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**RAPID COMMUNICATIONS**
*Arrhythmias*

# Oral anticoagulation in device-detected atrial fibrillation: effects of age, sex, cardiovascular comorbidities, and kidney function on outcomes in the NOAH-AFNET 6 trial

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# Introduction

Implanted pacemakers, defibrillators, and loop recorders detect short and rare episodes of device-detected atrial fibrillation [DDAF, previously also called atrial high-rate episodes or subclinical atrial fibrillation (AF)] in ~30% of patients. Device-detected atrial fibrillation rarely has therapeutic consequences in patients with ECG-documented AF. Device-detected atrial fibrillation without ECG-documented AF can lead to consideration of oral anticoagulation in clinical practice, especially in older patients with multiple stroke risk factors and/or very long DDAF episodes, largely based on observational data.[1] Two recent controlled trials, NOAH-AFNET 6[2] and ARTESiA,[3] observed a low rate of ischaemic stroke without anticoagulation (1.1%–1.2%/patient-year) in patients with DDAF and stroke risk factors, including in patients with very long DDAF episodes in NOAH-AFNET 6.[4] Current guidelines leave the decision to anticoagulate to clinical judgement, balancing the expected stroke risk, typically estimated by using stroke risk scores developed in patients with ECG-documented AF, and the stroke risk reduction induced by anticoagulation, with the increase in bleeding associated with anticoagulation therapy.[1]

# Methods

This is a pre-specified subgroup analysis of the NOAH-AFNET 6 trial data set comparing outcomes and the effect of oral anticoagulation in patients with DDAF without ECG-documented AF and a $CHA_2DS_2$-VASc score > 4 to those with fewer $CHA_2DS_2$-VASc factors. Sensitivity analyses were calculated based on a $CHA_2DS_2$-VASc score > 3 agnostic to sex. The analysis is enriched with *post hoc* regression analyses of the individual $CHA_2DS_2$-VASc components enhanced by kidney function and DDAF episodes ≥ 24 h and their association with thrombo-embolic and bleeding events. NOAH-AFNET 6 trial randomized and treated 2534 patients (78 years old, median $CHA_2DS_2$-VASc score = 4) to anticoagulation with edoxaban or no anticoagulation. The placebo contained aspirin in 682/1264 patients (54.8%, double-dummy design). All patients were switched from study medication to open-label anticoagulation upon ECG documentation of AF and censored at that point in time. All patients were followed up until the end of the trial for the primary outcome of stroke, systemic embolism, or cardiovascular death and for the safety outcome of major bleeding or all-cause death. The pre-specified outcome results are reported as subgroup-specific event rates per 100 patient-years and as adjusted estimated cause-specific hazard ratios (HRs) with a two-sided 95% confidence interval (CI) and corresponding *P*-value. The *post hoc* treatment-specific effects of the $CHA_2DS_2$-VASc score on the outcomes are presented using LOWESS (locally weighted scatterplot smoothing) with bandwidths of 0.8. To analyse the $CHA_2DS_2$-VASc components, a multivariable model of all components was estimated, which was extended by DDAF episode durations ≥ 24 h and estimated glomerular filtration rate (eGFR). Calculations were done in Stata, version 18.0 (StataCorp, College Station, TX, USA). All analyses are exploratory reflecting the limited power of subgroup analyses, and thus no adjustment was made for multiple testing.

# Results

Patient disposition to the randomized treatments was similar between the high and low $CHA_2DS_2$-VASc score groups [$CHA_2DS_2$-VASc score ≤ 4: 77 years old, mean $CHA_2DS_2$-VASc score 3.3 (range 2–4); $CHA_2DS_2$-VASc score > 4: 79 years old, mean $CHA_2DS_2$-VASc score 5.6 (range 5–9)]. In the subgroup of patients with a $CHA_2DS_2$-VASc score > 4, stroke, systemic embolism, or cardiovascular death occurred in 33/361 patients (4.6/100 patient-years) with anticoagulation and in 37/380 patients (5.3/100 patient-years) without anticoagulation [HR 0.88 (95% CI 0.55–1.41)]. The rate of stroke was low with and without anticoagulation (1.2–1.3/100 patient-years, *Figure 1A*). In the same subgroup, 62/361 patients (8.7/100 patient-years) with anticoagulation and 39/380 patients (5.6/100 patient-years) without anticoagulation experienced death or major bleeding [HR 1.59 (1.06–2.39)].

In the total population, efficacy and safety outcome rates increased with increasing $CHA_2DS_2$-VASc scores (*Figure 1B*) without treatment interaction (linear $CHA_2DS_2$-VASc: *P*-interaction = .57 for efficacy, *P*-interaction = .34 for safety, *Figure 1B*). Sensitivity analyses were consistent. Older age [HR 1.73 (1.35–2.22) per 10-year increase], diabetes [HR 1.66 (1.19–2.30)], and eGFR [HR 1.16 (1.06–1.27) per 10 mL/min/1.73 $m^2$ decrease] independently predicted the primary outcome. Anticoagulation [HR 1.31 (1.02–1.69)], age [HR 1.92 (1.56–2.36) per 10-year increase], heart failure [HR 1.53 (1.16–2.02)], diabetes [HR 1.67 (1.26–2.19)], prior stroke [HR 1.50 (1.05–2.13)], and eGFR [HR 1.12 (1.04–1.21) per 10 mL/min/1.73 $m^2$ decrease] predicted the safety outcome (*Figure 1C*).

# Discussion

This pre-specified subanalysis of NOAH-AFNET 6 does not suggest that anticoagulation is more effective in patients with DDAF and a high $CHA_2DS_2$-VASc score > 4 than in patients with lower $CHA_2DS_2$-VASc scores 2–4. Larger data sets may be able to detect subtle effects. Stroke rate was low in patients with a high $CHA_2DS_2$-VASc score > 4 without oral anticoagulation (1.3%/patient-year). Anticoagulation increased major bleeding or death in patients with a high $CHA_2DS_2$-VASc score. Older age, diabetes, and reduced kidney function were major predictors of thrombo-embolic and bleeding events in this large trial data set of patients with DDAF. In addition to these parameters, prior stroke and heart failure predicted the composite of bleeding or death. The analyses are hypothesis-generating due to limited power in each subgroup. Combining the data sets of NOAH-AFNET 6 and ARTESiA will refine the detection of subtle treatment effects. There are several potential reasons for the low rate of stroke and the weak effect of anticoagulation observed here and in meta-analyses:[5] better treatment of concomitant conditions compared to earlier observational data sets will reduce stroke, including more effective therapies for diabetes and heart failure and effective treatment of hypertension. Crucially, careful ECG assessment for AF every 6 months with a switch to open-label anticoagulation following current guidelines and the low arrhythmia burden in patients with DDAF[6,7] will have contributed to the low rate of stroke in patients with DDAF and a high comorbidity burden observed here. These findings extend the lower stroke rate in paroxysmal AF compared to non-paroxysmal AF[8] and the outcome-reducing effect of early rhythm control (1/3 fewer strokes numerically)[9] that is mediated by attaining sinus rhythm.[10]

Taking into account the limited statistical power of any subanalysis of a large controlled trial, our results highlight the ambiguous effects of anticoagulation in patients with DDAF, including in patients with multiple comorbidities and with long DDAF episodes.[4] The findings call for new methods to identify patients with DDAF at high risk of stroke who might benefit from anticoagulation.

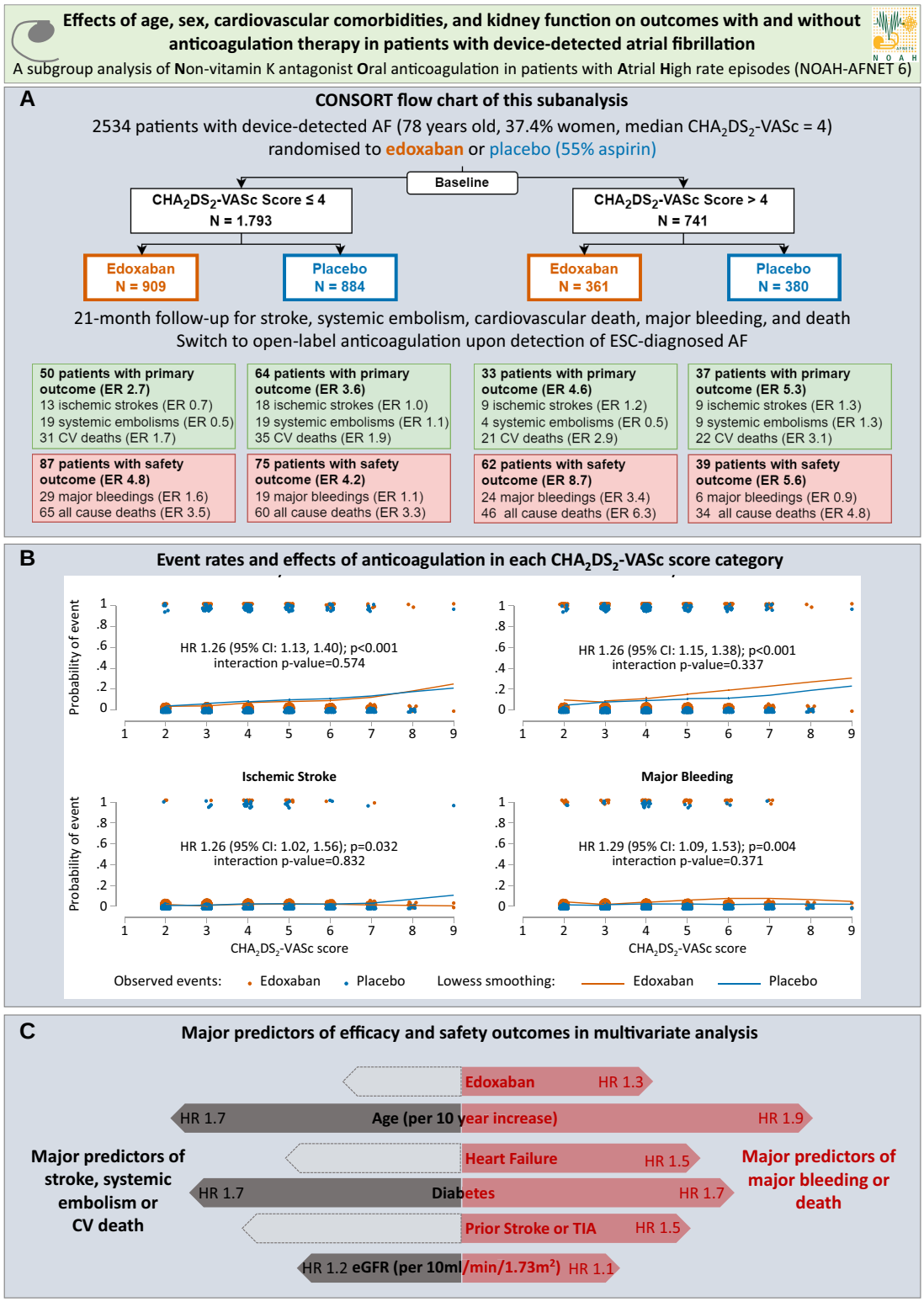


**Figure 1** (*A*) CONSORT flow chart of pre-specified secondary analysis of the NOAH-AFNET 6 trial. Displayed are the analysis population, the number of patients experiencing a primary or safety outcome, and the event rate for each outcome in each group. (*B*) Stroke, systemic embolism, or cardiovascular death (primary outcome), major bleeding or death (safety outcome), ischaemic stroke and major bleeding event rate estimates per $CHA_2DS_2$-VASc score and treatment group (edoxaban orange on the left, placebo blue on the right). The LOWESS (locally weighted scatterplot smoothing) curves show the dependence of the probability of an event on the $CHA_2DS_2$-VASc score. Each dot represents a patient. Patients with events are shown at the top and patients without events are shown at the bottom. (*C*) Forest plots of the major predictors of efficacy (left) and safety (right) outcomes in the entire study population ($n = 2534$). Grey shaded arrows indicate efficacy predictors with *P*-values > .05. Orange curves show LOWESS-estimated event rates with edoxaban, blue curves show LOWESS-estimated event rates without anticoagulation. AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ER, event rate per 100 patient-years follow-up; ESC, European Society of Cardiology; HR, hazard ratio; TIA, transient ischaemic attack

# Declarations

## Disclosure of Interest

G.Y.H.L.: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, 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. S.S. receives 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 receives honoraria for lectures from Boston Scientific. N.B. received speaker fees from Abbott and Medtronic and a grant from Biotronik, not related to this submitted work. C.B.-L. receives 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. B.M. received funding from Abbott, Astra Zeneca, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, CSL Behring, Daiichi Sankyo, DUKE Clinical Institute, Eli Lilly, Medtronic, Novartis, Terumo, and VIFOR (to institute). A.B. reports lecture honoraria from Boehringer Ingelheim and Bristol-Myers Squibb and research grants from Theravance, the Zealand Region, the Canadian Institutes of Health Research, and the Danish Heart Foundation outside the submitted work. M.C. receives personal fees from Astellas, Aparito, CIS Oncology, Halfloop, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK, Pfizer, Vertex, and the Patient-Centered Outcomes Research Institute outside the submitted work. In addition, a family member owns shares in GSK. M.C. also receives honoraria for lectures and reviews from University of Maastricht, South-Eastern Norway Regional Health Authority, Cochrane Portugal, and Singapore National Medical Research Council. M.C. is a member of the PROTEUS Consortium and receives consultancy fees from Genentech and PCORI. A.J.C. receives 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 and 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.-A.D. receives consulting fees from Sanofi and honoraria from Boehringer—Ingelheim, Bayer, Novartis, and Berlin Chemie. H.C.D. receives consulting fees from Pfizer, Böhringer Ingelheim, and Abbott. In addition, H.C.D. is a member of DSMB/advisory board for ELAN Study and CLOSURE-AF (no payment for both studies) and is author for WebMD. A.F. receives 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. receives consulting fees from Daiichi Sankyo and honoraria from Daiichi Sankyo, Bayer, Bristol_Meyers Squibb, Boehringer, Boston Scientific, Pfizer, and Medtronic. J.R.d.G. receives consulting fees from AtriaN Medical and honoraria from Atricure, Bayer, Berlin Chemie, Daiichi Sankyo, Menarini, Novartis, and Servier. In addition, he is chair of the DSMB for the Praetorian study (NEJM 2021 Feb 18;384(7):678–679. doi: 10.1056/NEJMc2034917) and holds stocks on personal account for pharming. J.R.d.G. receives funding from Atricure, Bayer, Boston Scientific, Daiichi Sankyo, Johnson & Johnson, and Medtronic (to institution). M.C. is director of the Birmingham Health Partners Centre for Regulatory Science and Innovation, director of the Centre for Patient Reported Outcomes Research, and is an NIHR senior investigator. M.C. receives funding from the NIHR, UK Research and Innovation (UKRI), NIHR Birmingham Biomedical Research Centre, NIHR Surgical Reconstruction and Microbiology Research Centre, NIHR, Applied Research Collaboration West Midlands, UK SPINE, Research England, European Regional Development Fund DEMAND Hub at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, and the NIHR Birmingham-Oxford Blood and Transplant Research Unit in Precision Transplant and Cellular Therapeutics; funding from Health Data Research UK, Innovate UK (part of UKRI), Macmillan Cancer Support, UCB Pharma, Janssen, GSK, Gilead Sciences, European Commission, European Federation of Pharmaceutical Industries and Associations, and the Brain Tumour Charity. H.C.D. received research support from Böhringer Ingelheim and Alexion (both to institution). 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A.-K.O. receives 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.S. receives consulting fees from Biosense, Webster, and Medtronic and honoraria from Biotronik, Microport, and Pfizer. In addition, A.S. is Scientific Program Committee Co-Chair for EHRA. R.B.S. has received lecture fees and advisory board fees from BMS/Pfizer and Bayer outside this work. U.S. receives 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 Your Rhythmics BV. T.T. receives consulting fees from Medtronic and Boston Scientific. P.V. receives consulting fees from Hygiea Hospital Group and European Society of Cardiology. A.Z. receives 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). P.K. received 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. P.K. has received honoraria from several pharmaceutical and medical device companies in the past, but not in the last three 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). J.N., E.B., V.B., G.C., W.D., A.H., A.L., K.R., D.S., E.S., D.W.: nothing to declare.

## Data Availability

Data will be available by AFNET on reasonable request. Please contact info@kompetenznetzvorhofflimmern.de.

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## Ethical Approval

The sponsor assured that approval of the local IRB/IEC in each country was obtained prior to study start in the respective study site or country in accordance with local requirements. All the patients provided written informed consent before enrolment. The trial was designed and overseen by a steering committee. During the trial, the steering committee was supported by a national coordinators committee. The trial was conducted in accordance with the principles of the Declaration of Helsinki and with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

## Pre-registered Clinical Trial Number

The pre-registered clinical trial numbers for NOAH-AFNET 6 are EudraCT number: 2015-003997-33. NCT number: NCT02618577, and ISRCTN number: ISRCTN17309850.

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