase of the trial. Patients with prior stroke or age of at least 75 years or greater could also be enrolled. Randomization allocated patients to apixaban 5 mg twice daily (2.5 mg twice daily if guideline-recommended dose-reduction criteria applied) or aspirin 81 mg daily in a double-blind, double-dummy design. In ARTESiA, open label aspirin on top of the study medication was permitted.

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

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

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

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

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

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

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

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

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

Data are at the study level. The combined annualized statistical heterogeneity was assessed by I^2 statistic. Substantial heterogeneity was indicated by an I^2 greater than 50%. We conducted 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).

Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

compared to patients without vascular disease (Figure 2, Table 2). Similarly, a higher thrombo-embolic event rate was observed in secondary analyses of ARTESiA and NOAH-AFNET 6 by CHA_2DS_2VASc score[13, 14] and in the small group of patients with a prior stroke[15], but in both cases with an increase in major bleeding and death (NOAH-AFNET 6) or in major bleeding (ARTESiA). Several common components of the CHA_2DS_2VASc score do not require antiplatelet therapy, including hypertension, diabetes, and heart failure. These patients were not included in the subgroup studied here, patients with vascular disease. The present findings can help to select the best antithrombotic therapy in patients with DDAF.

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

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

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

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

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

efficacy in patients with AF.[26,27] Additional analyses including an individual patient data meta-analysis may be useful to replicate the present finding.

Conclusions

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

Funding

NOAH-AFNET 6 was partially funded by BMBF (German Ministry of Education and Research, Berlin, Germany) through the DZHK (German Center for Cardiovascular Research, Berlin, Germany, grant number FKZ 81X2800182) and by Daiichi Sankyo Europe. Further support for analysis was provided by European Union CATCH ME (grant agreement No 633196) to PK and US and AFNET; AFFECT-EU (grant agreement 847770) to PK; MAESTRIA (grant agreement 965286) to AG, PK, US and AFNET; British Heart Foundation (AA/18/2/34218); German Research Foundation (Ki 509167694); DZHK (grant numbers 81Z0710116 and 81Z0710110), Leducq Foundation, and the Dutch Heart Foundation (EmbRACE, grant number 01-002-2022-0118).

The ARTESiA study was funded by grants from the Canadian Institutes of HealthResearch (201610PTJ-378238), the Bristol-Myers Squibb–Pfizer Alliance, the Heart and Stroke Foundation of Canada, the Canadian Stroke Prevention Intervention Network, Hamilton Health Sciences, the Accelerating Clinical Trials Network, the Population Health Research Institute, and Medtronic. The sponsors had no role in data analysis, interpretation, or publication.

RBS received funding from Union's Horizon 2020 research and innovation programme under the grant agreement No 648131, from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 847770 (AFFECT-EU), from the European Union's Horizon Europe research and innovation programme under the grant agreement ID: 101095480 and German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103 and 81Z0710114); German Ministry of Research and Education (BMBF 01ZX1408A) and ERACoSysMed3 (031L0239). Wolfgang Seefried project funding German Heart Foundation.

Acknowledgements

We wish to express our gratitude to all patients who participated in the trials and to the local study teams, to the dedicated staff, and to all committee members.

Declarations of interest

Renate B Schnabel
Lecture fees and advisory board fees from BMS/Pfizer and Bayer outside this work.
Juan Benezet-Mazuecos
Nothing to report.
Nina Becher
Speaker fees from Abbott and Medtronic and a grant from Biotronik, not related to this submitted work.
Marco Alings
Nothing to report
Dan Atar
Speaker fees from Amgen, Amarin, AstraZeneca, Bayer, Boehringer- Ingelheim, BMS, MSD, Novartis, NovoNordisk, Pfizer, Pharmacosmos, Philips, Roche-Diagnostics, Sanofi, Takeda, Vifor; Institutional grant support from BMS/Pfizer, Medtronic, Bayer, Roche-Diagnostics.
Alexander P Benz
Lecture fees from Bristol Myers Squibb, AstraZeneca; Participation in an educational program supported by Boston Scientific ("Fellowship Herzrhythmus").
Emanuele Bertaglia
Nothing to report.
David H Birnie
Nothing to report.
Carina Blomstrom-Lundquist
Honoraria from Medtronic, Cathprint, Boston Scientific, Johnson&Johnson, Abbott, Sanofi, Philips, Bayer, Organon, and Milestone. In addition, CBL is a member of DSMB/advisory board for Boston Scientific, Abbott, Milestone, and Medtronic.
A John Camm
Consulting fees from Bayer, Pfizer/BMS, Daiichi Sankyo, Acesion, InCarda, Abbott, Boston Scientific, Medtronic, Huya Bio, Biosense, and Webster and honoraria from Bayer, Sanofi, and Menarini. In addition, AJC is a member of DSMB/advisory board for Anthos, AFNET, Johnson and Johnson (all personal payment) and Attune, British Heart Foundation, and Charité (not paid). AJC has the following Leadership or fiduciary role in other board, society, committee or advocacy group: Drug Safety Research Unit, Arrhythmia Alliance, Atrial Fibrillation Association, European Society of Cardiology.
Gregory Chlouverakis
Nothing to report.
Wolfgang Dichtl
Research grants from Boston Scientific (not paid personally but to Medical University Innsbruck).
Educational grants from Abbott and Microport (not paid personally but to Tirol Kliniken GmbH).
Consulting fee from Reata Pharmaceuticals/Biogen.
Julia W Erath
Consulting fees, travel support and lecture fees from ZOLL Medical Corporation, travel grants from Bayer Vital, Boehringer Ingelheim, St. Jude Medical/Abbott, Novartis and lecture fees from Servier, Pfizer and Bayer, outside the submitted work.
Alexander Fierenz
Research support for statistical analysis from EU Horizon 2020, Biotronik, and Adrenomed AG (research support is not paid personally but to the institution IMBE).

Andreas Goette
Consulting fees from Daiichi Sankyo and honoraria from Daiichi Sankyo, Bayer, Bristol_Meyers Squibb, Boehringer, Boston Scientific, Pfizer, and Medtronic.
Christopher B Granger
Research grants from Bayer, Boehringer Ingelheim; Consultant to Anthos, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific Corporation, Bristol Myers Squibb, Cadrenal, Daiichi Sankyo Company, Janssen Global Services, LLC, Merck, Pfizer Inc., Tenac.io.
Emmanuel Simantirakis
Nothing to report
Valentina Kutyifa
Research grants from Boston Scientific, ZOLL, NIH, Spire Inc.; Speaker fees from Medtronic, Abbott, Biotronik; Consultant fees from Biotronik.
Shun Fu Lee
Nothing to report.
Cecilia Linde
Research support from Swedish Heart Lung Foundation, Swedish Royal Society of Science, Stockholm County Council; Consulting fees from AstraZeneca, Roche Diagnostics; Speaker honoraria from Novartis, Astra, Bayer, Vifor Pharma, Medtronic, Impulse Dynamics; Advisory boards for Astra Zeneca.
Gregory Y H Lip
Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. GYHL is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871.
Renato D Lopes
Research grants from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Medtronic, Novo Nordisk, Pfizer, Sanofi US Services Inc.; Consultant to Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo Company, GlaxoSmithKline, Medtronic, Merck, Novo Nordisk, Pfizer, Portola Pharmaceuticals, Sanofi US Services Inc.
Philippe Mabo
Nothing to report.
Eloi Marijon
Consulting fees and honoraria from Medtronic, Boston Scientific, Zoll, and Abbott and research grants from Abbott, Biotronik, Boston Scientific, Medtronic, MicroPort and Zoll.
William F McIntyre
Consultant to Servier Pharmaceuticals LLC.
Lena Rivard
Research grants from Bayer Inc., Heart and Stroke Foundation, Canadian Institutes of Health Research (CIHR), FRQS (Fonds de Recherche Quebec-Sante).
Ulrich Schotten
Consulting fees from Roche, YourRhythmics BV, and University Lugano and honoraria from Johnson & Johnson. In addition, US receives payments from Roche, YourRhythmics BV, and EP Solutions for DSMB or advisory board participation and holds stock/stock options from Your Rhythmics BV.
Susanne Sehner
Research support for statistical analysis from EU Horizon 2020, Biotronik, and Adrenomed AG (research support is not paid personally but to the institution IMBE) and honoraria for lectures from Boston Scientific.
Tobias Toennis

Consulting fees from Medtronic, and Boston Scientific.
Panos Vardas
Consulting fees from Hygiea Hospital Group and European Society of Cardiology.
Antonia Zapf
Honoraria for lectures from Boston Scientific. AZ received research support for statistical analysis from EU Horizon 2020, Biotronik, and Adrenomed AG (paid to the institution).
Jeff Healey
Research grants from Boston Scientific Corporation, Bristol Myers Squibb, Medtronic, Pfizer; Consultant for Bayer, Boston Scientific Corporation, Medtronic, Novartis, Servier Affaires Medicales; Expert witness for Bayer.
Paulus Kirchhof
Research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Center for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last five years. PK is listed as inventor on two issued patents held by University of Hamburg (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

Figure legends

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

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

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

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

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

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

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

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

Figure legend graphical abstract

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

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

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

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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)
Type of implanted device						
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_2DS_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

Data are number (%) or mean±standard deviation unless indicated otherwise. *Includes prior stroke or TIA (n=209). [#]Mainly peripheral artery disease but also various other indications.

Abbreviations: CHA_2DS_2-VASc, heart failure, hypertension, age 75 years, diabetes, stroke/systemic embolism, sex, prior vascular disease; HAS-BLED, uncontrolled hypertension, abnormal renal and/or hepatic function, stroke, bleeding history or predisposition, labile INR, elderly, drugs or excessive alcohol drinking.

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		**Apixaban**	**Aspirin**	**Apixaban vs. aspirin**		
	Vascular disease	**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	

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

*The primary outcome contains ischemic and unknown stroke.

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

2

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	Apixaban Events/PY (incidence per PY %)	Aspirin Events/PY (incidence per PY %)	Apixaban vs. 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

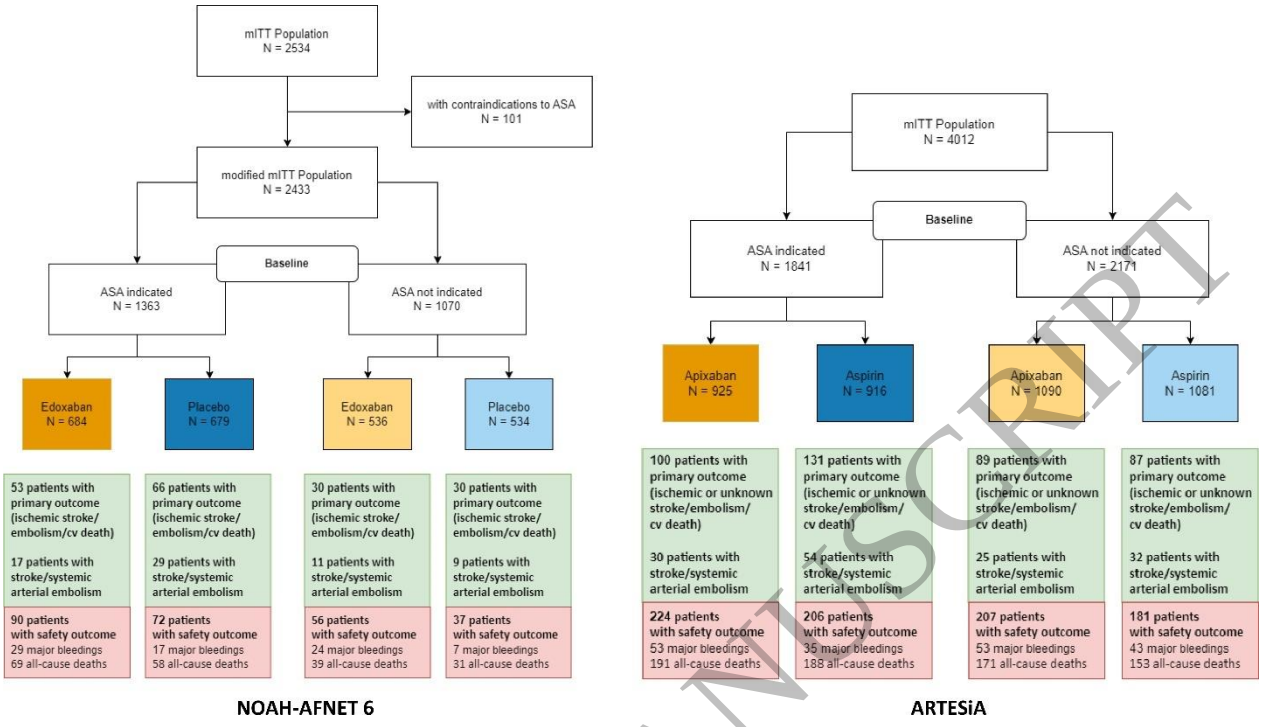


Figure 1
324x183 mm (DPI)

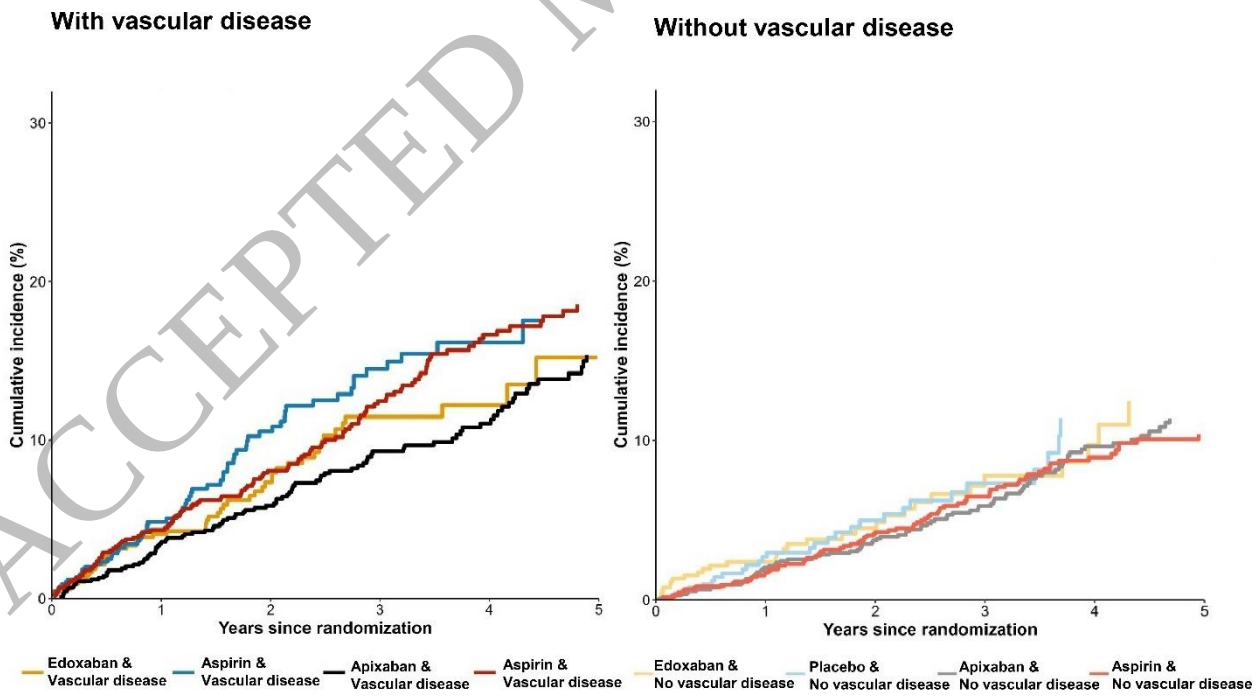


Figure 2A
319x174 mm (DPI)

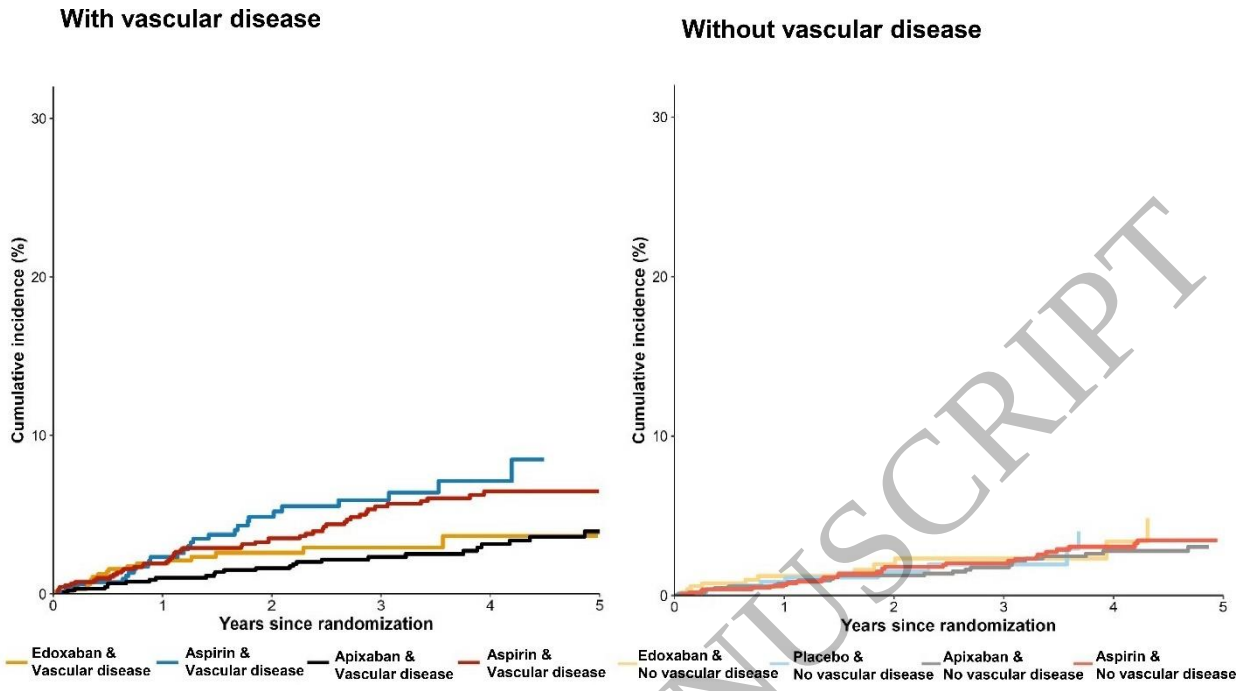


Figure 2B
319x171 mm (DPI)

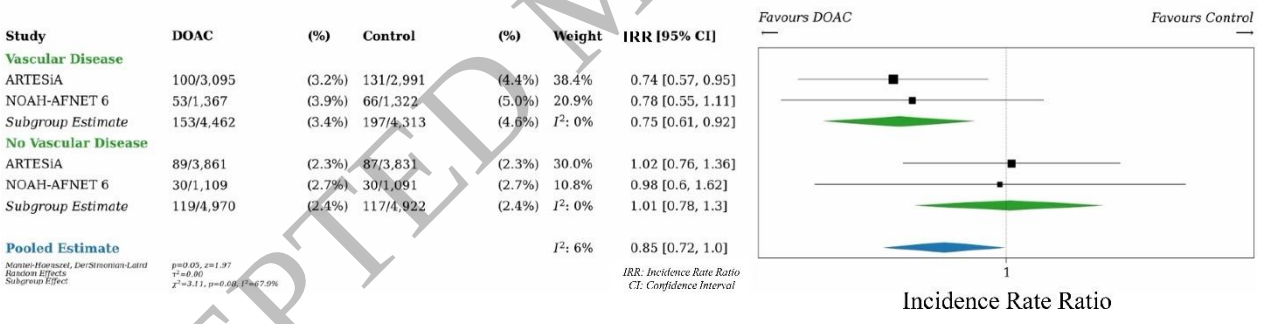


Figure 3A
319x79 mm (DPI)

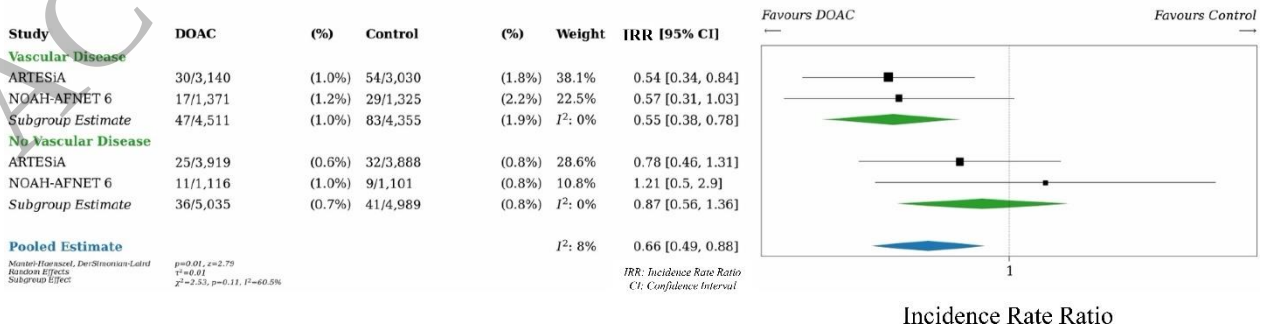


Figure 3B
317x82 mm (DPI)

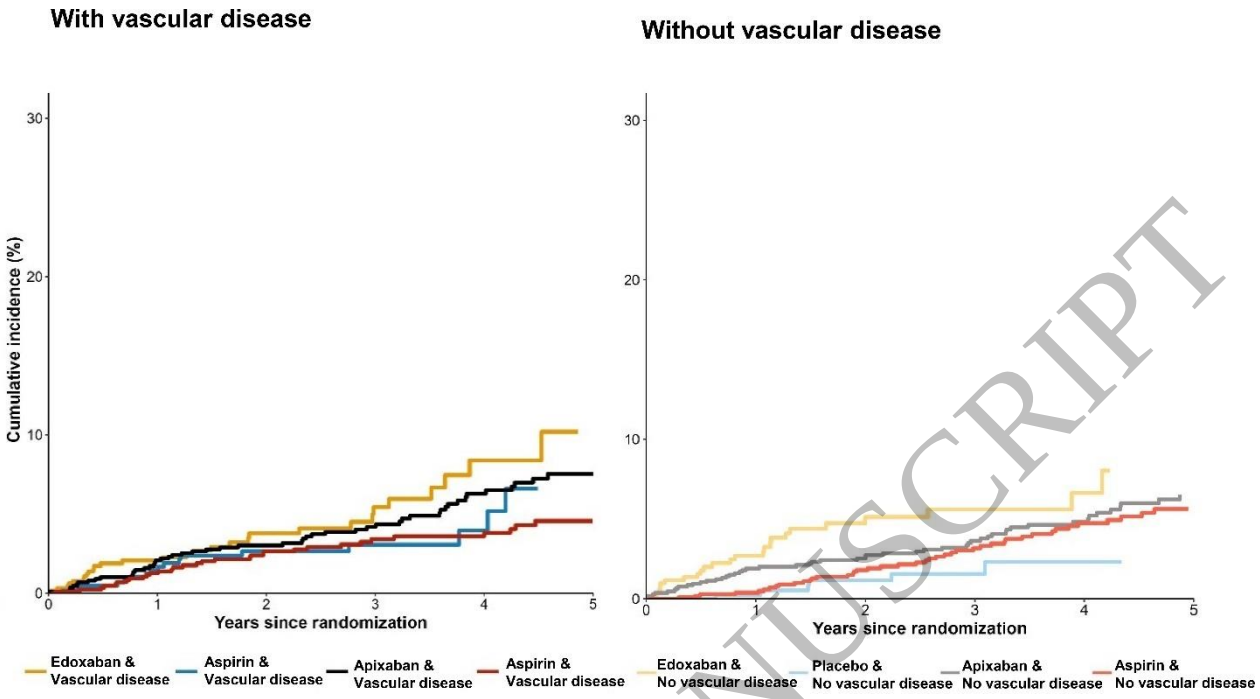


Figure 4A
319x174 mm (DPI)

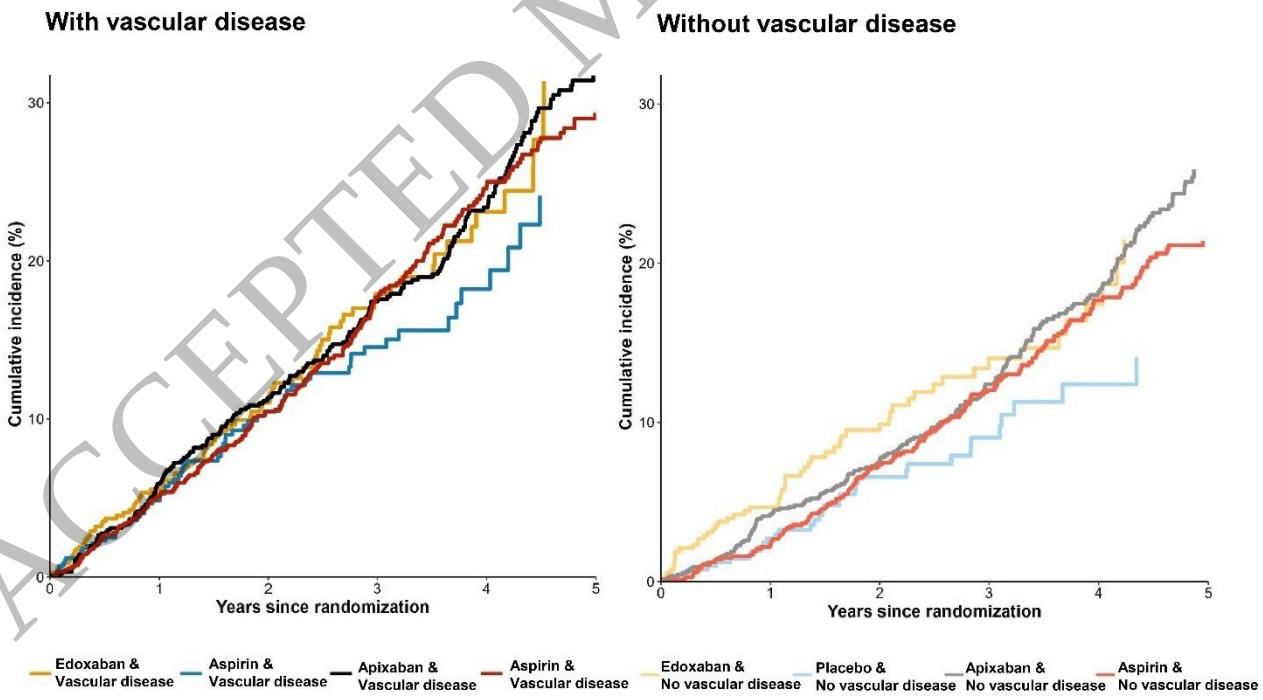


Figure 4B
319x174 mm (DPI)

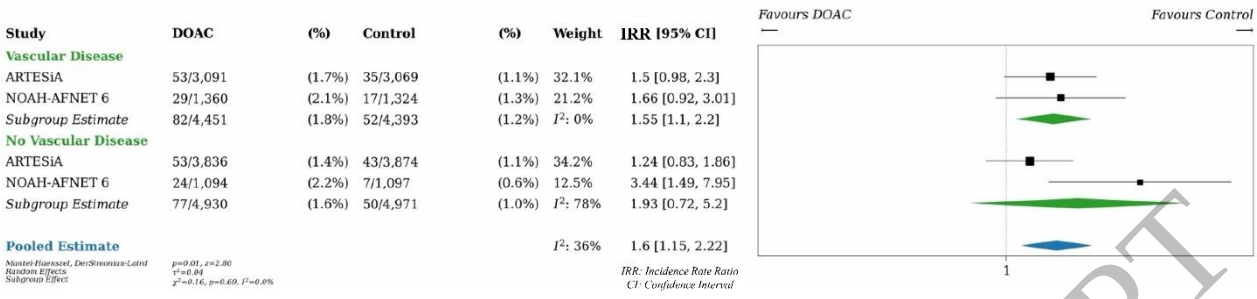


Figure 5A
317x81 mm (DPI)

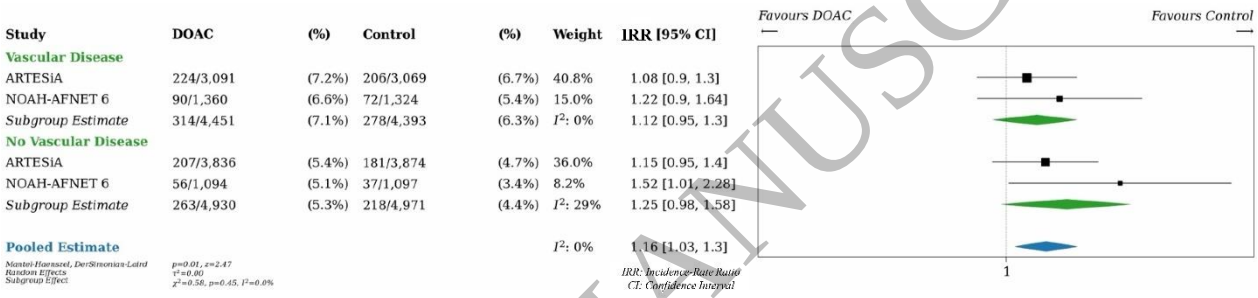


Figure 5B
317x83 mm (DPI)

Graphical Abstract

Key Question

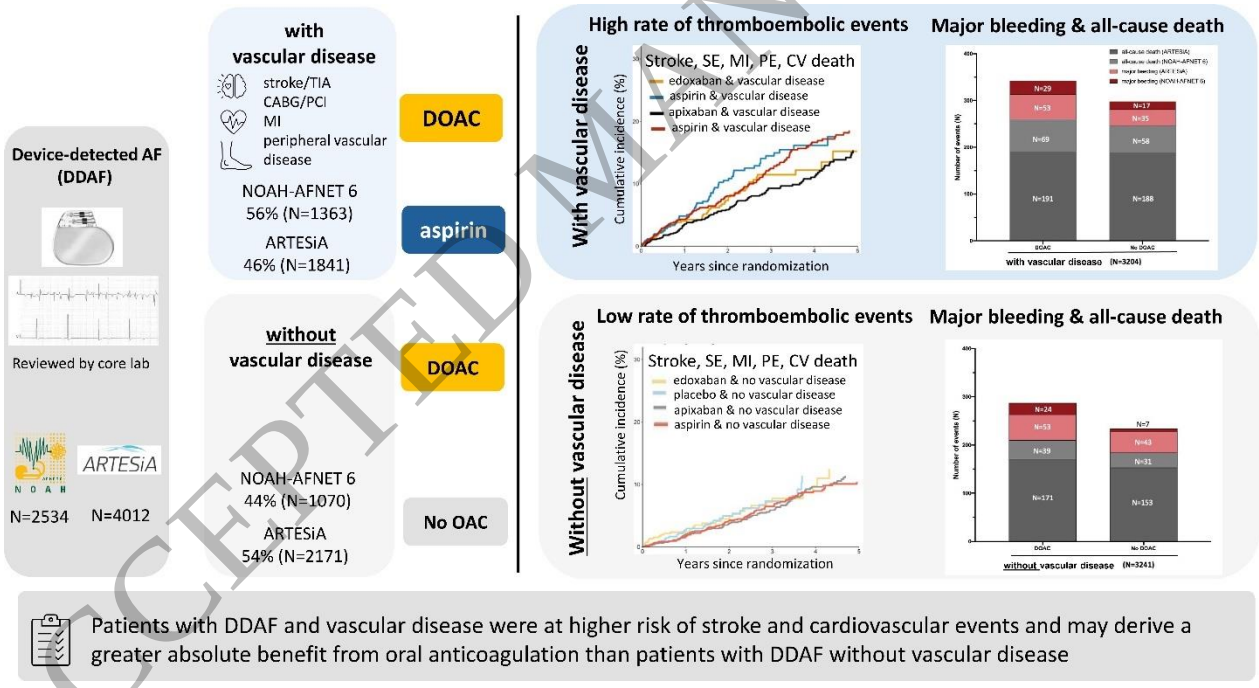
Does vascular disease with an established indication for aspirin affect the efficacy and safety of oral anticoagulation in patients with device-detected atrial fibrillation (DDAF)?

Key Finding

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

Take Home Message

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



Graphical Abstract
332x179 mm (DPI)