ESC European Society of Cardiology

European Heart Journal (2024) **45**, 4902–4916
https://doi.org/10.1093/eurheartj/ehae596

FASTTRACK – CLINICAL RESEARCH
Arrhythmias

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

Renate B. Schnabel [1,2,3], Juan Benezet-Mazuecos [4], Nina Becher [1,2], William F. McIntyre[5], Alexander Fierenz [6], Shun Fu Lee [7], Andreas Goette[8,9], Dan Atar [10], Emanuele Bertaglia[11], Alexander P. Benz[5,12], Gregory Chlouverakis [13], David H. Birnie[14], Wolfgang Dichtl[15], Carina Blomstrom-Lundqvist[16,17], A. John Camm [18], Julia W. Erath[19], Emmanuel Simantirakis [20], Valentina Kutyifa [21], Gregory Y. H. Lip[22,23], Philippe Mabo[24], Eloi Marijon [25], Lena Rivard [26], Ulrich Schotten [3,27], Marco Alings[28], Susanne Sehner [6], Tobias Toennis [1,2], Cecilia Linde [29], Panos Vardas[20,30], Christopher B. Granger[31], Antonia Zapf [6], Renato D. Lopes[32], Jeff S. Healey [5], and Paulus Kirchhof [1,2,3,33]*

[1]Department of Cardiology, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany; [2]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Luebeck, Hamburg, Germany; [3]Atrial Fibrillation NETwork (AFNET), Mendelstraße 11, 48149 Muenster, Germany; [4]Cardiology Department, Hospital Universitario La Luz, Madrid, Spain; [5]Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [6]Institute of Medical Biometry and Epidemiology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; [7]Department of Health Research Methods, Evaluation, and Impact, McMaster University, and Population Health Research Institute, Hamilton, Ontario, Canada; [8]Department of Cardiology and Intensive Care Medicine, St Vincenz-Hospital Paderborn, Paderborn, Germany; [9]Otto-von-Guericke Universität Magdeburg, Magdeburg, Germany; [10]Division of Cardiology, Oslo University Hospital Ulleval, and Institute of Clinical Medicine, University of Oslo, Norway; [11]Cardiology Unit, Camposampiero Hospital—AULSS, Padua, Italy; [12]Department of Cardiology, University Medical Center Mainz, Johannes Gutenberg-University, Mainz, Germany; [13]Biostatistics Lab, School of Medicine, University of Crete, Crete, Greece; [14]University of Ottawa Heart Institute, Ottawa, ON, Canada; [15]Department of Internal Medicine III, Cardiology and Angiology, Innsbruck Medical University, Innsbruck, Austria; [16]Department of Medical Science, Uppsala University, Uppsala, Sweden; [17]School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [18]Cardiovascular and Cell Sciences Research Institute, St George´s, University of London, London, UK; [19]Division of Clinical Electrophysiology, Department of Cardiology, University Hospital Frankfurt, J. W. Goethe University, Frankfurt, Germany; [20]Department of Cardiology, Heraklion University Hospital, Heraklion, Crete, Greece; [21]School of Medicine and Dentistry, University of Rochester, Rochester, NY, USA; [22]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; [23]Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [24]Cardiology and Vascular Disease Division, Rennes University Health Centre, Rennes, France; [25]Cardiology Division, European Georges Pompidou Hospital, Paris, France; [26]Department of Cardiology, Montreal Heart Institute, Université de Montréal, Montréal, Canada; [27]Departments of Cardiology and Physiology, Maastricht University, Maastricht, The Netherlands; [28]Amphia Ziekenhuis, Breda, Netherlands; [29]Department of Cardiology, Karolinska Institutet, Stockholm, Sweden; [30]Biomedical Research Foundation Academy of Athens (BRFAA), Greece and Hygeia Hospitals Group, Athens, Greece; [31]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [32]Duke Clinical Research Institute, Duke University, Durham, NC, USA; and [33]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK

Received 26 July 2024; revised 6 August 2024; accepted 21 August 2024; online publish-ahead-of-print 2 September 2024

See the editorial comment for this article 'Stroke risk in device-detected atrial fibrillation is modulated by the continuum of vascular disease burden', by D. Linz and S.-M. Chaldoupi, https://doi.org/10.1093/eurheartj/ehae797.

* Corresponding author. Tel: +49 40 741053824, Email: p.kirchhof@uke.de

Abstract

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 with no anticoagulation in patients with DDAF with or without vascular disease, defined as prior stroke/transient ischaemic 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%), 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 randomized groups). Meta-analysis found consistent results across both trials ($I^2_{\text{heterogeneity}} = 6\%$) with a trend for interaction with randomized therapy ($p_{\text{interaction}} = .08$). Stroke/SE behaved similarly. Anticoagulation equally increased major bleeding in vascular disease patients [edoxaban, 2.1%/patient-year; no anticoagulation, 1.3%/patient-year; apixaban, 1.7%/patient-years; 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.

Structured Graphical Abstract

Key Question

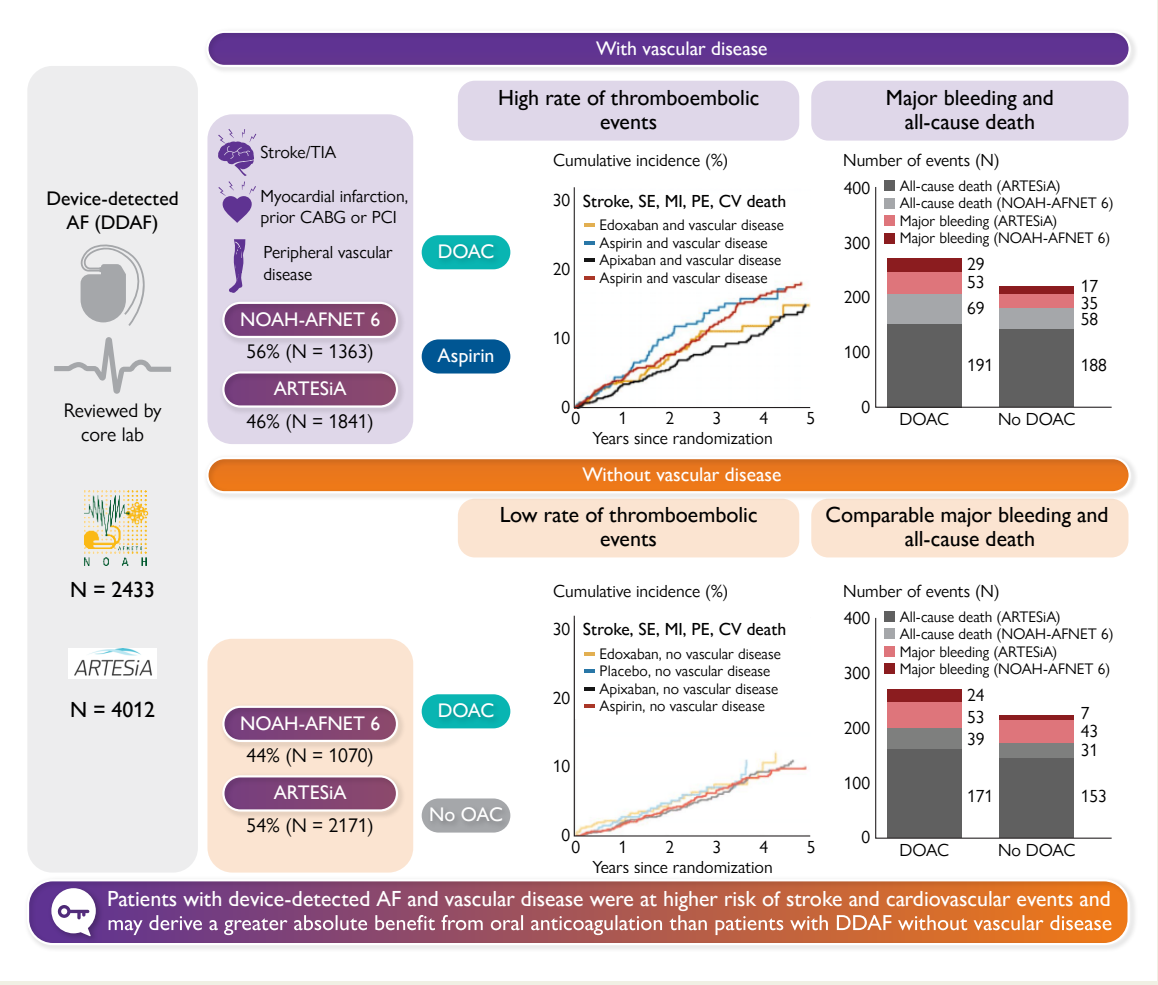
Does vascular disease with an established indication for acetyl-salicylic acid (aspirin) affect the efficacy and safety of oral anticoagulation therapy in patients with device-detected atrial fibrillation?

Key Finding

Patients with device-detected atrial fibrillation (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 DOAC 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.



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. 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

Keywords Atrial fibrillation • Device-detected atrial fibrillation • Oral anticoagulation • Trial • Stroke

Introduction

Device-detected atrial fibrillation (DDAF) is found in 20%–30% of older adults with cardiovascular disease, often in patients without electrocardiogram (ECG)-documented atrial fibrillation (AF).[1,2] Device-detected atrial fibrillation 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 with no anticoagulation in patients with DDAF and stroke risk factors, but

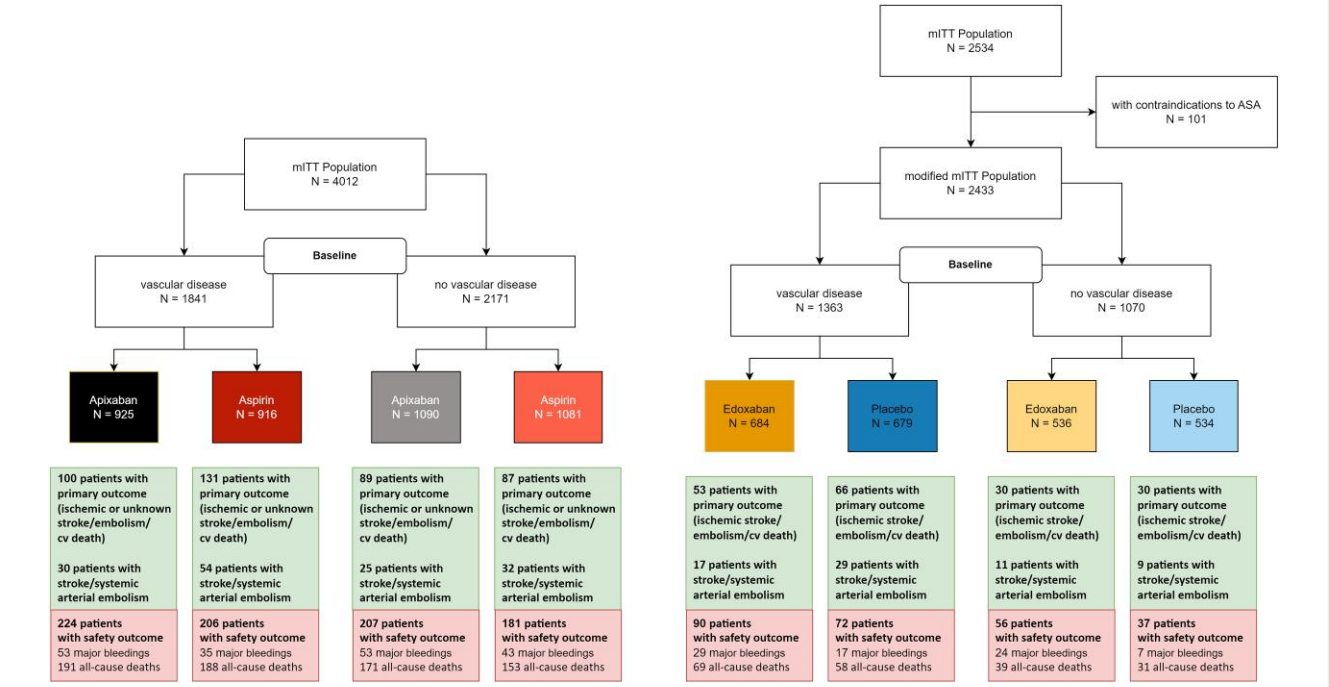


Figure 1 CONSORT flow chart of this secondary pre-specified sub-analysis. Shown is the analysis population in the intention to treat analysis for patients with and without vascular disease at baseline. The number of efficacy and safety outcomes used in this analysis is shown

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 min 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 (double dummy design). 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 min to 23:59 h to anticoagulation with apixaban or aspirin 81 mg once daily[6] and found a small stroke risk-reducing effect of anticoagulation compared with aspirin. Both trials consistently found a low rate of stroke without anticoagulation (1.1%–1.2% per patient-years), 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 concomitant vascular disease that creates an indication for antiplatelet therapy, usually aspirin, to prevent thromboembolic events including ischaemic stroke, myocardial infarction (MI), and systemic arterial embolism (SE).[8] Aspirin increases the risk of major bleeding compared with 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 with no anticoagulation in the NOAH-AFNET 6 trial. 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 randomized to edoxaban took a dummy tablet. Physician's decision could overrule aspirin indications.

In ARTESiA, patients with DDAF lasting between 6:01 min and 23:59 h 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 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 h 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:

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)
Indication for aspirin for prevention of stroke or ischaemic attack	0 (0.0)	445 (32.6)[a]	445 (18.3)			
Prior stroke or transient ischaemic 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[b]	0 (0.0)	175 (12.8)	175 (7.2)	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.
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.
[a]Includes prior stroke or TIA (*n* = 209).
[b]Mainly peripheral artery disease but also various other indications.

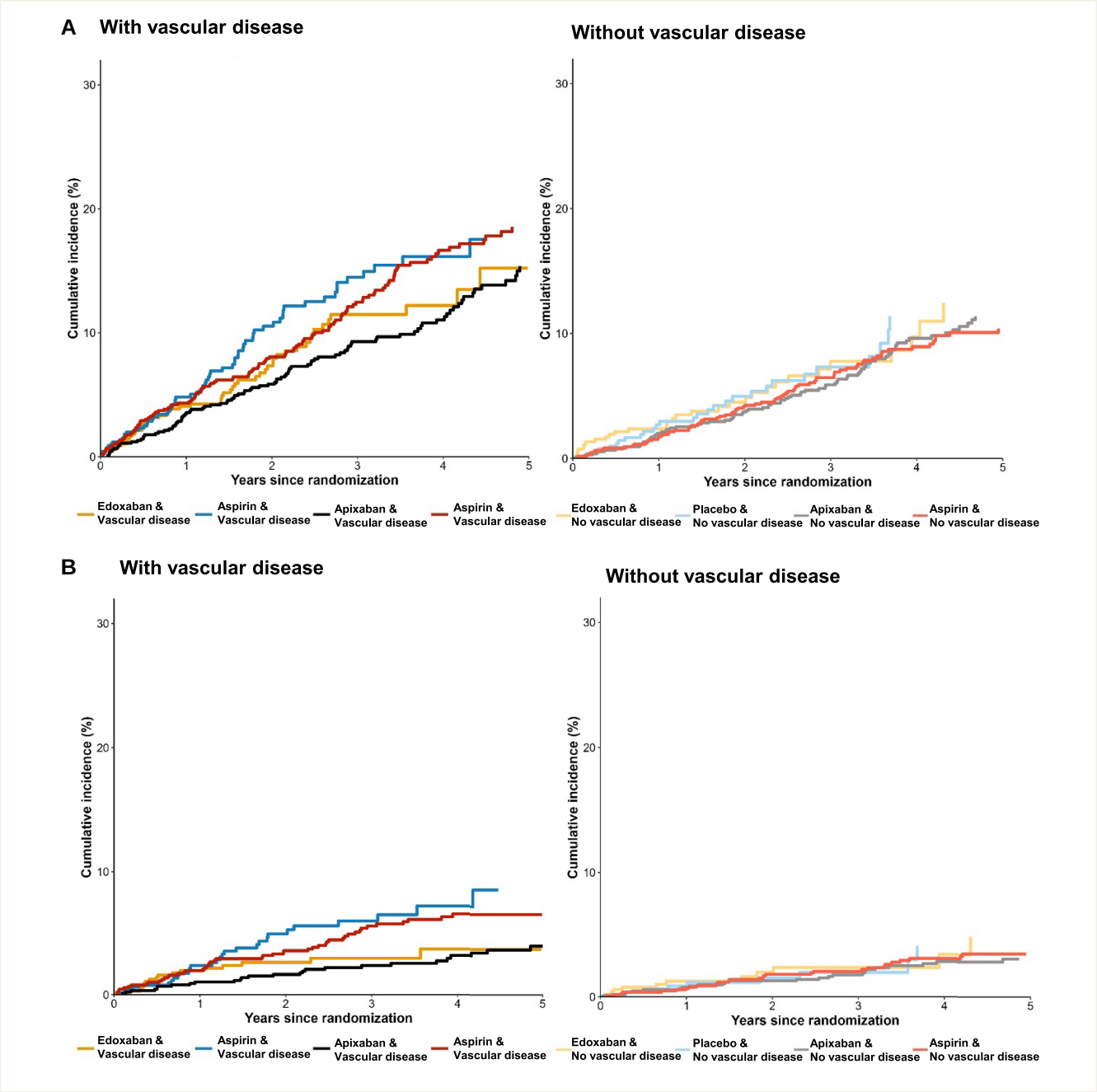


Figure 2 Aalen–Johansen cumulative incidence curves considering death as a competing event in the groups with and without vascular disease for the effect of anticoagulation vs. aspirin/placebo (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status. Orange and blue curves are NOAH-AFNET 6 data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

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 Supplementary Data. All patients were followed up until the end of the trial.

Outcomes

Outcomes of interest were primary composite outcomes for efficacy and safety of the main trials.[6,11] The efficacy outcomes were a composite of ischaemic 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 committee and adhere to good clinical practice. Details have been published (5,6).

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

Endpoint	Vascular disease	NOAH-AFNET 6 Edoxaban Events/PY (incidence per PY %)	Placebo Events/PY (incidence per PY %)	Edoxaban vs. placebo Hazard ratio (95% CI)	*P*-value	$P_{interaction}$
Primary NOAH (ischaemic stroke, SE, myocardial infarction, pulmonary embolism, cardiovascular death)	No	30/1109 (2.7)	30/1091 (2.7)	1.00 (0.60–1.66)	.99	.41
	Yes	53/1367 (3.9)	66/1322 (5.0)	0.78 (0.54,1.12)	.17	
Primary Artesia (stroke or SE)	No	11/1116 (0.99)	9/1101 (0.82)	1.20 (0.50–2.89)	.69	.17
	Yes	17/1371 (1.24)	29/1325 (2.19)	0.56 (0.31–1.02)	.059	
Major bleeding	No	24/1094 (2.19)	7/1097 (0.64)	3.47 (1.49–8.06)	.004	.16
	Yes	29/1360 (2.13)	17/1324 (1.28)	1.66 (0.91–3.02)	.10	
Major bleeding or death	No	56/1094 (5.12)	37/1097 (3.37)	1.54 (1.02–2.34)	.042	.40
	Yes	90/1360 (6.62)	72/1324 (5.44)	1.23 (0.90–1.67)	.20	

Endpoint	Vascular disease	ARTESiA Apixaban Events/PY (incidence per PY %)	Aspirin Events/PY (incidence per PY %)	Apixaban vs. aspirin Hazard ratio (95% CI)	*P*-value	$P_{interaction}$
Primary NOAH (stroke, SE, myocardial infarction, pulmonary embolism, cardiovascular death)[a]	No	89/3861 (2.31)	87/3831 (2.27)	1.02 (0.76–1.36)	.92	.11
	Yes	100/3095 (3.23)	131/2991 (4.38)	0.74 (0.57–0.96)	.021	
Primary Artesia (stroke or SE)	No	25/3919 (0.64)	32/3888 (0.82)	0.78 (0.46–1.31)	.35	.29
	Yes	30/3140 (0.96)	54/3030 (1.78)	0.54 (0.34–0.84)	.006	
Major bleeding	No	53/3836 (1.38)	43/3874 (1.11)	1.25 (0.83–1.86)	.285	.53
	Yes	53/3091 (1.71)	35/3069 (1.14)	1.50 (0.98–2.31)	.061	
Major bleeding or death	No	207/3836 (5.40)	181/3874 (4.67)	1.15 (0.95–1.41)	.16	.63
	Yes	224/3091 (7.25)	206/3069 (6.71)	1.08 (0.89–1.30)	.43	

CI, confidence interval; SE, systemic arterial embolism; PY, patient-years.
[a]The primary outcome contains ischaemic and unknown stroke.

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 χ^2 test 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

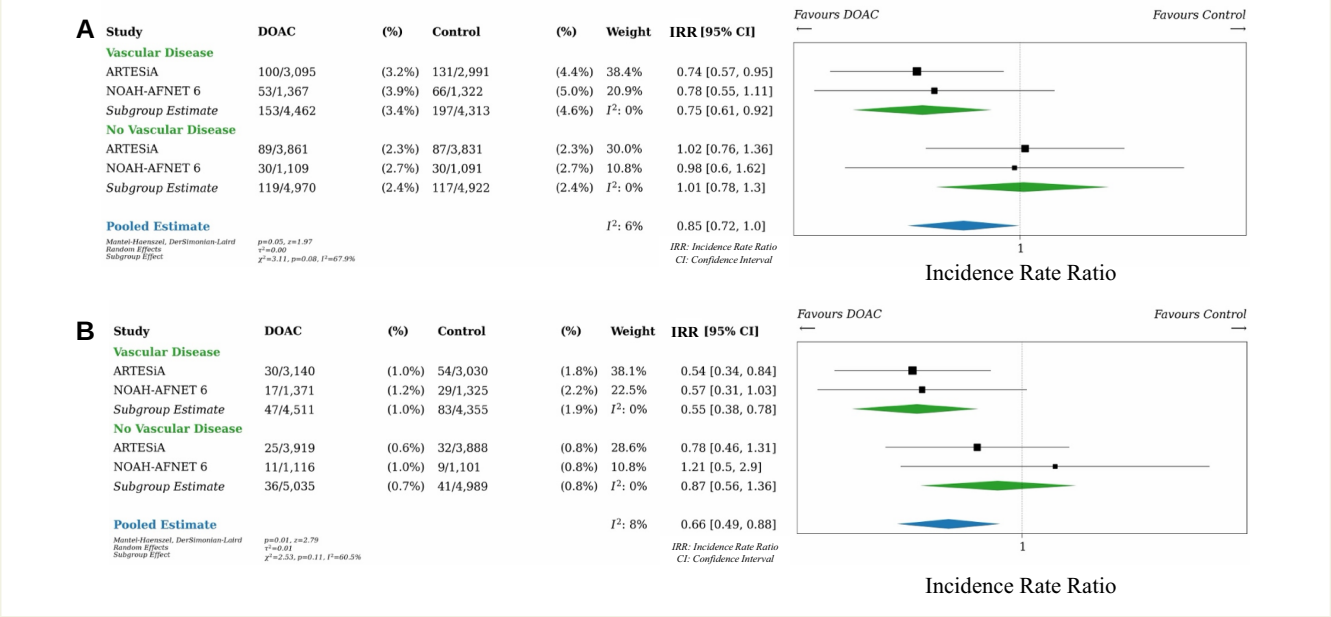


Figure 3 Random-effects meta-analysis for the effects of anticoagulation vs. aspirin/placebo (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status (*A*) for the combined outcome of stroke, systemic arterial embolism, myocardial infarction, pulmonary embolism, and cardiovascular death ($p_{interaction}$ = .08 and *B*) for the combined outcome of stroke and systemic arterial embolism. Incidence rate ratios were combined ($p_{interaction}$ = .11)

the corresponding main effects were added to the model. The outcome results are reported as group-specific event rates in percentage per patient-year and as estimated cause-specific hazard ratios (HRs) 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.

All analyses were conducted with the use of R software version 4.2.3 (R Project for statistical computing) and 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 $I^2 > 50\%$. 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 at 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 by 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's 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 randomized 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 patients/1367 patient-years with anticoagulation (3.9%/patient-year) and in 66 patients/1322 patient-years with placebo (5.0%/patient-year, HR 0.78, 95% CI 0.54–1.12, *Figure 2* and *Table 2*). The primary outcome occurred less frequently in patients without vascular disease and at an equal incidence rate in both randomized treatments [anticoagulation 30 patients/1109 patient-years (2.7%/patient-year), placebo 30 patients/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 ($p_{interaction}$ = .41).

In the 1841 patients with vascular disease enrolled in ARTESiA, there were 100 patients with event/3095 patient-years with anticoagulation (3.2%/patient-year) and 131 patients with event/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

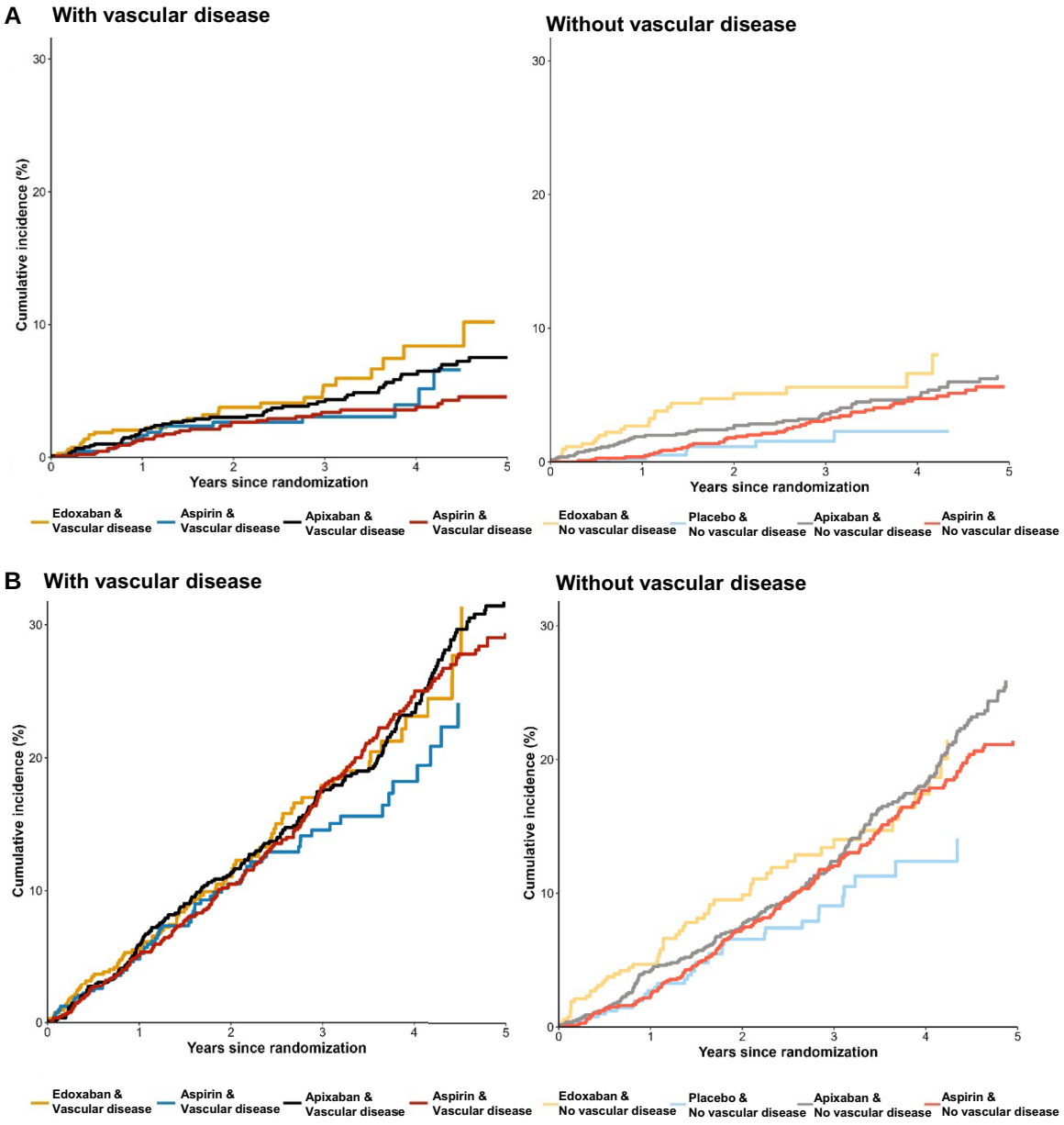


Figure 4 Cumulative incidence of the safety outcome major bleeding shown as Aalen–Johansen cumulative incidence curves considering death as a competing event for the effect of anticoagulation vs. aspirin/placebo (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status. Orange and blue curves are 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)

groups [anticoagulation 89 patients with event/3861 patient-years with event (2.3%/patient-year), aspirin 87 patients with event/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 ($p_{interaction} = .11$).

Meta-analysis showed an incidence rate ratio (IRR) in the vascular disease group for stroke/SE/MI/PE/cardiovascular death of 0.75, 95% CI 0.61–0.92, as compared with IRR 1.01, 95% CI 0.78–1.30, in the patients without vascular disease (*Figure 3*, $p_{interaction} = .08$). The results from the trials were consistent (I^2 statistic for heterogeneity = 6%).

Stroke or systemic arterial embolism

In NOAH-AFNET 6, stroke or systemic arterial embolism occured in 17 patients/1371 patient-years in patients with vascular disease randomized to anticoagulation (1.2%/patient-year) and 29 patients/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,

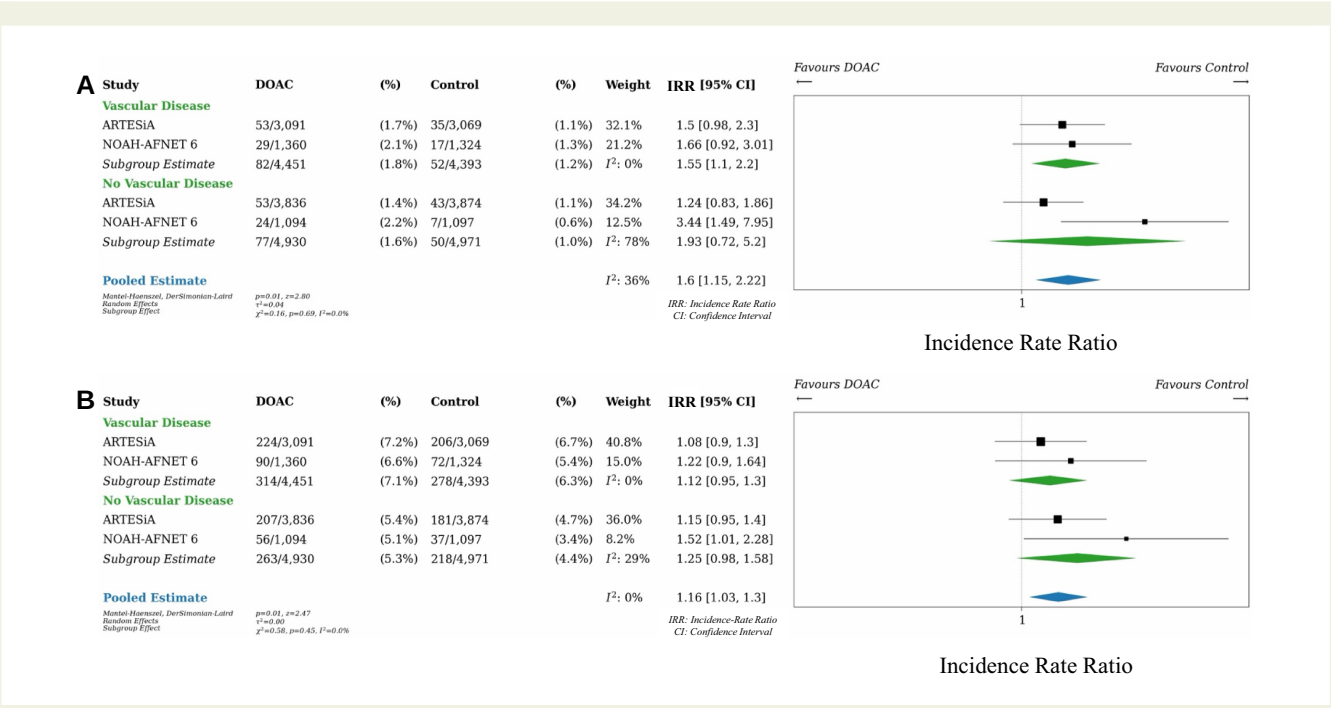


Figure 5 Random-effects meta-analysis for the effects of anticoagulation vs. aspirin/placebo (NOAH-AFNET 6) or aspirin (ARTESiA) by vascular disease status (*A*) for the safety outcome of major bleeding and (*B*) for the combined safety outcome of major bleeding and death. Incidence rate ratios were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

the outcome of stroke/SE occurred in 11 patients/1116 patient-years with anticoagulation (1.0%/patient-year) and in 9 patients/1101 patient-years without anticoagulation (0.8%/patient-year, HR 1.20, 95% CI 0.50–2.89, $p_{interaction} = .17$).

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 patients/916 patient-years in patients 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 patients/1090 patient-years randomized to anticoagulation (0.6%/patient-year) and in 32 patients/1081 patient-years randomized to aspirin (0.8%/patient-year, HR 0.78, 95% CI 0.46–1.31), $p_{interaction} = .29$).

In the meta-analysis of stroke/SE, the IRR in patients with vascular disease was 0.55, 95% CI 0.38–0.78; IRR in patients without vascular disease was 0.87, 95% CI 0.56–1.36; $p_{interaction} = .11$ (*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 patients with vascular disease, major bleeding occurred at 2.13% events/patient-year with edoxaban and 1.28%/patient-year with aspirin and 1.71%/patient-year with apixaban vs. 1.14%/patient-year with aspirin (*Table 2*). In patients without vascular disease, major bleeding occurred at 2.19%/patient-year with anticoagulation vs. 0.64%/patient-year with placebo in NOAH-AFNET 6, and in 1.38%/patient-year with apixaban, and in 1.11%/patient-year with 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; $p_{interaction} = .16$) compared to placebo. 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 was 1.25 (95% CI 0.83–1.86) in patients without vascular disease ($p_{interaction} = .53$).

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, $p_{interaction} = .40$, *Figure 4B* and *Table 2*). The increase in major bleeding appeared more pronounced in patients without vascular disease (where the comparator was placebo). There were 56 patients with major bleeding or death/1094 patient-years with edoxaban (5.1%/patient-year) and 37 patients/1097 patient-years with placebo (3.4%/patient-year, HR 1.54, 95% CI 1.02–2.34).

In ARTESiA, there were 224 patients with major bleeding or death/3091 patient-years with apixaban (7.25%/patient-year) and 206 patients/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 patients with event/3836 patient-years of the safety outcome with apixaban (5.4%/patient-year) and 181 patients/3874 patient-years on aspirin (4.7%/patient-year, HR 1.15, 95% CI 0.95–1.41, $p_{interaction} = .63$).

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 was 1.25, 95% CI 0.98–1.58 (*Figure 5*).

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

Endpoint	Vascular disease	NOAH-AFNET 6				
		Edoxaban	Placebo	Edoxaban vs. Placebo		
		Events/PY (incidence per PY %)	Events/PY (incidence per PY %)	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)	.69	.24
	Yes	16/1374 (1.16)	25/1329 (1.88)	0.61 (0.33–1.15)	.13	
Ischaemic stroke	No	9/1118 (0.81)	8/1103 (0.73)			
	Yes	13/1375 (0.95)	17/1334 (1.27)			
Haemorrhagic stroke	No	2/1120 (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	0/1122 (0.00)	0/1110 (0.00)			
	Yes	1/1390 (0.07)	4/1338 (0.30)			
Myocardial infarction	No	2/1120 (0.18)	6/1100 (0.55)			
	Yes	8/1389 (0.58)	9/1336 (0.67)			
Pulmonary embolism	No	3/1115 (0.27)	4/1104 (0.36)			
	Yes	0/1394 (0.00)	5/1341 (0.37)			
Cardiovascular death	No	19/1122 (1.69)	18/1110 (1.62)	1.07 (0.56–2.04)	.84	.61
	Yes	33/1394 (2.37)	37/1342 (2.76)	0.86 (0.54–1.38)	.53	
All-cause death	No	39/1122 (3.48)	31/1110 (2.79)	1.26 (0.79–2.02)	.34	.79
	Yes	69/1394 (4.95)	58/1342 (4.32)	1.15 (0.81–1.63)	.43	

Endpoint	Vascular disease	ARTESiA				
		Apixaban	Aspirin	Apixaban vs. aspirin		
		Events/PY (incidence per PY %)	Events/PY (incidence per PY %)	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)	.35	.34
	Yes	30/3140 (0.96)	52/3032 (1.72)	0.56 (0.36–0.87)	.011	
Ischaemic stroke	No	18/3923 (0.46)	27/3893 (0.69)	0.59 (0.37–0.96)	.033	.77
	Yes	27/3140 (0.86)	44/3035 (1.45)	0.67 (0.37–1.21)	.18	
Haemorrhagic stroke	No	7/3960 (0.18)	6/3942 (0.15)	1.17 (0.39–3.48)	.78	.24
	Yes	3/3194 (0.09)	7/3117 (0.22)	0.41 (0.11–1.60)	.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)	.49	.175
	Yes	18/3150 (0.57)	26/3084 (0.84)	0.68 (0.37–1.24)	.20	

Continued

Table 3 *Continued*

Endpoint	Vascular disease	ARTESiA				
		Apixaban	Aspirin	Apixaban vs. aspirin		
		Events/PY (incidence per PY %)	Events/PY (incidence per PY %)	Hazard ratio (95% CI)	*P* value	$P_{interaction}$
Pulmonary embolism	No	6/3957 (0.15)	11/3921 (0.28)	0.54 (0.20–1.46)	.23	.48
	Yes	9/3190 (0.28)	10/3114 (0.32)	0.88 (0.36–2.16)	.77	
Cardiovascular death	No	45/3964 (1.14)	41/3947 (1.04)	1.09 (0.71–1.67)	.685	.42
	Yes	60/3195 (1.88)	67/3124 (2.14)	0.87 (0.62–1.23)	.44	
All-cause death	No	171/3964 (4.31)	153/3947 (3.88)	1.11 (0.89–1.38)	.34	
	Yes	191/3195 (5.98)	188/3124 (6.02)	0.99 (0.81–1.21)	.92	

CI, confidence interval; PY, patient-years.

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 deviations from the main analyses 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 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 thromboembolic events and of major bleeding. In this subgroup, anticoagulation therapy may reduce thromboembolic events with a greater magnitude than in patients without vascular disease, though without formal statistical interaction ($p_{interaction}$ in meta-analysis .08). In patients without vascular disease, the effect of anticoagulation on thromboembolic 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 (*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 analyses is desirable.

Differences in clinical characteristics in patients with device-detected atrial fibrillation by vascular disease status

The main feature differentiating patients with DDAF and an indication for aspirin compared with 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 thromboembolic events without anticoagulation in patients with DDAF and vascular disease compared with patients without vascular disease (*Figure 2* and *Table 2*). Similarly, a higher thromboembolic event rate was observed in secondary analyses of ARTESiA and NOAH-AFNET 6 by CHA_2DS_2-VASc 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 female sex, hypertension, diabetes, and heart failure. These patients were assigned to the no vascular disease group in this analysis. The present findings can help to select the best antithrombotic therapy in patients with DDAF.

Device-detected atrial fibrillation in the context of electrocardiogram-diagnosed atrial fibrillation and no atrial fibrillation

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] Direct oral anticoagulants 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 not be needed, patients without vascular disease. The signal was consistent using different outcome definitions for efficacy and safety (*Figure 2* and *Figure 3*).

Thromboembolic event rates in patients with device-detected atrial fibrillation with and without vascular disease and effect of anticoagulation

Anticoagulation with edoxaban or apixaban reduced thromboembolic 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 thromboembolic event (stroke or SE)

without anticoagulation was 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 thromboembolic events in patients with DDAF without vascular disease, and anticoagulation did not reduce the rate of thromboembolic 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 without anticoagulation in both trials. 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-years in NOAH-AFNET 6 and of 1.8%/patient-years in ARTESiA. Vascular disease patients appear to be a group in whom anticoagulation can reduce thromboembolic events with an acceptable safety profile. These findings are not supported by formal statistical tests for interaction but can help support shared decision-making on anticoagulation in patients with DDAF as suggested by a recent expert consensus paper.[24]

Bleeding events in patients with device-detected atrial fibrillation 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-years).[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 sub-analyses, 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 (see Supplementary Data). A small proportion of patients in NOAH-AFNET 6 received aspirin outside the study definition of aspirin indication (1.2%) in the no vascular disease. In ARTESiA, some patients received non-prescribed combination therapy of aspirin and study medication. Such a treatment is not recommended for routine use. It may have diluted the results of the 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 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 thromboembolic 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.

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.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

R.B.S.: Lecture fees and advisory board fees from BMS/Pfizer and Bayer outside this work. J.B.-M.: Nothing to report. N.B.: Speaker fees from Abbott and Medtronic and a grant from Biotronik, not related to this submitted work. M.A.: Nothing to report. D.A.: Speaker fees from Amgen, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, MSD, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Philips, Roche Diagnostics, Sanofi, Takeda, and Vifor; institutional grant support from BMS/Pfizer, Medtronic, Bayer, and Roche Diagnostics. A.P.B.: Lecture fees from Bristol Myers Squibb and AstraZeneca; participation in an educational programme supported by Boston Scientific ('Fellowship Herzrhythmus'). E.B.: Nothing to report. D.H.B.: Nothing to report. C.B.-L.: Honoraria from Medtronic, Cathprint, Boston Scientific, Johnson & Johnson, Abbott, Sanofi, Philips, Bayer, Organon, and Milestone. In addition, C.B.-L. is a member of DSMB/advisory board for Boston Scientific, Abbott, Milestone, and Medtronic. A.J.C.: 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, A.J.C. is a member of DSMB/advisory board for Anthos, AFNET, Johnson & Johnson (all personal payment) and Attune, British Heart Foundation, and Charité (not paid). A.J.C. has the following leadership or fiduciary role in other board, society, committee, or advocacy group: Drug Safety Research Unit, Arrhythmia Alliance, Atrial Fibrillation Association, and European Society of Cardiology. G.C.: Nothing to report. W.D.: 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); and consulting fee from Reata Pharmaceuticals/Biogen. J.W.E.: Consulting fees, travel support, and lecture fees from ZOLL Medical Corporation; travel grants from Bayer Vital, Boehringer Ingelheim, St. Jude Medical/Abbott, and Novartis; and lecture fees from Servier, Pfizer, and Bayer, outside the submitted work. A.F.: Research support for statistical analysis from EU Horizon 2020, Biotronik, and Adrenomed AG (research support is not paid personally but to the institution IMBE). A.G.: Consulting fees from Daiichi Sankyo and honoraria from Daiichi Sankyo, Bayer, Bristol Myers Squibb, Boehringer, Boston Scientific, Pfizer, and Medtronic. C.B.G.: Research grants from Bayer and Boehringer Ingelheim and consultant fees from Anthos, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific Corporation, Bristol, Myers Squibb, Cadrenal, Daiichi Sankyo Company, Janssen Global Services, LLC, Merck, Pfizer Inc., and Tenac.io. E.S.: Nothing to report. V.K.: Research grants from Boston Scientific, ZOLL, NIH, and Spire Inc.; speaker fees from Medtronic, Abbott, and Biotronik; consultant fees from Biotronik. S.F.L.: Nothing to report. C.L.: Research support from Swedish Heart Lung Foundation, Swedish Royal Society of Science, and Stockholm County Council; consulting fees from AstraZeneca and Roche Diagnostics; speaker honoraria from Novartis, Astra, Bayer, Vifor Pharma, Medtronic, and Impulse Dynamics; and advisory boards for AstraZeneca. G.Y.H.L.: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Anthos. No fees are received personally. G.Y.H.L. 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. R.D.L.: Research grants from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Medtronic, Novo Nordisk, Pfizer, and Sanofi US Services Inc.; consultant to Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo Company, GlaxoSmithKline, Medtronic, Merck, Novo Nordisk, Pfizer, Portola Pharmaceuticals, and Sanofi US Services Inc. P.M.: Nothing to report. E.M.: Consulting fees and honoraria from Medtronic, Boston Scientific, ZOLL, and Abbott; and research grants from Abbott, Biotronik, Boston Scientific, Medtronic, MicroPort, and ZOLL. W.F.M.: Consultant to Servier Pharmaceuticals LLC. L.R.: Research grants from Bayer Inc., Heart and Stroke Foundation, Canadian Institutes of Health Research (CIHR), and FRQS (Fonds de Recherche Quebec-Sante). U.S.: Consulting fees from Roche, YourRhythmics BV, and University Lugano and honoraria from Johnson & Johnson. In addition, U.S. receives payments from Roche, YourRhythmics BV, and EP Solutions for DSMB or advisory board participation and holds stock/stock options from YourRhythmics BV. S.S.: 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. T.T.: Consulting fees from Medtronic and Boston Scientific. P.V.: Consulting fees from Hygiea Hospital Group and European Society of Cardiology. A.Z.: Honoraria for lectures from Boston Scientific. A.Z. received research support for statistical analysis from EU Horizon 2020, Biotronik, and Adrenomed AG (paid to the institution). J.H.: Research grants from Boston Scientific Corporation, Bristol Myers Squibb, Medtronic, and Pfizer; consultant fees for Bayer, Boston Scientific Corporation, Medtronic, Novartis, Servier, and Affaires Medicales; and expert witness for Bayer. P.K.: Research support for basic, translational, and clinical research projects from the European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre 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 5 years. P.K. is listed as inventor on two issued patents held by University of Hamburg (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

NOAH-AFNET 6 was partially funded by BMBF (German Ministry of Education and Research, Berlin, Germany) through the DZHK (German Centre 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 P.K. and U.S. and AFNET; AFFECT EU (grant agreement 847770) to P.K.; MAESTRIA (grant agreement 965286) to A.G., P.K., U.S. 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. R.B.S. 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 Centre for Cardiovascular Research (DZHK e.V.) (81Z1710103 and 81Z0710114); German Ministry of Research and Education (BMBF 01ZX1408A) and ERACoSysMed3 (031L0239); and Wolfgang Seefried project funding German Heart Foundation.

Ethical Approval

Both trials were approved at all participating institutions. All patients gave written informed consent prior to participation.

Pre-registered Clinical Trial Number

Both trials are registered (NOAH-AFNET 6 NCT02618577; ARTESiA NCT01938248).

References

1. Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, de Graaf JJ, *et al.* Subclinical atrial fibrillation in older patients. *Circulation* 2017;**136**:1276–83. https://doi.org/10.1161/CIRCULATIONAHA.117.028845
2. Toennis T, Bertaglia E, Brandes A, Dichtl W, Fluschnik N, de Groot JR, *et al.* The influence of atrial high-rate episodes on stroke and cardiovascular death: an update. *Europace* 2023;**25**:euad166. https://doi.org/10.1093/europace/euad166
3. Kirchhof P, Schotten U, Zapf A. Anticoagulation with edoxaban in patients with atrial high-rate episodes. Reply. *N Engl J Med* 2023;**389**:2302–3. https://doi.org/10.1056/NEJMc2312837
4. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–62. https://doi.org/10.1016/S0140-6736(13)62343-0
5. Kirchhof P, Toennis T, Goette A, Camm AJ, Diener HC, Becher N, *et al.* Anticoagulation with edoxaban in patients with atrial high-rate episodes. *N Engl J Med* 2023;**389**:1167–79. https://doi.org/10.1056/NEJMoa2303062
6. Healey JS, Lopes RD, Granger CB, Alings M, Rivard L, McIntyre WF, *et al.* Apixaban for stroke prevention in subclinical atrial fibrillation. *N Engl J Med* 2024;**390**:107–17. https://doi.org/10.1056/NEJMoa2310234
7. McIntyre WF, Benz AP, Becher N, Healey JS, Granger CB, Rivard L, *et al.* Direct oral anticoagulants for stroke prevention in patients with device-detected atrial fibrillation: a study-level meta-analysis of the NOAH-AFNET 6 and ARTESiA trials. *Circulation* 2024;**149**:981–8. https://doi.org/10.1161/CIRCULATIONAHA.123.067512
8. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, *et al.* Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319–30. https://doi.org/10.1056/NEJMoa1709118
9. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–60. https://doi.org/10.1016/S0140-6736(09)60503-1
10. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, *et al.* Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018;**379**:1509–18. https://doi.org/10.1056/NEJMoa1805819
11. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, *et al.* Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9. https://doi.org/10.1056/NEJMoa1105575
12. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x
13. Lopes RD, Granger CB, Wojdyla DM, McIntyre WF, Alings M, Mani T, *et al.* Apixaban versus aspirin according to CHA2DS2VASc score in subclinical atrial fibrillation: insights from ARTESiA. *J Am Coll Cardiol* 2024;**84**:354–64. https://doi.org/10.1016/j.jacc.2024.05.002
14. Lip GYH, Nikorowitsch J, Sehner S, Becher N, Bertaglia E, Blomstrom-Lundqvist C, *et al.* Oral anticoagulation in device-detected atrial fibrillation: effects of age, sex, cardiovascular comorbidities, and kidney function on outcomes in the NOAH-AFNET 6 trial. *Eur Heart J* 2024;**45**:1733–7. https://doi.org/10.1093/eurheartj/ehae225
15. Diener H-C, Becher N, Sehner S, Toennis T, Bertaglia E, Blomstrom-Lundquist C, *et al.* Anticoagulation in patients with device-detected atrial fibrillation with and without a prior stroke or transient ischemic attack: the NOAH-AFNET 6 trial. *J Am Heart Assoc* 2024:e036429. https://doi.org/10.1161/JAHA.124.036429
16. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–17. https://doi.org/10.1056/NEJMoa1007432
17. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, *et al.* Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–78. https://doi.org/10.1056/NEJMoa0901301
18. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern Med* 2007;**147**:590–2. https://doi.org/10.7326/0003-4819-147-8-200710160-00018
19. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, *et al.* Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906–17. https://doi.org/10.1056/NEJMoa1813959
20. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, *et al.* Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–201. https://doi.org/10.1056/NEJMoa1802686
21. Becher N, Metzner A, Toennis T, Kirchhof P, Schnabel RB. Atrial fibrillation burden: a new outcome predictor and therapeutic target. *Eur Heart J* 2024;**45**:2824–38. https://doi.org/10.1093/eurheartj/ehae373
22. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498. https://doi.org/10.1093/eurheartj/ehaa612
23. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, *et al.* 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;**149**:e1–156. https://doi.org/10.1161/CIR.0000000000001193
24. Linz D, Andrade JG, Arbelo E, Boriani G, Breithardt G, Camm AJ, *et al.* Longer and better lives for patients with atrial fibrillation: the 9th AFNET/EHRA consensus conference. *Europace* 2024;**26**:euae070. https://doi.org/10.1093/europace/euae070
25. ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, *et al.* Effects of aspirin for primary prevention in persons with diabetes Mellitus. *N Engl J Med* 2018;**379**:1529–39. https://doi.org/10.1056/NEJMoa1804988
26. Muscente F, De Caterina R. The new in anticoagulation: factor XI inhibitors. *Eur Heart J Suppl* 2023;**25**:B65–8. https://doi.org/10.1093/eurheartjsupp/suad070
27. Piccini JP, Patel MR, Steffel J, Ferdinand K, Van Gelder IC, Russo AM, *et al.*; OCEANIC-AF Steering Committee and Investigators. Asundexian versus Apixaban in Patients with Atrial Fibrillation. *N Engl J Med* 2024. https://doi.org/10.1056/NEJMoa2407105. Epub ahead of print. PMID: 39225267.