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Short Title: Oral Anticoagulation in patients with AHRE≥24 hrs

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Abstract

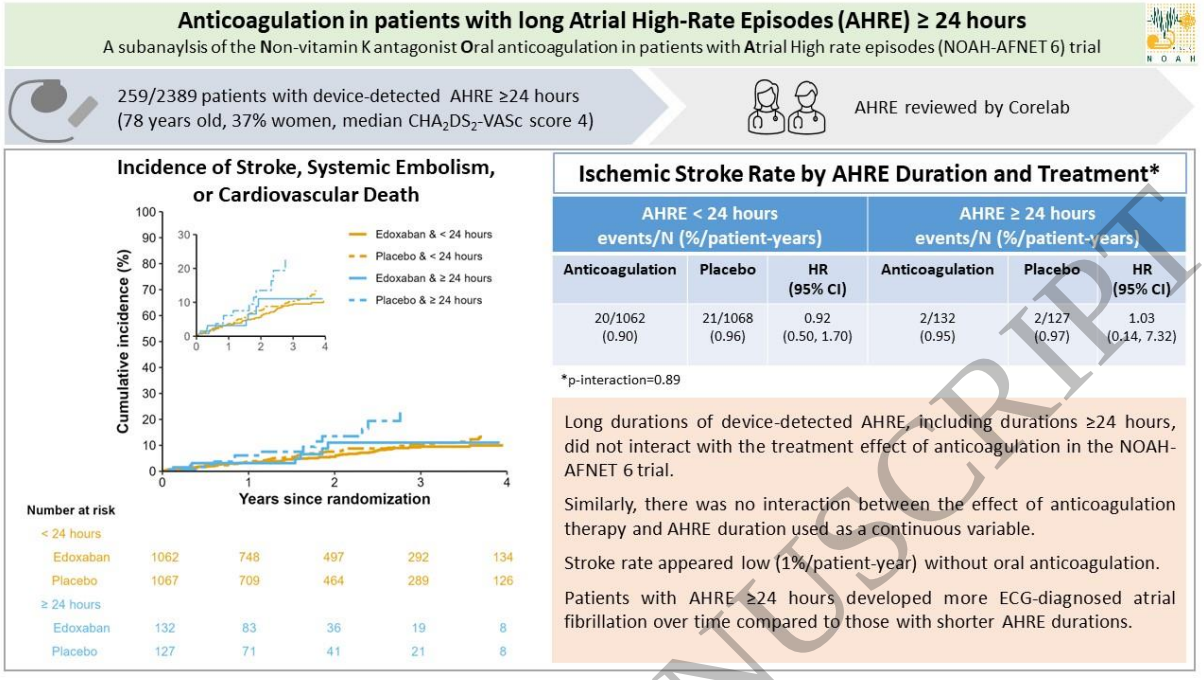
Background and Aims. Patients with long atrial high-rate episodes (AHRE) ≥24 hours and stroke risk factors are often treated with anticoagulation for stroke prevention. Anticoagulation has never been compared to no anticoagulation in these patients.

Methods. This secondary prespecified analysis of NOAH-AFNET 6 examined interactions between AHRE duration at baseline and anticoagulation with edoxaban compared to 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 ECG-diagnosed atrial fibrillation.

Results. AHRE ≥24 hours were present at baseline in 259/2389 patients enrolled in NOAH-AFNET 6 (11%, 78±7 years old, 28% women, CHA_2DS_2-VASc score 4). Clinical characteristics were not different from patients with shorter AHRE. During a median follow-up of 1.8 years, the primary outcome occurred in 9/132 patients with AHRE ≥24 hours (4.3%/patient-year, 2 strokes) treated with anticoagulation and in 14/127 patients treated with placebo (6.9%/patient-year, 2 strokes). AHRE duration did not interact with the efficacy (p-interaction=0.65) or safety (p-interaction=0.98) of anticoagulation. Analyses including AHRE as a continuous parameter confirmed this. Patients with AHRE ≥24 hours developed more ECG-diagnosed atrial fibrillation (17.0%/patient-year) than patients with shorter AHRE (8.2%/patient-year; p <0.001).

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.

Keywords: atrial high-rate episodes, stroke, atrial fibrillation, NOAH-AFNET 6



Graphical Abstract
160x90 mm (x DPI)

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

Baseline AHRE duration did not interact with the efficacy and safety of anticoagulation in the NOAH-AFNET 6 trial. 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.

Abbreviations

AF	Atrial fibrillation
AHRE	Atrial high-rate episodes
ECG	Electrocardiogram
IQR	Interquartile range
ISTH	International Society on Thrombosis and Haemostasis
NOAH – AFNET	Non vitamin K antagonist Oral anticoagulants in patients with Atrial High-rate episodes trial

Introduction

Atrial high-rate episodes (AHRE), short atrial arrhythmias lasting a few minutes (5 to 6 minutes 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 ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reducing Atrial Pacing) trial and a meta-analysis by Uittenbogaart et al suggest a higher stroke risk associated with AHRE lasting ≥24 hours[4, 5]. In clinical practice, data from these relatively small observational studies and the resemblance of long AHRE episodes with AF often result in use of oral anticoagulation for stroke prevention in patients with AHRE ≥24 hours 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 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 to 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 (approximately 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 AHRE episodes in a core lab[8] enabled a granular sub-analysis of patients with very long AHRE episodes.

Methods

This is a secondary prespecified 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 hours and patients limited to episodes lasting from 6 minutes to 23:59 hours (termed <24 hours). Patients were classified as AHRE ≥24 hours when at least one episode was longer than 24 hours 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 analyzed.

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 randomised to edoxaban took a dummy aspirin tablet. Each patient was seen to hand out study medication every six 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. 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 AHRE Episodes

All AHRE reports and recordings were uploaded onto the electronic trial management system. An independent core laboratory based at Maastricht University, Netherlands, reanalyzed all AHRE episodes 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 episode in relation to baseline, performed quality control and provided feedback to trial sites regarding their uploaded AHRE data if necessary. All patients with adequate AHRE episodes 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 ischemic stroke and systemic embolism, excluding pulmonary embolism and myocardial infarction. The primary safety outcome was a composite of major bleeding according to the ISTH 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 1st and 3rd quartile (interquartile 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, lost to follow-up, or withdrew consent. The primary efficacy outcome and the safety outcome were also analyzed for the safety population (all randomized patients), the per-protocol population, and a population that was not censored for AF-onset or unblinding. All Ukrainian patients were censored on 24th 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 hours and ≥24 hours using chi-squared 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 centers 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 hours and ≥24 hours and categories by median). The outcome results are reported as group-specific event rates in percent per patient-year and as adjusted estimated cause-specific hazard ratio with a two-sided 95% confidence interval 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 (**Figure 1**, **Table 1 and Supplementary Table S1**) with three exceptions: patients with AHRE ≥24 hours were more likely to be men and had a slightly higher body mass index and lower estimated glomerular filtration rate.

AHRE Characteristics

Adequate baseline AHRE recordings were confirmed by the core lab in 2389/2536 patients (94.2%). Maximal AHRE durations ≥24 hours at baseline were found in 259/2389 patients (11%, **Table 1)**. In patients with AHRE ≥24 hours, the median duration of the longest AHRE was 53.1

hours (IQR 32.3, 96.0), whilst in patients with AHRE <24 hours the median longest AHRE duration was 2.2 hours (IQR 0.64, 5.9). At baseline, patients with AHRE ≥24 hours had a higher median number of AHRE than patients with shorter AHRE duration (AHRE ≥24 hours: 9 (IQR 2, 27); AHRE <24 hours: 4 (IQR 1, 14); p<0.001, **Figure 2, Table 1**, **Supplementary Table S1**). The distribution of maximal AHRE duration at baseline (longest single episode) are shown in **Figure 2A** and **Figure 2B.** The median time between last AHRE to the baseline visit was 60 days (IQR 22,149) in the total population. That duration was shorter in patients with AHRE ≥24 hours (43 days, IQR 12.0, 108) than in patients with shorter AHRE (65 days, IQR 23, 157, p=0.002, **Table 1** and **Supplementary Table S1, Figure 2B).**

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 **Graphical Abstract** by treatment group in patients with AHRE ≥24 hours and patients with shorter AHRE durations. There was no interaction between randomized treatment and AHRE duration (p-interaction=0.65). The point estimates of the event rates were not identical. In patients with AHRE duration ≥24 hours, the primary outcome occurred in 9/132 (6.8%) patients with anticoagulation (4.3%/patient-year) and 14/127 (11%) patients with placebo (6.9%/patient-year, AHRE ≥24 hours 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 hours with anticoagulation (3.2%/patient-year) and in 80/1068 patients with placebo (3.7%/patient-year, AHRE <24 hours edoxaban vs. placebo adjusted HR 0.66, 95% CI 0.28-1.53; **Figure 3A** and **Table 2**).

When AHRE duration was evaluated as a continuous variable, there was no interaction with the treatment effect (p-interaction=0.98). Likewise, there was no treatment interaction when AHRE

duration was categorized by median duration (≤2.82 hours and >2.82 hours, p-interaction=0.4, **Supplementary Table S2 und 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 (**Supplementary Table S3**).

Safety Outcome

AHRE ≥24 hours 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 hours compared to patients with shorter AHRE (AHRE ≥24 hours HR 1.30, 95% CI 0.62-2.71; AHRE <24 hours HR 1.32, 95% CI 1.01-1.73, p-interaction=0.96, **Table 2** and **Figure 3D**). 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=0.65 for split by median AHRE duration; p-interaction=0.88 for AHRE as continuous variable).

Secondary Outcomes

Ischemic stroke occurred in 2/132 patients with AHRE ≥24 hours randomized to anticoagulation (0.95%/patient-year) and in 2/127 patients with AHRE ≥24 hours randomized to placebo (0.97%/patient-year, AHRE ≥24 hours edoxaban vs. placebo adjusted HR 1.03, 95% CI 0.14, 7.32). In patients with AHRE <24 hours, ischemic stroke occurred in 20/1062 patients randomized to anticoagulation (0.90%/patient-year) and 21/1068 patients randomized to placebo (0.96%/patient-year) (AHRE <24 hours edoxaban vs. placebo HR 0.92, 95% CI 0.50-1.70, **Table**

2, Figure 3B and Graphical Abstract). There was no interaction between AHRE duration and randomized treatment for the outcome ischemic stroke (p-interaction=0.89).

The post-hoc outcome combining ischemic stroke and systemic embolism excluding pulmonary embolism and myocardial infarction in patients with AHRE ≥24 hours occurred in 8/132 patients (3.8%/patient-year) randomized to anticoagulation and 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 61/1068 patients with placebo (2.8%/patient-year, HR 0.97 (0.68, 1.38); p-interaction=0.45). No hemorrhagic 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 hours and >2.82 hours) (**Supplementary Table S2** and **Figure S2**).

Adjusted multiple regression analysis, 3-way interaction analysis for the CHA_2DS_2-VAS_C score (≤4 and >4), and for the AHRE duration ≥24 hours and <24 hours showed no differences between treatment groups (**Supplementary Figure S3)**.

Time from AHRE to ECG-diagnosed AF

Patients with AHRE ≥24 hours 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<0.001). Consequently, the median follow-up time on active study medication was shorter in patients with AHRE ≥24 hours (1.5 years, IQR 0.6, 2.5) than in patients with AHRE <24 hours (1.9 years, IQR 0.9, 3.3).

Discussion

Main Findings

This secondary prespecified analysis of the NOAH-AFNET 6 trial based on standardized, core-lab analysis of all qualifying AHRE episodes at baseline identified the following: (i) long durations of device-detected AHRE, including durations ≥24 hours, 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 hours 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 hours developed more ECG-diagnosed AF over time compared to 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 AHRE 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 to patients with ECG-diagnosed AF[1]. This prespecified 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 (**Graphical abstract**). Unexpectedly, the stroke rate appeared low in patients across AHRE durations, including in patients with AHRE ≥24 hours not receiving anticoagulation (1%/year).

The observed stroke rate in patients with long AHRE durations is comparable to 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 to this data set (ASSERT: age 77.2 years, CHA_2DS_2-VAS_C score 4), suggested a higher rate of stroke[4, 5]. Patients randomized in NOAH-AFNET 6 had an ECG recorded every six months and received anticoagulation upon ECG documentation of AF, in accordance with current guidelines on the initiation of anticoagulation in patients with ECG-documented AF[11]. In patients with AHRE ≥24 hours, 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 ischemic events in patients with AHRE ≥24 hours, and the point estimates for thrombotic events were higher in patients with long AHRE randomized to no anticoagulation compared to 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 AHRE from ECG-diagnosed Atrial Fibrillation?

The overwhelming majority of AHRE recorded in NOAH-AFNET 6 show features consistent with AF during episodes, including a high atrial rate (>200 bpm) and irregular RR intervals. NOAH-AFNET 6 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 hours, 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 to the stroke risk in paroxysmal atrial fibrillation[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 AHRE 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 the 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 to 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 thromboembolic events. The findings were consistent whether analysing AHRE duration categorically split by 24 hour 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 hours in ARTESiA, such an effort will not generate more data in patients with very long AHRE durations. Most of the analyses presented here were prespecified 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. NOAH-AFNET 6 only tested anticoagulation with edoxaban. Efficacy and safety of anticoagulation with other anticoagulants can only be inferred. NOAH-AFNET 6 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 dyslipidemias and diabetes, and heart failure therapy. Furthermore, an ECG every six 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 prespecified secondary analysis of the NOAH-AFNET 6 trial, there was no interaction between the duration of the longest AHRE episode and the efficacy and safety of oral anticoagulation. The rate of stroke and thrombotic events appeared low in patients with long AHRE ≥24 hours. Patients experiencing AHRE durations ≥24 hours 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.

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Figure Legends

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

Figure 1: CONSORT flow chart of this secondary prespecified subanalysis. 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 ECG-diagnosed atrial fibrillation in each group.

Figure 2. Atrial high-rate episodes (AHRE) characteristics by AHRE duration. **A:** Number of AHRE episodes prior to at baseline. **B:** Time from last adequate AHRE to baseline by AHRE duration in months. **C:** Duration of the maximal AHRE at baseline (longest single episode) in minutes and days. All three panels depict AHRE <24 hours in orange, and AHRE ≥24 hours in blue. The apparent peak at four days (99 hours) AHRE duration is due to the fact that some manufacturers only store precise AHRE durations up to 99 hours, while other manufacturers and devices precisely capture AHRE durations up to 9999 hours. All graphs show separate distributions for each randomized group in the 2389 patients with adequate AHRE. There were no differences between randomized groups.

Figure 3. Cumulative incidence curves of the primary outcome and secondary outcomes incidence curves considering death competing event (Aalen Johansen curve).

3 A: Primary outcome, a composite of stroke, systemic embolism and cardiovascular death

3B: All-cause death and major bleeding.

3C: Ischemic stroke

3D: Ischemic stroke or systemic embolism

Figure 4. Cumulative incidence curve from baseline to ECG-diagnosed atrial fibrillation considering death as competing event (Aalen Johansen curve) ($p<0.001$). Survival curves are shown for patients with long AHRE ≥24 hours (blue) and shorter AHRE (orange) split by randomized group.

Table 1. Demographic variable, clinical parameters, and AHRE characteristics at baseline by maximal AHRE duration <24 hours and ≥24 hours and by randomized treatment group.

	AHRE duration at baseline <24 hours		AHRE duration at baseline ≥24 hours		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/1.73m^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 bpm 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 AHRE episodes at baseline [bpm]					
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)
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%)

AHRE, atrial high-rate episode; bpm, beats per minutes; CKD-EPI, chronic kidney disease–epidemiology collaboration equation; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; TIA, transient ischemic attack

[a] clinically overt or LVEF < 45%.

[b] chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mmHg

The HASBLED 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.

Table 2: Efficacy and safety outcomes for the primary and secondary outcomes by AHRE duration <24 hours and ≥24 hours and by randomized treatment group.

	AHRE duration at baseline <24 hours			AHRE duration at baseline ≥24 hours			p-value interaction
	Edoxaban	Placebo	Edoxaban vs. Placebo	Edoxaban	Placebo	Edoxaban vs. Placebo	
	no. of patients with event/patient-yr. (% per patient-yr)		Adjusted HR (95% CI)	no. of patients with event/patient-yr. (% per patient-yr)		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)	0.65
Secondary efficacy outcomes							
Ischemic 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)	0.89
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)	0.51
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)	0.58
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)	0.89
Ischemic 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)	0.71
Ischemic stroke or systemic arterial	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)	0.45

embolism (post hoc definition*)							
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)	0.96
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)	0.97
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 = 0.04

§§ p=0.003

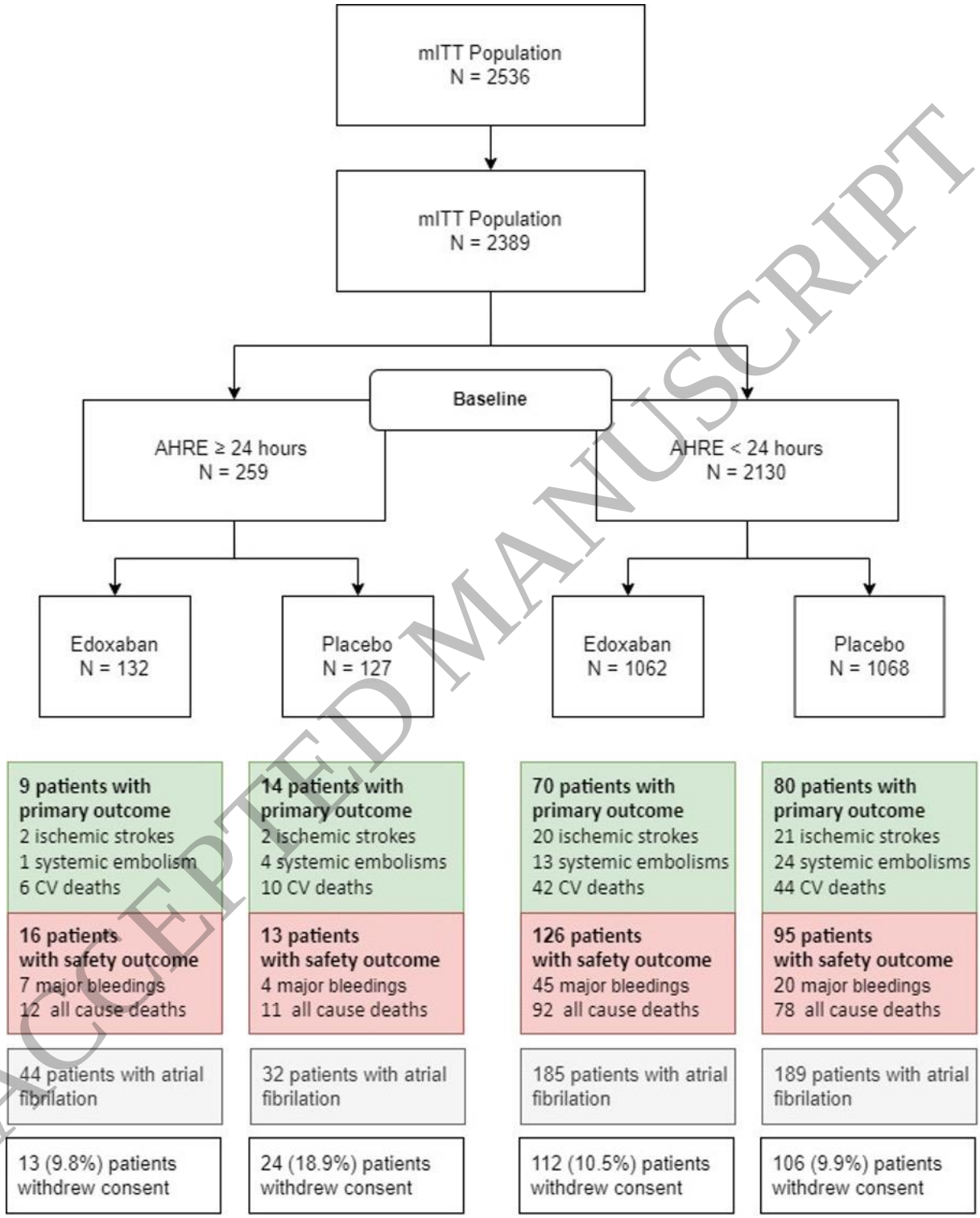

Figure 1
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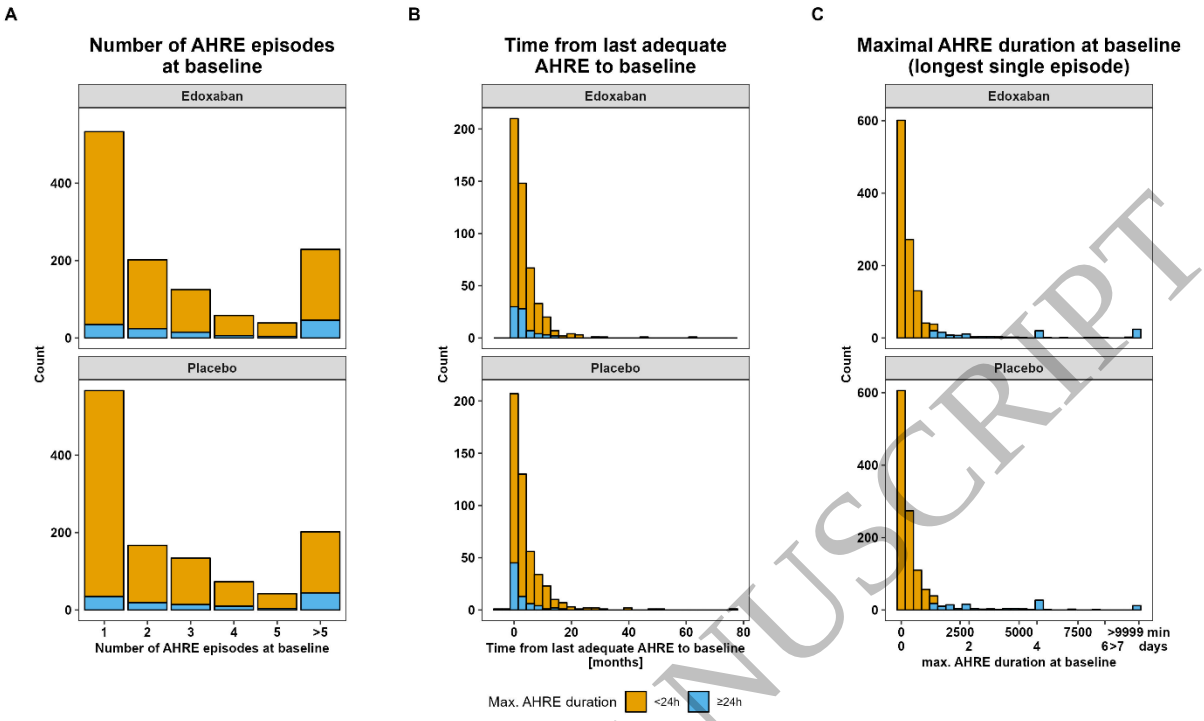

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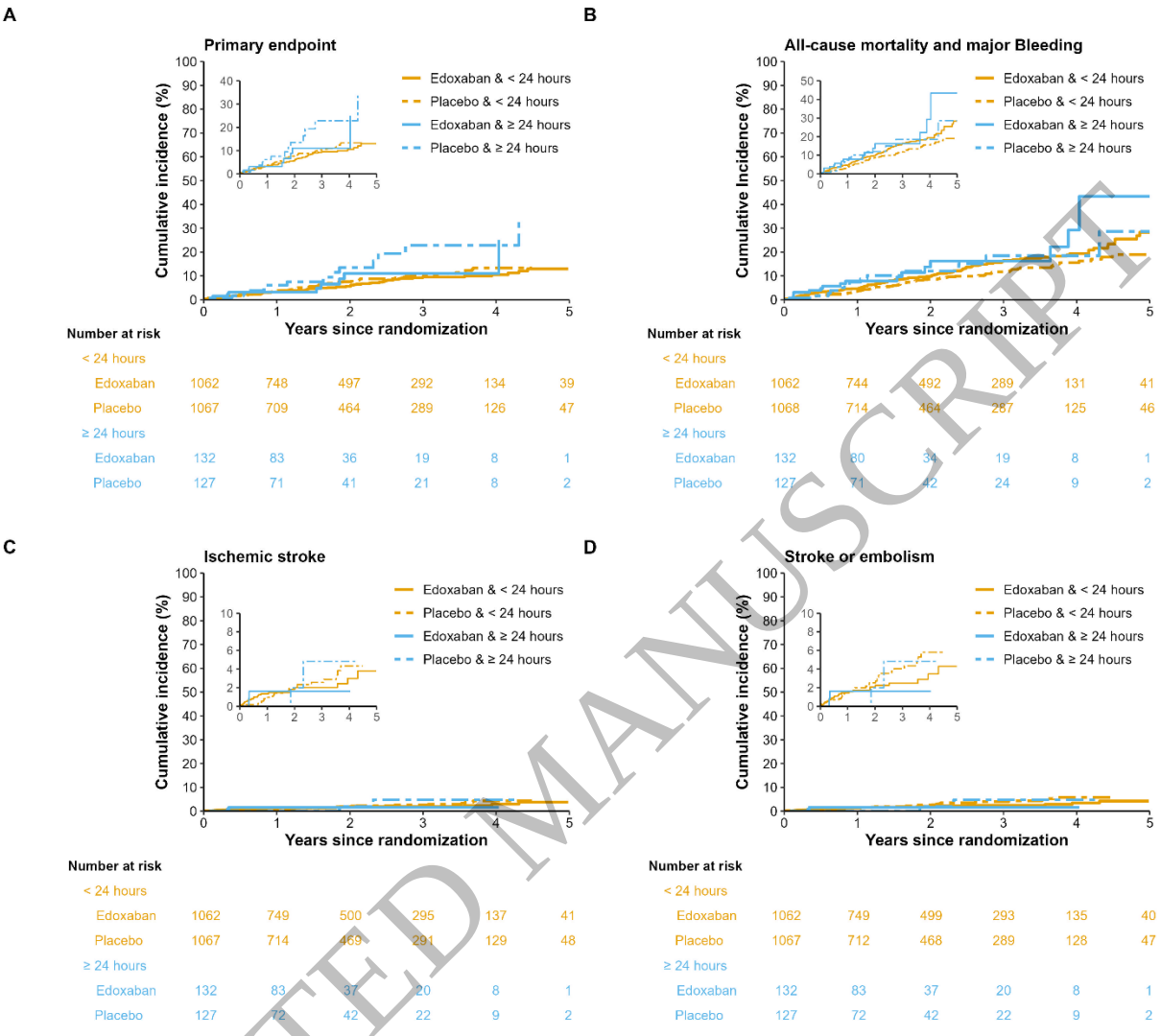

Figure 3

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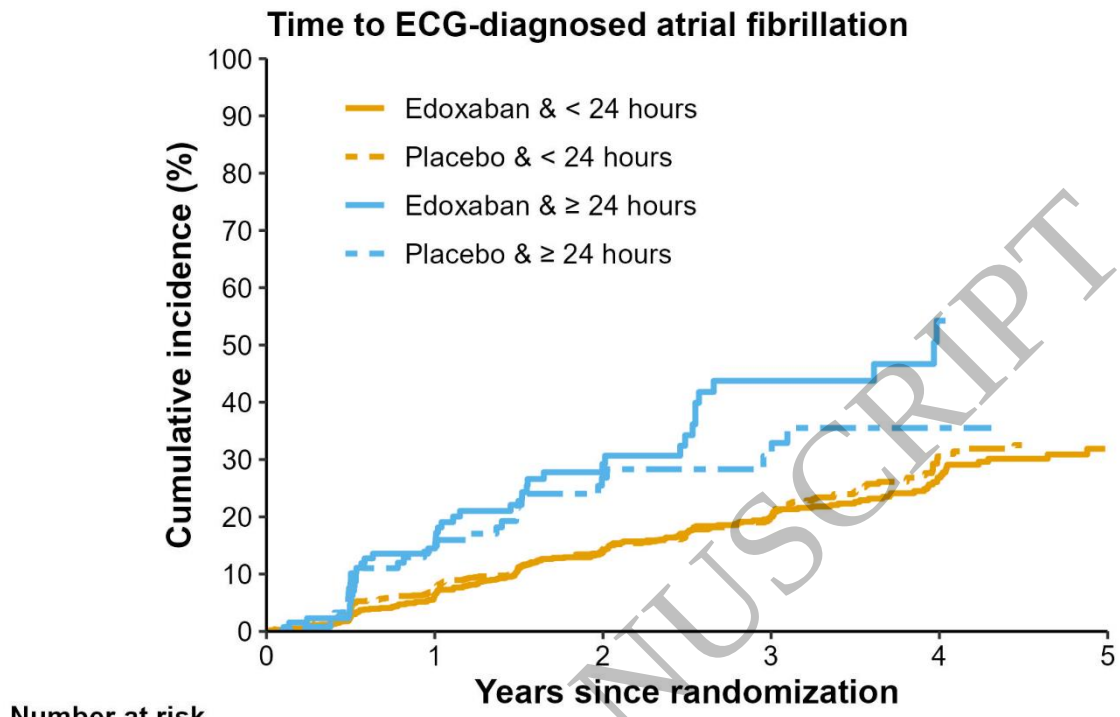

Number at risk

< 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
160x160 mm (x DPI)

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