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FASTTRACK CLINICAL RESEARCH
Arrhythmias

Anticoagulation with edoxaban in patients with long atrial high-rate episodes ≥24 h

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Abstract

Background and Aims Patients with long atrial high-rate episodes (AHREs) ≥24 h and stroke risk factors are often treated with anticoagulation for stroke prevention. Anticoagulation has never been compared with no anticoagulation in these patients.

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Methods This secondary pre-specified analysis of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High-rate episodes (NOAH-AFNET 6) trial examined interactions between AHRE duration at baseline and anticoagulation with edoxaban compared with placebo in patients with AHRE and stroke risk factors. The primary efficacy outcome was a composite of stroke, systemic embolism, or cardiovascular death. The safety outcome was a composite of major bleeding and death. Key secondary outcomes were components of these outcomes and electrocardiogram (ECG)-diagnosed atrial fibrillation.

Results Median follow-up of 2389 patients with core lab-verified AHRE was 1.8 years. AHRE ≥24 h were present at baseline in 259/2389 patients (11%, 78 ± 7 years old, 28% women, CHA2DS2-VASc 4). Clinical characteristics were not different from patients with shorter AHRE. The primary outcome occurred in 9/132 patients with AHRE ≥24 h (4.3%/patient-year, 2 strokes) treated with anticoagulation and in 14/127 patients treated with placebo (6.9%/patient-year, 2 strokes). Atrial high-rate episode duration did not interact with the efficacy (*P*-interaction = .65) or safety (*P*-interaction = .98) of anticoagulation. Analyses including AHRE as a continuous parameter confirmed this. Patients with AHRE ≥24 h developed more ECG-diagnosed atrial fibrillation (17.0%/patient-year) than patients with shorter AHRE (8.2%/patient-year; *P* < .001).

Conclusions This hypothesis-generating analysis does not find an interaction between AHRE duration and anticoagulation therapy in patients with device-detected AHRE and stroke risk factors. Further research is needed to identify patients with long AHRE at high stroke risk.

Structured Graphical Abstract

Key Question

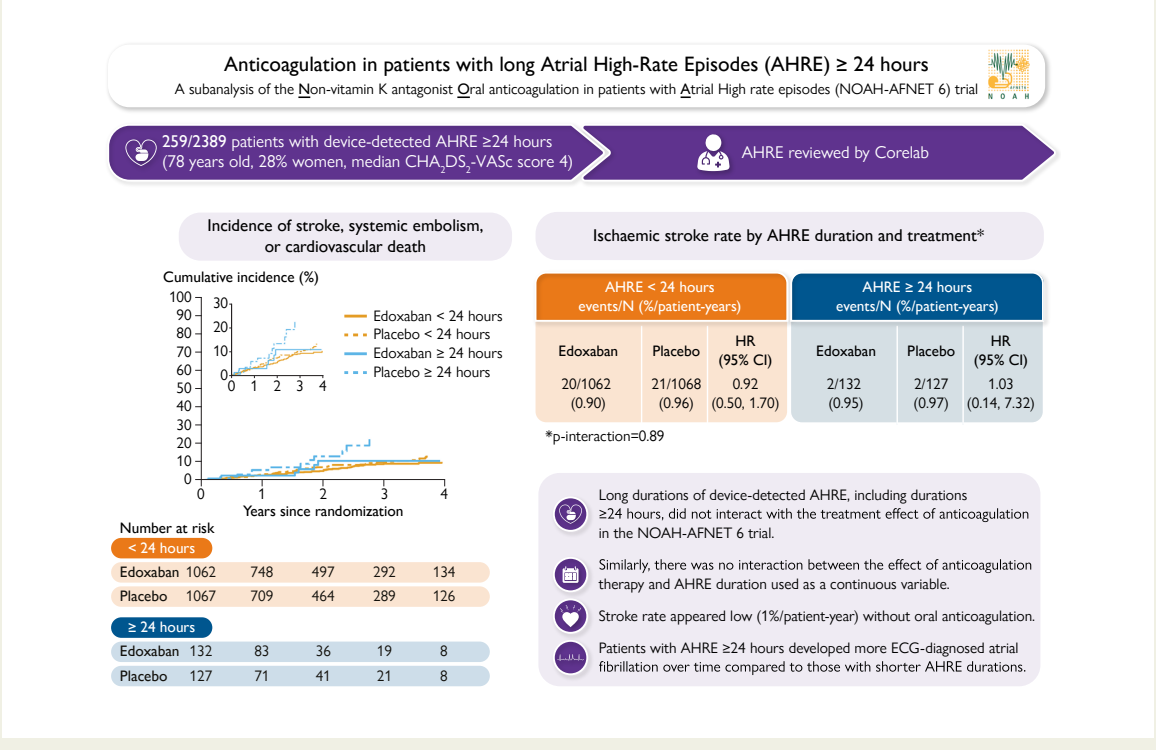
Does the duration of atrial high-rate episodes (AHRE) interact with the efficacy and safety of oral anticoagulation in patients with AHRE and stroke risk factors, especially when episodes are longer than 24 hours?

Key Finding

In the NOAH-AFNET 6 trial baseline AHRE duration did not interact with the efficacy and safety of anticoagulation. Clinical characteristics were not different between patients with AHRE ≥24 hours and those with shorter AHRE. Stroke rate appeared low across AHRE durations (approximately 1%/year).

Take Home Message

Duration of the longest AHRE episode does not have a strong effect on the efficacy and safety of anticoagulation. Better methods to identify patients with AHRE at high risk of stroke are needed.



Anticoagulation with edoxaban in patients with long AHRE ≥24 h. AHRE, atrial high-rate episodes; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio.

Keywords Atrial high-rate episodes • Stroke • Atrial fibrillation • NOAH-AFNET 6

Introduction

Atrial high-rate episodes (AHREs), short atrial arrhythmias lasting a few minutes (5–6 min or more) that are typically asymptomatic and resemble short episodes of atrial fibrillation (AF), are detected in approximately every fifth patient with an implanted pacemaker, defibrillator, or loop recorder.[1] Patients with AHRE, also called sub-clinical AF, have a higher stroke risk than patients without AHRE.[2] Approximately half of the patients with AHRE have electrocardiogram (ECG)-documented AF.[3] The stroke risk associated with AHRE in the absence of ECG-documented AF is lower than the stroke risk associated with ECG-documented AF.[1] A sub-analysis of the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reducing Atrial Pacing (ASSERT) trial and a meta-analysis by Uittenbogaart *et al.*[4] suggest a higher stroke risk associated with AHRE lasting ≥24 h.[5] In clinical practice, data from these relatively small observational studies and the resemblance of long AHREs with AF often result in the use of oral anticoagulation for stroke prevention in patients with AHRE ≥24 h without ECG-documented AF.[6] Randomized data evaluating anticoagulation in these patients were lacking.

Recently, the double-blind, double dummy Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High-rate episodes (NOAH-AFNET 6) trial found that oral anticoagulation with edoxaban does not reduce the composite outcome of stroke, systemic embolism, or cardiovascular death compared with no anticoagulation in elderly patients with AHRE and stroke risk factors.[7] The main effect of anticoagulation therapy was an increase in major bleeding. The low stroke rate observed without oral anticoagulation (~1%/year) in an elderly population with multiple stroke risk factors (mean age 78 years, median CHA_2DS_2-VASc score 4) reduced the power of the trial to detect an effect of anticoagulation on stroke. Central analysis of all AHREs in a core lab[8] enabled a granular sub-analysis of patients with very long AHREs.

Methods

This is a secondary pre-specified analysis of the NOAH-AFNET 6 trial data set.[7] We investigated the effects of AHRE duration at the time of randomization (termed at baseline), split into patients with maximal AHRE duration ≥24 h and patients limited to episodes lasting from 6 min to 23:59 h (termed <24 h). Patients were classified as AHRE ≥24 h when at least one episode was longer than 24 h at baseline. We also split patients by their median longest AHRE duration and investigated the interaction of baseline AHRE duration as a continuous variable. The interaction of these AHRE categories with the efficacy and safety of oral anticoagulation in patients randomized to anticoagulation or placebo was analysed.

Trial design and population

Details of the design of the trial have been reported.[8] NOAH-AFNET 6 was approved by ethics board in all participating countries and institutions. All patients provided written informed consent prior to participation. In brief, 206 sites in 18 European countries randomized 2608 patients with AHRE, but without ECG-documented AF, aged ≥65 years and with at least one additional stroke risk factor to oral anticoagulation with edoxaban in the dose approved for stroke prevention in AF or to no anticoagulation (placebo). Patients randomized to no anticoagulation who had an accepted indication for aspirin received aspirin 100 mg/day with the study medication. Those without an indication for aspirin and all patients randomized to edoxaban took a dummy aspirin tablet. Each patient was seen to hand out study medication every 6 months. These visits included an ECG. Per protocol, all patients were switched from study medication to open-label anticoagulation upon ECG documentation of AF. The primary analysis population consisted of all 2389 patients who were randomized, took at least one dose of study drug, and had core lab-verified information about maximum AHRE duration at baseline (*Figure 1*). All events were centrally adjudicated by an independent event review committee. All patients were followed up for outcomes until the end of the trial.

Review of atrial high-rate episodes

All AHRE reports and recordings were uploaded onto the electronic trial management system. An independent core laboratory based at Maastricht University, The Netherlands, re-analysed all AHREs to verify whether AHRE data uploaded by trial sites fulfilled the inclusion criteria. The following features were reviewed: start of recording, end of recording, date of first AHRE, number of all AHRE, number of adequate AHRE, maximal duration of AHRE, and maximum atrial rate during AHRE (all at baseline). The core laboratory also determined the time of the last AHRE in relation to baseline, performed quality control, and provided feedback to trial sites regarding their uploaded AHRE data if necessary. All patients with adequate AHREs after core lab review were included in this analysis.

Primary and secondary outcomes

The primary efficacy outcome and safety outcome of this analysis are identical to the outcomes in the main trial.[7,8] The primary efficacy outcome was a composite of stroke, systemic embolism, and cardiovascular death. Secondary outcomes included stroke, systemic embolism, a composite of stroke and systemic embolism, and cardiovascular death, and a secondary *post-hoc* outcome consisting of a composite of ischaemic stroke and systemic embolism, excluding pulmonary embolism and myocardial infarction. The primary safety outcome was a composite of major bleeding according to the International Society on Thrombosis and Heamostasis definition and all-cause death.[8]

Statistical analysis

Categorical data are summarized by numbers and percentages. Continuous data are summarized by mean and standard deviation or median with first and third quartiles (inter-quartile range, IQR) as appropriate. The primary analysis population consisted of all randomized patients receiving at least one dose of the study drug, i.e. a modified intention-to-treat population. 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. The primary efficacy outcome and the safety outcome were also analysed for the safety population (all randomized patients), the per-protocol population, and a population who was not censored for AF-onset or unblinding. All Ukrainian patients were censored on 24 February 2022, the day of the Russian invasion. Sensitivity analyses including these patients were conducted.

Baseline characteristics were compared between patients with maximal AHRE duration at baseline <24 h and ≥24 h using χ^2 test for categorical data, *t*-test for non-skewed continuous data, and Mann–Whitney U test for skewed continuous data.

A cause-specific Cox-proportional hazards model using the Breslow method to handle tied failures was conducted, with frailty for centres and the fixed effects random group, the randomization strata indication for acetylsalicylic acid, maximum AHRE duration, and the interaction between the random group and maximum AHRE duration under the assumption of independent censoring. Maximum AHRE duration was included as a continuous variable on a natural logarithmic scale. In a further model, maximum AHRE duration was considered as a categorical variable (categories <24 h and ≥24 h and categories by median). The outcome

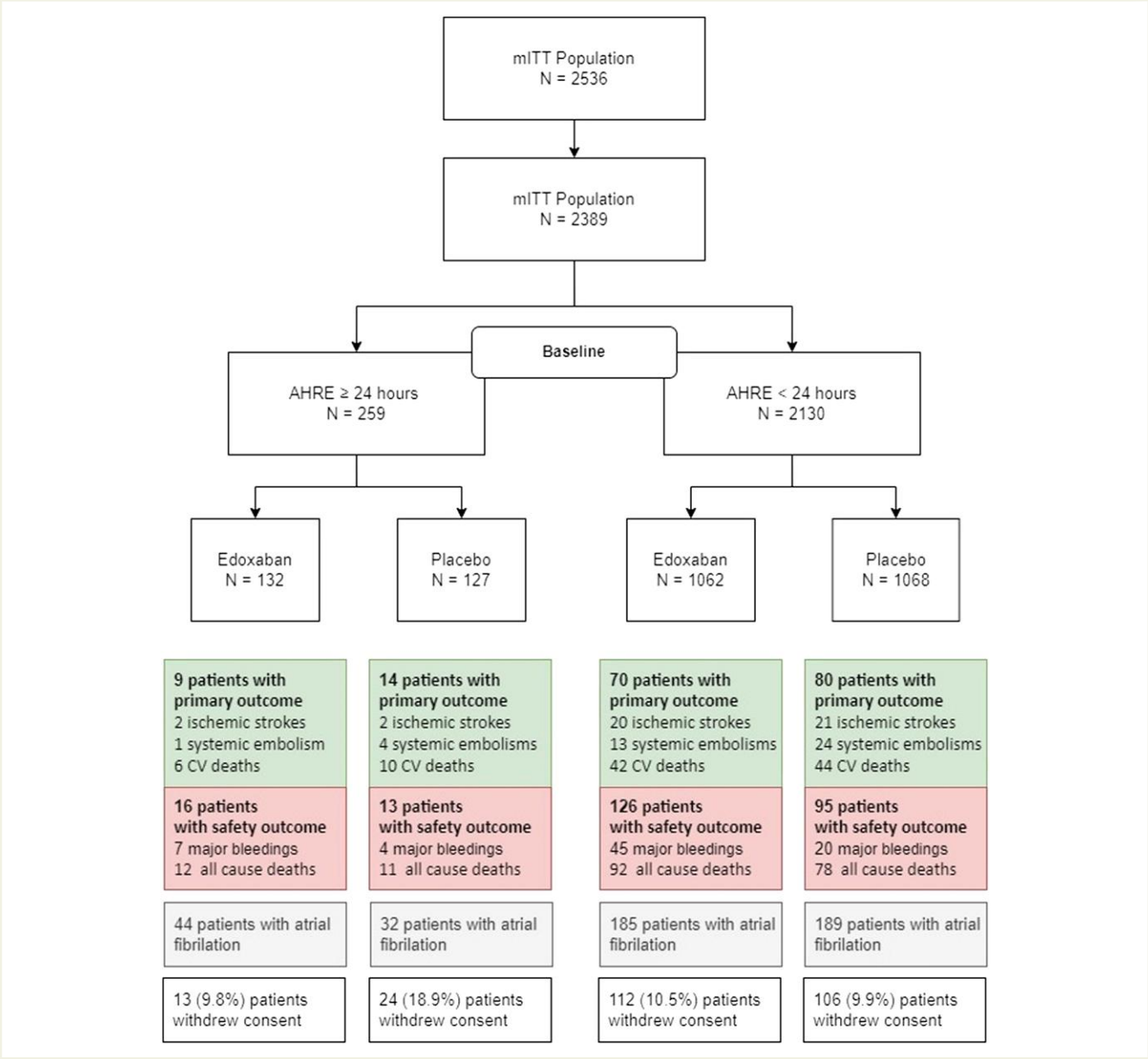


Figure 1 Consolidated standards of reporting trails (CONSORT) flow chart of this secondary pre-specified sub-analysis. Shown is the analysis population, the number of patients with a primary efficacy outcome, the number of patients with a safety outcome, and the number of patients who developed electrocardiogram-diagnosed atrial fibrillation in each group

results are reported as group-specific event rates in per cent per patient-year and as adjusted estimated cause-specific hazard ratio (HR) with a two-sided 95% confidence interval (CI) and corresponding *P*-value. Cumulative incidence curves are shown using Aalen–Johansen estimates that take competing events into account; otherwise, Kaplan–Meier curves are used. The proportional hazard assumption was checked graphically via Schoenfeld residuals and the linearity assumption for continuous predictors via martingale residuals.

The interaction between maximal AHRE duration and CHA_2DS_2-VASc score (≤4 and >4) was also considered in a model for the primary outcome. The effect of maximal AHRE duration at baseline on time to AF onset was analysed in a model without inclusion of the random group and without censoring for unblinding or withdrawal of consent.

For all outcomes, the worst-case scenario was used for missing values, i.e. deaths of unknown cause were classified as cardiovascular death. No other imputation was conducted. No adjustment for multiple testing was conducted.

Sample size calculation for the primary study can be found in the recently published main paper.[7] All analyses were conducted using R (version 4.2.3).

Results

Demographics and clinical characteristics

Demographics, clinical characteristics, and comorbidities did not differ between AHRE duration and treatment groups (*Table 1*; see Supplementary data online, *Table S1*) with three exceptions: patients with AHRE ≥24 h were more likely to be men and had a slightly higher body mass index and lower estimated glomerular filtration rate.

Table 1 Demographic variable, clinical parameters, and atrial high-rate episode characteristics at baseline by maximal atrial high-rate episode duration <24 and ≥24 h and by randomized treatment group

	AHRE duration at baseline <24 h		AHRE duration at baseline ≥24 h		Total
	Edoxaban (*N* = 1062)	Placebo (*N* = 1068)	Edoxaban (*N* = 132)	Placebo (*N* = 127)	(*N* = 2389)
Demographics					
Age, mean ± SD	78 ± 6.5	78 ± 6.7	77 ± 6.5	78 ± 7.6	78 ± 6.6
Age ≥ 75 years, *n* (%)	714 (67%)	729 (68%)	88 (67%)	81 (64%)	1612 (68%)
Female sex, *n* (%)	398 (38%)	405 (38%)	32 (24%)	40 (32%)	875 (37%)
Clinical					
BMI (kg/m^2), median (IQR)	27.7 (25.1, 31.3)	27.7 (25.0, 30.8)	28.3 (25.3, 31.9)	27.2 (25.5, 31.4)	27.7 (25.1, 31.1)
CHA_2DS_2-VASc score, median (IQR)	4 (3, 5)	4 (3, 5)	4 (3, 5)	4.0 (3, 5)	4 (3, 5)
CHA_2DS_2-VA score, median (IQR)	3 (3, 4)	3 (3, 4)	4 (3, 4)	3.0 (3, 4.)	3 (3, 4)
Modified HAS-BLED score, median (IQR)	3 (3, 4)	3 (3, 4)	3 (3, 4)	3 (3, 4)	3 (3, 4)
Comorbidities					
Heart failure[a], *n* (%)	292 (28%)	283 (27%)	45 (34%)	32 (25%)	652 (27%)
Hypertension[b], *n* (%)	909 (86%)	927 (87%)	117 (89%)	115 (91%)	2068 (87%)
Diabetes mellitus, *n* (%)	288 (27%)	276 (26%)	41 (31%)	38 (30%)	643 (27%)
Prior stroke or TIA, *n* (%)	101 (10%)	112 (11%)	11 (8%)	14 (11%)	238 (10%)
Prior myocardial infarction, PCI, or CABG, *n* (%)	300 (28%)	267 (25%)	38 (29%)	32 (25%)	637 (27%)
eGFR (CKD-EPI) (mL/min/1.73 m^2)	64.4 ± 17.4	64.5 ± 17.5	60.7 ± 16.7	61.4 ± 16.5	64.1 ± 17.4
AHRE characteristics					
AHRE (≥170 b.p.m. atrial rate and ≥6 min duration)	1023 (96%)	1037 (97%)	128 (97%)	123 (97%)	2311 (97%)
Number of total AHRE at baseline, median (IQR)	4.0 (1.0, 15.0)	4.0 (1.0, 13.8)	10.5 (2.0, 36.2)	9.0 (2.0, 24.0)	4.0 (1.0, 15.0)
Maximum duration of AHRE at baseline (h), median (IQR)	2.2 (0.7, 5.9)	2.2 (0.6, 5.9)	58.0 (30.7, 100.0)	52.5 (33.4, 96.0)	2.8 (0.8, 9.4)
Time from first adequate AHRE to baseline in (days), median (IQR)	117.0 (46.2, 245.0)	126.0 (49.0, 252.0)	155.0 (56.0, 300.0)	121.0 (41.0, 220.0)	122.0 (47.0, 249.0)
Maximum atrial rate during AHREs at baseline (b.p.m.)					
Mean ± SD	433.9 ± 135.9	421.1 ± 137.0	474.9 ± 120.5	465.5 ± 124.9	432.4 ± 135.7
Median (IQR)	400.0 (331.0, 549.0)	400.0 (308.0, 545.0)	404.0 (400.0, 600.0)	400.0 (400.0, 600.0)	400.0 (330.0, 549.0)

Continued

Table 1 *Continued*

	AHRE duration at baseline <24 h		AHRE duration at baseline ≥24 h		Total
	Edoxaban (*N* = 1062)	Placebo (*N* = 1068)	Edoxaban (*N* = 132)	Placebo (*N* = 127)	(*N* = 2389)
Time between the last AHRE and baseline (days)					
Median (IQR)	63.0 (22.0, 146.0)	69.0 (24.0, 168.5)	54.0 (20.5, 114.0)	30.0 (8.0, 95.0)	60.0 (22.0, 149.0)
≤3 months	252/422 (60%)	235/407 (58%)	51/75 (68%)	53/73 (73%)	591/977 (60%)
>3 months	170/422 (40%)	172/407 (42%)	24/75 (32%)	20/73 (27%)	386/977 (40%)

The HAS-BLED score was modified for this analysis of a population exposed to NOAC. The point for labile INR values was not considered. Information about major bleeding was limited to the assessment available at the baseline visit of the trial. All patients were considered suitable for NOAC therapy by the site investigators.
[a]Clinically overt or LVEF < 45%.
[b]Chronic treatment for hypertension, estimated need for continuous antihypertensive therapy, or resting blood pressure >145/90 mmHg.
AHRE, atrial high-rate episode; CKD-EPI, chronic kidney disease-epidemiology collaboration equation; eGFR, estimated glomerular filtration rate; IQR, inter-quartile range; SD, standard deviation; TIA, transient ischaemic attack.

Atrial high-rate episode characteristics

Adequate baseline AHRE recordings were confirmed by the core lab in 2389/2536 patients (94.2%; *Figure 1*). Maximal AHRE durations ≥24 h at baseline were found in 259/2389 patients (11%, *Table 1*). In patients with AHRE ≥24 h, the median duration of the longest AHRE was 53.1 h (IQR 32.3, 96.0), while in patients with AHRE <24 h, the median longest AHRE duration was 2.2 h (IQR 0.64, 5.9). At baseline, patients with AHRE ≥24 h had a higher median number of AHRE than patients with shorter AHRE duration [AHRE ≥24 h: 9 (IQR 2, 27); AHRE <24 h: 4 (IQR 1, 14); $P < .001$; *Figure 2A*; *Table 1*; see Supplementary data online, *Table S1*]. The median time between last AHRE and the baseline visit was 60 days (IQR 22, 149) in the total population. That duration was shorter in patients with AHRE ≥24 h (43 days, IQR 12.0, 108) than in patients with shorter AHRE (65 days, IQR 23, 157, $P = .002$; *Table 1*; *Figure 2B*; see Supplementary data online, *Table S1*). The distribution of the maximal AHRE duration at baseline (longest single episode) is shown in *Figure 2C*.

Primary efficacy outcome

Cumulative incidence curves of the primary efficacy outcome (composite of stroke, systemic embolism, or death from cardiovascular causes) are shown in *Figure 3A* and *Structured Graphical Abstract* by treatment group in patients with AHRE ≥24 h and patients with shorter AHRE durations. The median follow-up of the study population was 1.8 years. There was no interaction between randomized treatment and AHRE duration (*P*-interaction = .65). The point estimates of the event rates were not identical. In patients with AHRE duration ≥24 h, the primary outcome occurred in 9/132 (6.8%) patients with anticoagulation (4.3%/patient-year) and in 14/127 (11%) patients with placebo (6.9%/patient-year, AHRE ≥24 h edoxaban vs. placebo adjusted HR 0.86, 95% CI 0.62–1.19). The primary efficacy outcome occurred in 70/1062 patients with AHRE <24 h with anticoagulation (3.2%/patient-year) and in 80/1068 patients with placebo (3.7%/patient-year, AHRE <24 h edoxaban vs. placebo adjusted HR 0.66, 95% CI 0.28–1.53; *Figure 3A*; *Table 2*).

When AHRE duration was evaluated as a continuous variable, there was no interaction with the treatment effect (*P*-interaction = .98). Likewise, there was no treatment interaction when AHRE duration was categorized by median duration (≤2.82 and >2.82 h, *P*-interaction = .4; see Supplementary data online, *Table S2* and *Figure S1*).

The findings of the sensitivity analysis of the primary efficacy outcome and safety outcome, a safety population, a per-protocol population along with population without censoring for AF onset, and unblinding displayed a high degree of consistency with the primary efficacy and safety analysis (see Supplementary data online, *Table S3*).

Safety outcome

AHRE ≥24 h did not interact with the safety outcome, a composite of bleeding and death. The point estimates for the primary safety outcomes were almost identical in patients with AHRE ≥24 h compared with patients with shorter AHRE (AHRE ≥24 h HR 1.30, 95% CI 0.62–2.71; AHRE <24 h HR 1.32, 95% CI 1.01–1.73, *P*-interaction = .96; *Table 2*; *Figure 3B*). Splitting AHRE duration by its median or including AHRE duration as a continuous parameter did not identify an interaction between anticoagulation therapy and AHRE duration for the safety outcome either (*P*-interaction = .65 for split by median AHRE duration; *P*-interaction = .88 for AHRE as continuous variable).

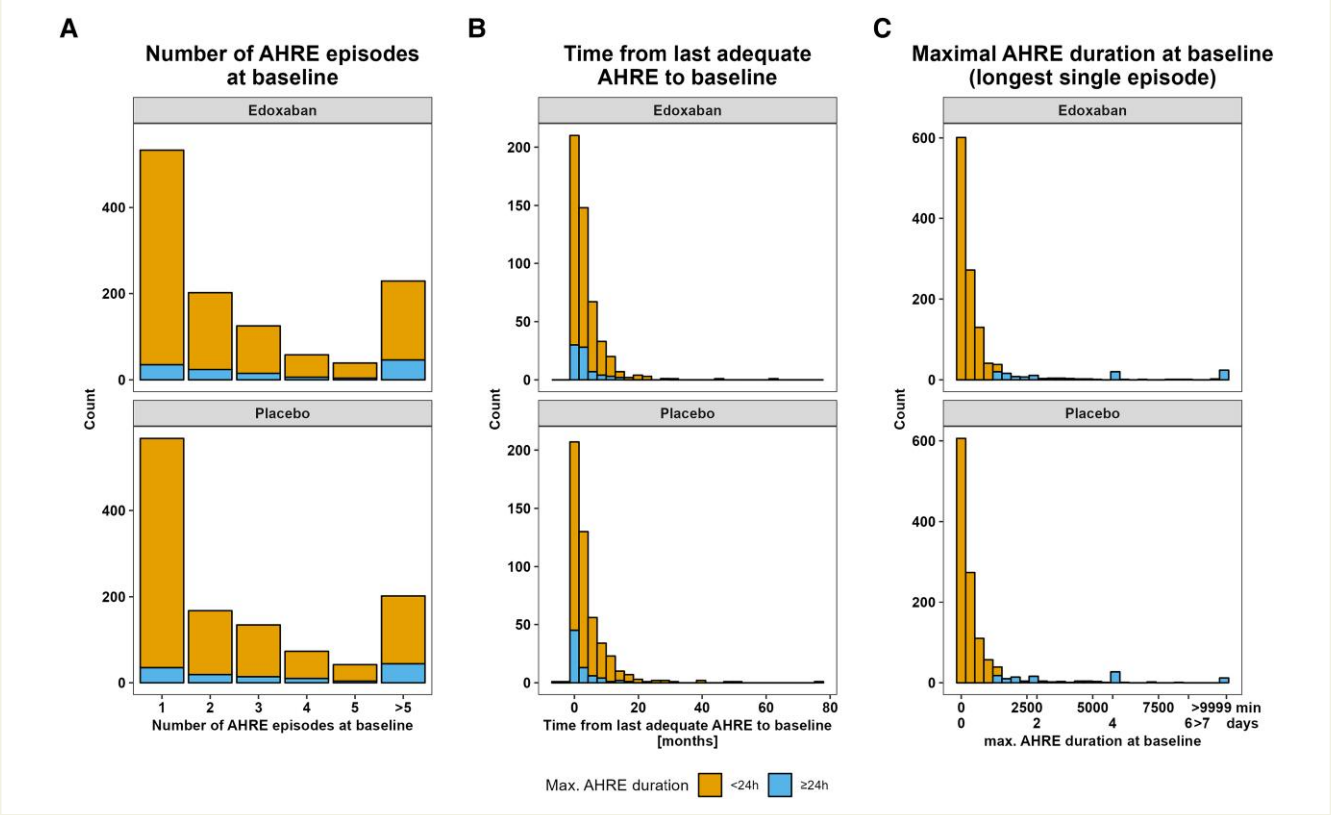


Figure 2 Atrial high-rate episodes (AHREs) characteristics by atrial high-rate episode duration. (*A*) Number of atrial high-rate episodes prior to at baseline. (*B*) Time from last adequate atrial high-rate episode to baseline by atrial high-rate episode duration in months. (*C*) Duration of the maximal atrial high-rate episode at baseline (longest single episode) in minutes and days. The apparent peak at 4 days (99 h) atrial high-rate episode duration is due to the fact that some manufacturers only store precise atrial high-rate episode durations up to 99 h, while other manufacturers and devices precisely capture atrial high-rate episode durations up to 9999 h. All graphs show separate distributions for each randomized group in the 2389 patients with adequate atrial high-rate episode. There were no differences between randomized groups

Secondary outcomes

Ischaemic stroke occurred in 2/132 patients with AHRE ≥24 h randomized to anticoagulation (0.95%/patient-year) and in 2/127 patients with AHRE ≥24 h randomized to placebo (0.97%/patient-year, AHRE ≥24 h edoxaban vs. placebo adjusted HR 1.03, 95% CI 0.14–7.32). In patients with AHRE <24 h, ischaemic stroke occurred in 20/1062 patients randomized to anticoagulation (0.90%/patient-year) and in 21/1068 patients randomized to placebo (0.96%/patient-year) (AHRE <24 h edoxaban vs. placebo HR 0.92, 95% CI 0.50–1.70; *Table 2*; *Figure 3C and D*; *Structured Graphical Abstract*). There was no interaction between AHRE duration and randomized treatment for the outcome ischaemic stroke (*P*-interaction = .89).The *post-hoc* outcome combining ischaemic stroke and systemic embolism excluding pulmonary embolism and myocardial infarction in patients with AHRE ≥24 h occurred in 8/132 patients (3.8%/patient-year) randomized to anticoagulation and in 13/127 patients randomized to placebo [6.4%/patient-year, HR 0.63 (0.26–1.52)]. In patients with shorter AHRE durations, this outcome occurred in 60/1062 patients with anticoagulation (2.7%/patient-year) and in 61/1068 patients with placebo [2.8%/patient-year, HR 0.97 (0.68–1.38); *P*-interaction = .45]. No haemorrhagic stroke occurred in either group. Similar results were observed for the secondary outcomes and the *post-hoc* outcomes using AHRE duration as a continuous variable or as a categorical variable by median AHRE duration (≤2.82 and >2.82 h; see Supplementary data online, *Table S2* and *Figure S2*).

Adjusted multiple regression analysis, three-way interaction analysis for the CHA_2DS_2-VASc score (≤4 and >4), and for the AHRE duration ≥24 and <24 h showed no differences between treatment groups (see Supplementary data online, *Figure S2*).

Time from atrial high-rate episode to electrocardiogram-diagnosed atrial fibrillation

Patients with AHRE ≥24 h at baseline developed more ECG-diagnosed AF [76/259 (29.3%)] than patients with shorter AHRE durations [374/2130 (17.6%); *Figure 4*], also reflected by a higher incidence of ECG-diagnosed AF during follow-up (17.0%/patients-year) than patients with shorter AHRE (8.2%/patient-year, HR 2.20; 95% CI 1.71–2.84, *P* < .001). Consequently, the median follow-up time on active study medication was shorter in patients with AHRE ≥24 h (1.5 years, IQR 0.6, 2.5) than in patients with AHRE <24 h (1.9 years, IQR 0.9, 3.3).

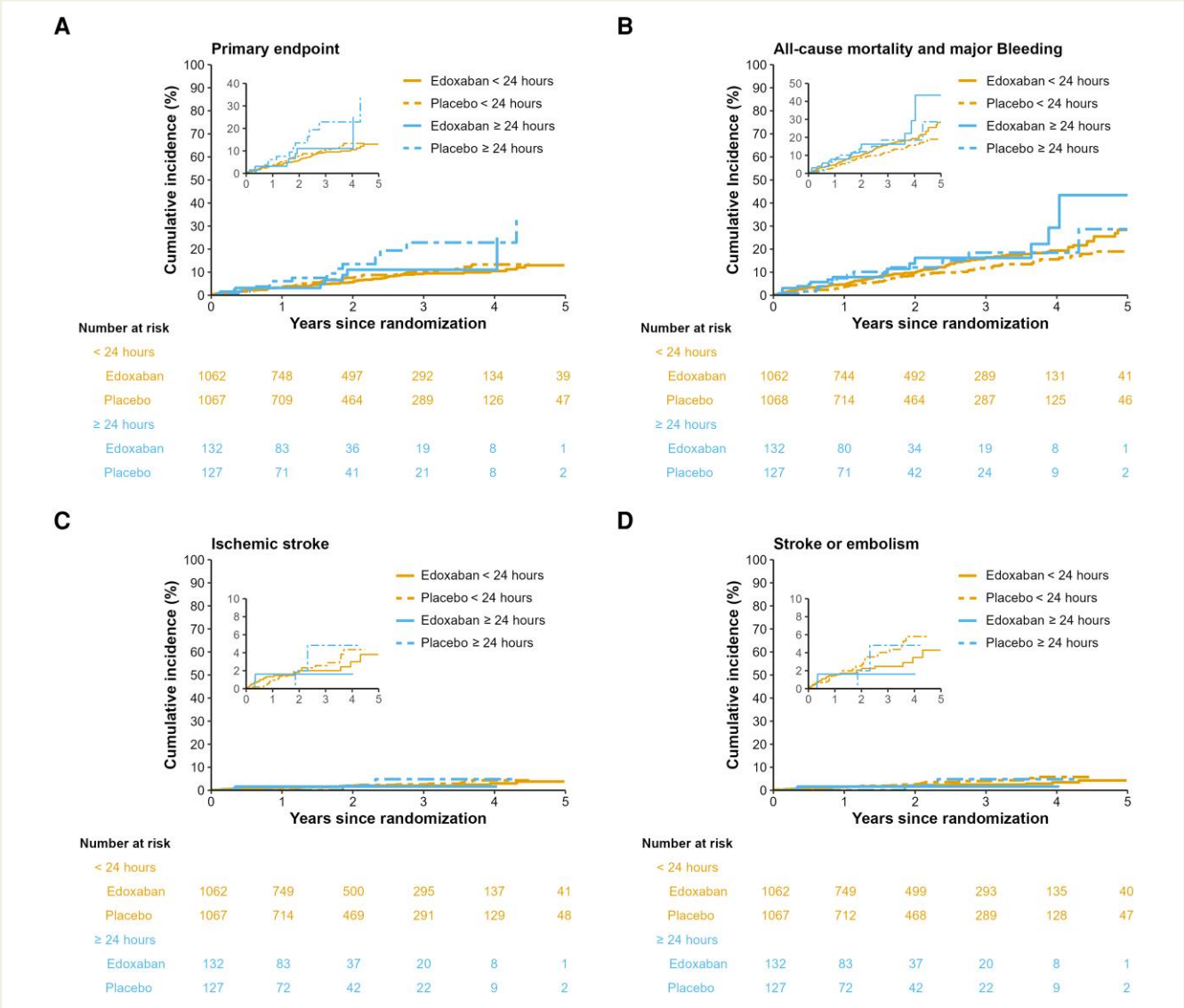


Figure 3 Cumulative incidence curves of the primary outcome and secondary outcomes incidence curves considering death competing event (Aalen–Johansen curve). (*A*) Primary outcome, a composite of stroke, systemic embolism, and cardiovascular death. (*B*) All-cause death and major bleeding. (*C*) Ischaemic stroke. (*D*) Ischaemic stroke or systemic embolism

Discussion

Main findings

This secondary pre-specified analysis of the NOAH-AFNET 6 trial based on standardized, core lab analysis of all qualifying AHREs at baseline identified the following: (i) long durations of device-detected AHRE, including durations ≥24 h, did not interact with the treatment effect of anticoagulation in the NOAH-AFNET 6 trial; (ii) similarly, there was no interaction between the effect of anticoagulation therapy and AHRE duration used as a continuous variable; (iii) stroke rate appeared low (1%/patient-year) without oral anticoagulation in patients with AHRE ≥24 h and in the overall population of patients with AHRE despite multiple clinical stroke risk factors (median CHA_2DS_2-VASc = 4); and (iv) patients with AHRE ≥24 h developed more ECG-diagnosed AF over time compared with those with shorter AHRE durations.

This is the first analysis assessing the interaction between AHRE duration and anticoagulation therapy in patients with AHRE and stroke risk factors. The hypothesis-generating findings illustrate the need for further research into factors to identify patients with AHRE at high risk of stroke.

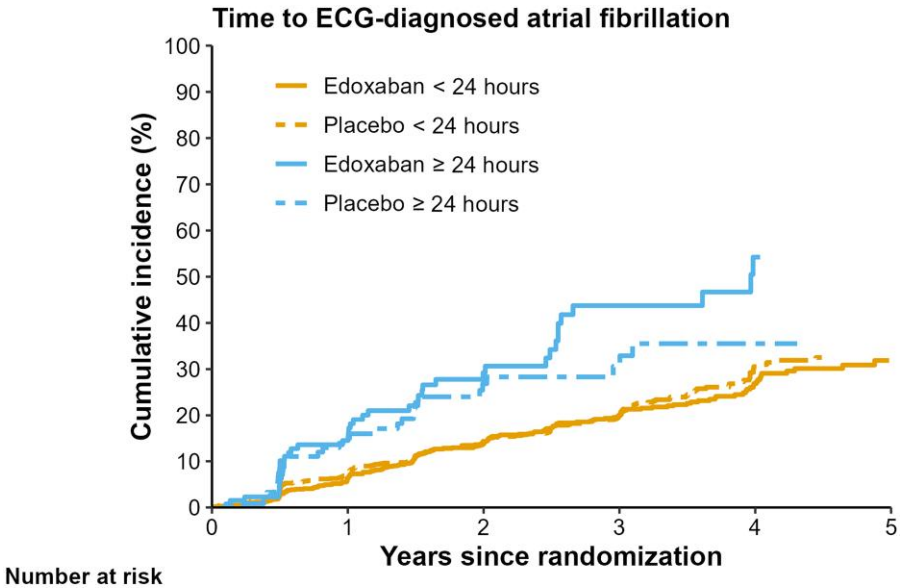
Which factors could explain the low rate of stroke and thrombotic events without anticoagulation in patients with long atrial high-rate episode in NOAH-AFNET 6?

Patients with device-detected AHRE have a higher stroke risk than patients without AHRE, although the stroke risk appears lower compared with patients with ECG-diagnosed AF.[1] This pre-specified secondary analysis of the NOAH-AFNET 6 trial did not find that AHRE duration interacts with the efficacy and safety of oral anticoagulation in a large, randomized, double-blind trial (*Structured Graphical Abstract*). Unexpectedly, the stroke rate appeared low in patients across AHRE durations, including in patients with AHRE ≥24 h not receiving

Table 2 **Efficacy and safety outcomes for the primary and secondary outcomes by atrial high-rate episode duration <24 and ≥24 h and by randomized treatment group**

	AHRE duration at baseline <24 h			AHRE duration at baseline ≥24 h			*P*-value interaction
	Edoxaban No. of patients with event/patient-year (% per patient-year)	Placebo No. of patients with event/patient-year (% per patient-year)	Edoxaban vs. placebo Adjusted HR (95% CI)	Edoxaban No. of patients with event/patient-year (% per patient-year)	Placebo No. of patients with event/patient-year (% per patient-year)	Edoxaban vs. placebo Adjusted HR (95% CI)	
Primary efficacy outcome*	70/2218.7 (3.16)	80/2164.7 (3.70)	0.86 (0.62–1.19)	9/209.1 (4.30)	14/202.3 (6.92)	0.66 (0.28–1.53)	.65
Secondary efficacy outcomes							
Ischaemic stroke	20/2233.1 (0.90)	21/2183.6 (0.96)	0.92 (0.50–1.70)	2/211.0 (0.95)	2/207.1 (0.97)	1.03 (0.14–7.32)	.89
Systemic embolism	13/2240.9 (0.58)	24/2174.8 (1.10)	0.55 (0.28–1.08)	1/209.1 (0.48)	4/203.1 (1.97)	0.25 (0.03–2.26)	.51
Myocardial infarction	9/2250.8 (0.40)	14/2179.1 (0.64)		1/209.1 (0.48)	2/207.9 (0.96)		
Pulmonary embolism	3/2248.6 (0.13)	8/2188.5 (0.37)		0	1/207.9 (0.48)		
Peripheral limb	1/2252.2 (0.04)	2/2193.1 (0.09)		0	1/206.1 (0.49)		
Abdominal embolism	0	1/2193.9 (0.05)		0	0		
Cardiovascular death	42/2255.4 (1.86)	44/2193.6 (2.01)	0.94 (0.61–1.44)	6/211.0 (2.84)	10/209.4 (4.78)	0.63 (0.23–1.76)	.58
MACE	78/2198.2 (3.55)	85/2147.1 (3.96)	0.90 (0.66–1.23)	9/206.4 (4.36)	12/207.0 (5.80)	0.79 (0.33–1.88)	.89
Ischaemic stroke or systemic arterial embolism	23/2226.3 (1.03)	32/2173.8 (1.47)	0.71 (0.41–1.21)	2/211.0 (0.95)	2/207.1 (0.97)	1.01 (0.14–7.20)	.71
Ischaemic stroke or systemic arterial embolism (*post-hoc* definition*)	60/2229.9 (2.69)	61/2183.0 (2.79)	0.97 (0.68–1.38)	8/211.0 (3.79)	13/203.8 (6.38)	0.63 (0.26–1.52)	.45
Safety outcomes							
All cause death and major bleeding	126/2201.0 (5.72)	95/2165.7 (4.39)	1.32 (1.01–1.73)*	16/204.4 (7.83)	13/206.1 (6.31)	1.30 (0.62–2.71)	.96
All cause death	92/2255.4 (4.08)	78/2193.6 (3.56)	1.16 (0.85–1.57)	12/211.0 (5.69)	11/209.4 (5.25)	1.15 (0.50–2.61)	.97
Major bleeding	45/2201.0 (2.04)	20/2165.7 (0.92)	2.22 (1.31–3.76)**	7/204.4 (3.43)	4/206.1 (1.94)	1.78 (0.52–6.12)	0.69

*$P = .04$.
**$P = .003$.



Number at risk

< 24 hours						
Edoxaban	1062	771	523	313	144	44
Placebo	1068	736	492	304	136	50
≥ 24 hours						
Edoxaban	132	89	44	21	8	1
Placebo	127	80	46	25	10	2

Figure 4 Cumulative incidence curve from baseline to electrocardiogram-diagnosed atrial fibrillation considering death as competing event (Aalen–Johansen curve; $P < .001$). Survival curves are shown for patients with long atrial high-rate episode ≥24 h and shorter atrial high-rate episode split by randomized group

anticoagulation (1%/year). The observed stroke rate in patients with long AHRE durations is comparable with the stroke rate in large routine care databases of patients with AHRE and stroke risk factors.[9,10]

Small observational data sets, including a subgroup analysis of the ASSERT trial with similar demographic and clinical characteristics compared with this data set (ASSERT: age 77.2 years, CHA_2DS_2-VASc score 4), suggested a higher rate of stroke.[4,5] Patients randomized in NOAH-AFNET 6 had an ECG recorded every 6 months and received anticoagulation upon ECG documentation of AF, in accordance with the current guidelines on the initiation of anticoagulation in patients with ECG-documented AF.[11] In patients with AHRE ≥24 h, these ECGs found AF in 17%/year and in 29% of the patients during the duration of the trial. It is unclear how many patients received anticoagulation after ECG documentation of AF in ASSERT.[5] Timely detection of ECG-documented AF and initiation of open-label anticoagulation is a likely contributor to the lower rate of stroke in NOAH-AFNET 6. There was a numerical signal for more ischaemic events in patients with AHRE ≥24 h, and the point estimates for thrombotic events were higher in patients with long AHRE randomized to no anticoagulation compared with patients with long AHRE randomized to anticoagulation. Within the limitations of this analysis, our results do not identify an interaction between AHRE duration and the efficacy and safety of oral anticoagulation in patients with AHRE and stroke risk factors.

What differentiates atrial high-rate episode from electrocardiogram-diagnosed atrial fibrillation?

The overwhelming majority of AHRE recorded in NOAH-AFNET 6 shows features consistent with AF during episodes, including a high atrial rate (>200 b.p.m.) and irregular RR intervals. NOAH-AFNT-6 trial enrolled patients without an upper limit for AHRE duration and therefore included patients with very long AHRE. Despite several approaches to analysing AHRE duration at baseline, including a cut-off of ≥24 h, a split by median duration, and integrating AHRE duration as a continuous parameter, no subgroup of patients was identified that had a substantially higher stroke risk than the overall population. The main finding in the overall trial, a low rate of stroke, extends to the population with long AHRE durations in this analysis. Overall, this hypothesis-generating analysis suggests that the arrhythmia burden in patients with AHRE may be too low to create a stroke risk that is comparable with the stroke risk in paroxysmal AF.[12–16] The neutral outcome of the intervention tested in the LOOP study, initiation of oral anticoagulation upon AHRE detection by an implanted loop recorder, may support the concept that device-detected AHREs are only associated with a relatively small increase in stroke risk. In LOOP, the overall arrhythmia burden was low (mean estimate 0.13%[17,18]). The arrhythmia burden in a patient with ECG-diagnosed AF not undergoing rhythm control is likely to be higher (estimated at 11%[19]). Early rhythm control

therapy reduced cardiovascular events in the EAST-AFNET 4 trial.[20] This outcome-reducing effect was mediated by attaining sinus rhythm.[21] In view of the low AF burden on rhythm control therapy (0.2% AF burden after AF ablation, 2% AF burden on antiarrhythmic drugs),[22] a lower arrhythmia burden on rhythm control therapy is a likely driver of reduced outcomes with early rhythm control. Further research on the interaction of stroke risk and arrhythmia burden is needed. Such research would become much easier if reliable methods for atrial arrhythmia quantification and a uniform definition of atrial arrhythmia burden across devices were available.[23] In view of the authors, a higher arrhythmia burden is a likely contributor to the higher rate of stroke between the population studied here and patients with paroxysmal AF enrolled in anticoagulation trials.[14]

Arrhythmia detection by wearable electronic devices

The detection rate of atrial arrhythmias resembling AF by wearables[24,25] is lower than the AHRE rate detected by implanted devices.[1,24,26] This is probably due to at least three factors: first, the younger age and lower comorbidity burden in the populations studied using wearables; second, the shorter monitoring duration limited to the time during which the devices are worn; and third, the incomplete detection of arrhythmias by algorithms and systems used in wearable electronics. Given the low stroke rate in patients with long AHRE durations found here (1%/year), there is a need for randomized trials comparing oral anticoagulation with no anticoagulation in patients with rare atrial arrhythmia episodes. The design of such trials can be improved by including methods to detect patients with rare atrial arrhythmias who are at a high risk of stroke. In addition to clinical stroke risk factors, quantitative proxies for stroke risk obtained from imaging or from circulating biomolecules[27,28] may be helpful to identify patients with AHRE at high risk of stroke.

Limitations

This analysis is not sufficient to rule out interaction effects between anticoagulation and AHRE duration on thrombo-embolic events. The findings were consistent whether analysing AHRE duration categorically split by 24 h episode duration, by median, or as a continuous variable. The findings need validation in independent and larger cohorts. An individual patient meta-analysis of the data collected in NOAH-AFNET 6 and ARTESiA[29] can help to identify subgroups of patients at high risk of stroke. Due to the exclusion of patients with AHRE ≥24 h in ARTESiA, such an effort will not generate more data in patients with very long AHRE durations. Most of the analyses presented here were pre-specified in the analysis plan, but some of the outcome definitions were defined *post-hoc*. This analysis found a numerically higher event rate in patients with long AHRE randomized to no anticoagulation. This illustrates the need for adequately powered randomized trials of anticoagulation therapy in patients with long device-detected atrial arrhythmias. The NOAH-AFNET 6 trial only tested anticoagulation with edoxaban. Efficacy and safety of anticoagulation with other anticoagulants can only be inferred. The NOAH-AFNET 6 trial was conducted in Europe, and most patients had access to evidence-based management of cardiovascular conditions to reduce stroke risk, including blood pressure control, treatment of dyslipidaemias and diabetes, and heart failure therapy. Furthermore, an ECG every 6 months was used to detect AF, triggering treatment with open-label anticoagulation. This may have contributed to the low event rates. Effects in other ethnicities and effects of other anticoagulants can only be deduced from the present data. Furthermore, the enrolment bias inherent in randomized trials may have affected event rates. All devices captured AHRE characteristics, but the methods to quantify the total duration of AHRE and to estimate the monitored time differ between devices and manufactures. Therefore, quantification of the arrhythmia burden at baseline, a candidate predictor of stroke risk,[30,31] was not possible in this analysis. Further analyses may enable quantification of the effect of baseline arrhythmia burden on the efficacy and safety of oral anticoagulation.

Conclusions

In this pre-specified secondary analysis of the NOAH-AFNET 6 trial, there was no interaction between the duration of the longest AHRE and the efficacy and safety of oral anticoagulation. The rate of stroke and thrombotic events appeared low in patients with long AHRE ≥24 h. Patients experiencing AHRE durations ≥24 h are more likely to develop AF over time, calling for regular ECG follow-up. Further research is needed to identify patients with AHRE at higher risk of stroke and other cardiovascular events.

Supplementary data

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

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Declarations

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Data Availability

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

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Ethical Approval

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 co-ordinator's 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

ClinicalTrials.gov number: NCT02618577; ISRCT number: ISRCTN17309850.

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