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# Anticoagulation with edoxaban in patients with long Atrial High-Rate Episodes $\geq 24$ hours

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32 **Short Title:** Oral Anticoagulation in patients with AHRE $\geq$ 24 hrs

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5  
6  
7 **Abstract**

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

11 **Methods.** This secondary prespecified analysis of NOAH-AFNET 6 examined interactions  
12 between AHRE duration at baseline and anticoagulation with edoxaban compared to placebo in  
13 patients with AHRE and stroke risk factors. The primary efficacy outcome was a composite of  
14 stroke, systemic embolism, or cardiovascular death. The safety outcome was a composite of major  
15 bleeding and death. Key secondary outcomes were components of these outcomes and ECG-  
16 diagnosed atrial fibrillation.

17 **Results.** AHRE  $\geq 24$  hours were present at baseline in 259/2389 patients enrolled in NOAH-  
18 AFNET 6 (11%,  $78 \pm 7$  years old, 28% women, CHA<sub>2</sub>DS<sub>2</sub>-VASc score 4). Clinical characteristics  
19 were not different from patients with shorter AHRE. During a median follow-up of 1.8 years, the  
20 primary outcome occurred in 9/132 patients with AHRE  $\geq 24$  hours (4.3%/patient-year, 2 strokes)  
21 treated with anticoagulation and in 14/127 patients treated with placebo (6.9%/patient-year, 2  
22 strokes). AHRE duration did not interact with the efficacy (p-interaction=0.65) or safety (p-  
23 interaction=0.98) of anticoagulation. Analyses including AHRE as a continuous parameter  
24 confirmed this. Patients with AHRE  $\geq 24$  hours developed more ECG-diagnosed atrial fibrillation  
25 (17.0%/patient-year) than patients with shorter AHRE (8.2%/patient-year; p < 0.001).

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

4  
5 **Keywords:** atrial high-rate episodes, stroke, atrial fibrillation, NOAH-AFNET 6  
6

ACCEPTED MANUSCRIPT

## Anticoagulation in patients with long Atrial High-Rate Episodes (AHRE) $\geq 24$ hours

A subanalysis of the Non-vitamin K antagonist Oral anticoagulation in patients with Atrial High rate episodes (NOAH-AFNET 6) trial

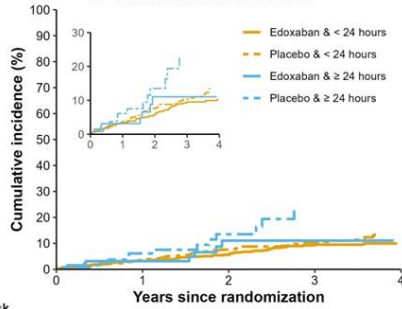


259/2389 patients with device-detected AHRE  $\geq 24$  hours  
(78 years old, 37% women, median CHA<sub>2</sub>DS<sub>2</sub>-VASc score 4)



AHRE reviewed by Corelab

### Incidence of Stroke, Systemic Embolism, or Cardiovascular Death



Number at risk

< 24 hours

Edoxaban

Placebo

$\geq 24$  hours

Edoxaban

Placebo

| Years since randomization | 0    | 1   | 2   | 3   | 4   |
|---------------------------|------|-----|-----|-----|-----|
| Edoxaban < 24 hours       | 1062 | 748 | 497 | 292 | 134 |
| Placebo < 24 hours        | 1067 | 709 | 464 | 289 | 126 |
| Edoxaban $\geq 24$ hours  | 132  | 83  | 36  | 19  | 8   |
| Placebo $\geq 24$ hours   | 127  | 71  | 41  | 21  | 8   |

### Ischemic Stroke Rate by AHRE Duration and Treatment\*

| AHRE < 24 hours<br>events/N (%/patient-years) |                |                   | AHRE $\geq 24$ hours<br>events/N (%/patient-years) |              |                   |
|---|----------------|-------------------|--|--------------|-------------------|
| Anticoagulation                               | Placebo        | HR (95% CI)       | Anticoagulation                                    | Placebo      | HR (95% CI)       |
| 20/1062 (0.90)                                | 21/1068 (0.96) | 0.92 (0.50, 1.70) | 2/132 (0.95)                                       | 2/127 (0.97) | 1.03 (0.14, 7.32) |

\*p-interaction=0.89

Long durations of device-detected AHRE, including durations  $\geq 24$  hours, did not interact with the treatment effect of anticoagulation in the NOAH-AFNET 6 trial.

Similarly, there was no interaction between the effect of anticoagulation therapy and AHRE duration used as a continuous variable.

Stroke rate appeared low (1%/patient-year) without oral anticoagulation.

Patients with AHRE  $\geq 24$  hours developed more ECG-diagnosed atrial fibrillation over time compared to those with shorter AHRE durations.

Graphical Abstract  
160x90 mm (x DPI)

1  
2  
3  
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1 **Key Question**

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

5 **Key Finding**

6 Baseline AHRE duration did not interact with the efficacy and safety of anticoagulation in the  
7 NOAH-AFNET 6 trial. Clinical characteristics were not different between patients with AHRE  
8  $\geq 24$  hours and those with shorter AHRE. Stroke rate appeared low across AHRE durations  
9 (approximately 1%/year).

10 **Take-Home-Message**

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

1 **Abbreviations**

2

|   |              |  |
|---|--------------|--|
| 3 | AF           | Atrial fibrillation  |
| 4 | AHRE         | Atrial high-rate episodes  |
| 5 | ECG          | Electrocardiogram  |
| 6 | IQR          | Interquartile range  |
| 7 | ISTH         | International Society on Thrombosis and Haemostasis                        |
| 8 | NOAH – AFNET | Non vitamin K antagonist Oral anticoagulants in patients with Atrial High- |
| 9 |              | rate episodes trial  |



## 1 **Introduction**

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

16           Recently, the double-blind, double dummy Non vitamin K antagonist Oral anticoagulants  
17 Atrial High rate episodes (NOAH-AFNET 6) trial found that oral anticoagulation with edoxaban  
18 does not reduce the composite outcome of stroke, systemic embolism, or cardiovascular death  
19 compared to no anticoagulation in elderly patients with AHRE and stroke risk factors<sup>7</sup>. The main  
20 effect of anticoagulation therapy was an increase in major bleeding. The low stroke rate observed  
21 without oral anticoagulation (approximately 1%/year) in an elderly population with multiple stroke  
22 risk factors (mean age 78 years, median CHA<sub>2</sub>DS<sub>2</sub>-VASc score 4) reduced the power of the trial to  
23 detect an effect of anticoagulation on stroke. Central analysis of all AHRE episodes in a core lab<sup>8</sup>  
24 enabled a granular sub-analysis of patients with very long AHRE episodes.

1

## 2 **Methods**

3 This is a secondary prespecified analysis of the NOAH-AFNET 6 trial data set<sup>7</sup>. We  
4 investigated the effects of AHRE duration at the time of randomization (termed at baseline), split  
5 into patients with maximal AHRE duration  $\geq 24$  hours and patients limited to episodes lasting from  
6 6 minutes to 23:59 hours (termed  $< 24$  hours). Patients were classified as AHRE  $\geq 24$  hours when at  
7 least one episode was longer than 24 hours at baseline. We also split patients by their median  
8 longest AHRE duration and investigated the interaction of baseline AHRE duration as a continuous  
9 variable. The interaction of these AHRE categories with the efficacy and safety of oral  
10 anticoagulation in patients randomized to anticoagulation or placebo was analyzed.

11

### 12 Trial Design and Population

13 Details of the design of the trial have been reported<sup>8</sup>. NOAH-AFNET 6 was approved by  
14 ethics board in all participating countries and institutions. All patients provided written informed  
15 consent prior to participation. In brief, 206 sites in 18 European countries randomized 2608 patients  
16 with AHRE, but without ECG-documented AF, aged  $\geq 65$  years and with at least one additional  
17 stroke risk factor to oral anticoagulation with edoxaban in the dose approved for stroke prevention  
18 in AF or to no anticoagulation (placebo). Patients randomized to no anticoagulation who had an  
19 accepted indication for aspirin received aspirin 100 mg/day with the study medication. Those  
20 without an indication for aspirin and all patients randomised to edoxaban took a dummy aspirin  
21 tablet. Each patient was seen to hand out study medication every six months. These visits included  
22 an ECG. Per protocol, all patients were switched from study medication to open-label  
23 anticoagulation upon ECG documentation of AF. The primary analysis population consisted of all  
24 2389 patients who were randomized, took at least one dose of study drug and had core-lab verified

1 information about maximum AHRE duration at baseline. All events were centrally adjudicated by  
2 an independent event review committee. All patients were followed up for outcomes until the end  
3 of the trial.

#### 4 5 Review of AHRE Episodes

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

#### 15 16 Primary and Secondary Outcomes

17 The primary efficacy outcome and safety outcome of this analysis are identical to the  
18 outcomes in the main trial<sup>7, 8</sup>. The primary efficacy outcome was a composite of stroke, systemic  
19 embolism and cardiovascular death. Secondary outcomes included stroke, systemic embolism, a  
20 composite of stroke and systemic embolism, and cardiovascular death, and a secondary post-hoc  
21 outcome consisting of a composite of ischemic stroke and systemic embolism, excluding  
22 pulmonary embolism and myocardial infarction. The primary safety outcome was a composite of  
23 major bleeding according to the ISTH definition and all-cause death<sup>8</sup>.

24

## 1 Statistical Analysis

2 Categorical data are summarized by numbers and percentages. Continuous data are  
3 summarized by mean and standard deviation or median with 1<sup>st</sup> and 3<sup>rd</sup> quartile (interquartile range,  
4 IQR) as appropriate. The primary analysis population consisted of all randomized patients  
5 receiving at least one dose of the study drug, i.e., a modified intention-to-treat population. For the  
6 primary time-to-event analyses, patients were censored when they developed ECG-documented  
7 AF, were unblinded, lost to follow-up, or withdrew consent. The primary efficacy outcome and the  
8 safety outcome were also analyzed for the safety population (all randomized patients), the per-  
9 protocol population, and a population that was not censored for AF-onset or unblinding. All  
10 Ukrainian patients were censored on 24<sup>th</sup> February 2022, the day of the Russian invasion.  
11 Sensitivity analyses including these patients were conducted.

12 Baseline characteristics were compared between patients with maximal AHRE duration at  
13 baseline <24 hours and  $\geq$ 24 hours using chi-squared test for categorical data, *t*-test for non-skewed  
14 continuous data, and Mann-Whitney U test for skewed continuous data.

15 A cause-specific Cox-proportional hazards model using the Breslow method to handle tied  
16 failures was conducted, with frailty for centers and the fixed effects random group, the  
17 randomization strata indication for acetylsalicylic acid, maximum AHRE duration, and the  
18 interaction between the random group and maximum AHRE duration under the assumption of  
19 independent censoring. Maximum AHRE duration was included as a continuous variable on a  
20 natural logarithmic scale. In a further model maximum AHRE duration was considered as a  
21 categorical variable (categories <24 hours and  $\geq$ 24 hours and categories by median). The outcome  
22 results are reported as group-specific event rates in percent per patient-year and as adjusted  
23 estimated cause-specific hazard ratio with a two-sided 95% confidence interval and corresponding  
24 p-value. Cumulative incidence curves are shown using Aalen-Johansen estimates that take

1 competing events into account, otherwise, Kaplan-Meier curves are used. The proportional hazard  
2 assumption was checked graphically via Schoenfeld residuals and the linearity assumption for  
3 continuous predictors via martingale residuals.

4 The interaction between maximal AHRE duration and CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $\leq 4$  and  $>4$ )  
5 was also considered in a model for the primary outcome. The effect of maximal AHRE duration at  
6 baseline on time to AF-onset was analysed in a model without inclusion of the random group and  
7 without censoring for unblinding or withdrawal of consent.

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

11 Sample size calculation for the primary study can be found in the recently published main  
12 paper<sup>7</sup>. All analyses were conducted using R (version 4.2.3).

## 14 **Results**

### 15 Demographics and Clinical Characteristics

16 Demographics, clinical characteristics and comorbidities did not differ between AHRE  
17 duration and treatment groups (**Figure 1, Table 1 and Supplementary Table S1**) with three  
18 exceptions: patients with AHRE  $\geq 24$  hours were more likely to be men and had a slightly higher  
19 body mass index and lower estimated glomerular filtration rate.

### 21 AHRE Characteristics

22 Adequate baseline AHRE recordings were confirmed by the core lab in 2389/2536 patients  
23 (94.2%). Maximal AHRE durations  $\geq 24$  hours at baseline were found in 259/2389 patients (11%,  
24 **Table 1**). In patients with AHRE  $\geq 24$  hours, the median duration of the longest AHRE was 53.1

1 hours (IQR 32.3, 96.0), whilst in patients with AHRE <24 hours the median longest AHRE duration  
2 was 2.2 hours (IQR 0.64, 5.9). At baseline, patients with AHRE  $\geq$ 24 hours had a higher median  
3 number of AHRE than patients with shorter AHRE duration (AHRE  $\geq$ 24 hours: 9 (IQR 2, 27);  
4 AHRE <24 hours: 4 (IQR 1, 14);  $p < 0.001$ , **Figure 2, Table 1, Supplementary Table S1**). The  
5 distribution of maximal AHRE duration at baseline (longest single episode) are shown in **Figure**  
6 **2A** and **Figure 2B**. The median time between last AHRE to the baseline visit was 60 days (IQR  
7 22,149) in the total population. That duration was shorter in patients with AHRE  $\geq$ 24 hours (43  
8 days, IQR 12.0, 108) than in patients with shorter AHRE (65 days, IQR 23, 157,  $p = 0.002$ , **Table 1**  
9 and **Supplementary Table S1, Figure 2B**).

#### 11 Primary Efficacy Outcome

12 Cumulative incidence curves of the primary efficacy outcome (composite of stroke,  
13 systemic embolism, or death from cardiovascular causes) are shown in **Figure 3A** and **Graphical**  
14 **Abstract** by treatment group in patients with AHRE  $\geq$ 24 hours and patients with shorter AHRE  
15 durations. There was no interaction between randomized treatment and AHRE duration ( $p$ -  
16 interaction=0.65). The point estimates of the event rates were not identical. In patients with AHRE  
17 duration  $\geq$ 24 hours, the primary outcome occurred in 9/132 (6.8%) patients with anticoagulation  
18 (4.3%/patient-year) and 14/127 (11%) patients with placebo (6.9%/patient-year, AHRE  $\geq$ 24 hours  
19 edoxaban vs. placebo adjusted HR 0.86, 95% CI 0.62-1.19). The primary efficacy outcome  
20 occurred in 70/1062 patients with AHRE <24 hours with anticoagulation (3.2%/patient-year) and  
21 in 80/1068 patients with placebo (3.7%/patient-year, AHRE <24 hours edoxaban vs. placebo  
22 adjusted HR 0.66, 95% CI 0.28-1.53; **Figure 3A** and **Table 2**).

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

1 duration was categorized by median duration ( $\leq 2.82$  hours and  $> 2.82$  hours,  $p$ -interaction=0.4,  
2 **Supplementary Table S2 und Figure S1**).

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

### 7 8 Safety Outcome

9 AHRE  $\geq 24$  hours did not interact with the safety outcome, a composite of bleeding and  
10 death. The point estimates for the primary safety outcomes were almost identical in patients with  
11 AHRE  $\geq 24$  hours compared to patients with shorter AHRE (AHRE  $\geq 24$  hours HR 1.30, 95% CI  
12 0.62-2.71; AHRE  $< 24$  hours HR 1.32, 95% CI 1.01-1.73,  $p$ -interaction=0.96, **Table 2 and Figure**  
13 **3D**). Splitting AHRE duration by its median or including AHRE duration as a continuous parameter  
14 did not identify an interaction between anticoagulation therapy and AHRE duration for the safety  
15 outcome either ( $p$ -interaction=0.65 for split by median AHRE duration;  $p$ -interaction=0.88 for  
16 AHRE as continuous variable).

### 17 18 Secondary Outcomes

19 Ischemic stroke occurred in 2/132 patients with AHRE  $\geq 24$  hours randomized to  
20 anticoagulation (0.95%/patient-year) and in 2/127 patients with AHRE  $\geq 24$  hours randomized to  
21 placebo (0.97%/patient-year, AHRE  $\geq 24$  hours edoxaban vs. placebo adjusted HR 1.03, 95% CI  
22 0.14, 7.32). In patients with AHRE  $< 24$  hours, ischemic stroke occurred in 20/1062 patients  
23 randomized to anticoagulation (0.90%/patient-year) and 21/1068 patients randomized to placebo  
24 (0.96%/patient-year) (AHRE  $< 24$  hours edoxaban vs. placebo HR 0.92, 95% CI 0.50-1.70, **Table**

1 **2, Figure 3B and Graphical Abstract**). There was no interaction between AHRE duration and  
2 randomized treatment for the outcome ischemic stroke (p-interaction=0.89).

3 The post-hoc outcome combining ischemic stroke and systemic embolism excluding  
4 pulmonary embolism and myocardial infarction in patients with AHRE  $\geq 24$  hours occurred in  
5 8/132 patients (3.8%/patient-year) randomized to anticoagulation and 13/127 patients randomized  
6 to placebo (6.4%/patient-year, HR 0.63 (0.26, 1.52)). In patients with shorter AHRE durations, this  
7 outcome occurred in 60/1062 patients with anticoagulation (2.7%/patient-year) and 61/1068  
8 patients with placebo (2.8%/patient-year, HR 0.97 (0.68, 1.38); p-interaction=0.45). No  
9 hemorrhagic stroke occurred in either group. Similar results were observed for the secondary  
10 outcomes and the post-hoc outcomes using AHRE duration as a continuous variable or as a  
11 categorical variable by median AHRE duration ( $\leq 2.82$  hours and  $> 2.82$  hours) (**Supplementary**  
12 **Table S2 and Figure S2**).

13 Adjusted multiple regression analysis, 3-way interaction analysis for the CHA<sub>2</sub>DS<sub>2</sub>-VASC  
14 score ( $\leq 4$  and  $> 4$ ), and for the AHRE duration  $\geq 24$  hours and  $< 24$  hours showed no differences  
15 between treatment groups (**Supplementary Figure S3**).

#### 17 Time from AHRE to ECG-diagnosed AF

18 Patients with AHRE  $\geq 24$  hours at baseline developed more ECG-diagnosed AF (76/259  
19 (29.3%)) than patients with shorter AHRE durations (374/2130 (17.6%)), **Figure 4**), also reflected  
20 by a higher incidence of ECG-diagnosed AF during follow-up (17.0%/patients-year) than patients  
21 with shorter AHRE (8.2%/patient-year, HR 2.20; 95% CI 1.71-2.84, p<0.001). Consequently, the  
22 median follow-up time on active study medication was shorter in patients with AHRE  $\geq 24$  hours  
23 (1.5 years, IQR 0.6, 2.5) than in patients with AHRE  $< 24$  hours (1.9 years, IQR 0.9, 3.3).

24



## 1 **Discussion**

### 2 **Main Findings**

3 This secondary prespecified analysis of the NOAH-AFNET 6 trial based on standardized,  
4 core-lab analysis of all qualifying AHRE episodes at baseline identified the following: (i) long  
5 durations of device-detected AHRE, including durations  $\geq 24$  hours, did not interact with the  
6 treatment effect of anticoagulation in the NOAH-AFNET 6 trial; (ii) similarly, there was no  
7 interaction between the effect of anticoagulation therapy and AHRE duration used as a continuous  
8 variable; (iii) stroke rate appeared low (1%/patient-year) without oral anticoagulation in patients  
9 with AHRE  $\geq 24$  hours and in the overall population of patients with AHRE despite multiple clinical  
10 stroke risk factors (median CHA<sub>2</sub>DS<sub>2</sub>-VASc= 4); and (iv) patients with AHRE  $\geq 24$  hours  
11 developed more ECG-diagnosed AF over time compared to those with shorter AHRE durations.

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

### 16 17 **Which factors could explain the low rate of stroke and thrombotic events without** 18 **anticoagulation in patients with long AHRE in NOAH-AFNET 6?**

19 Patients with device-detected AHRE have a higher stroke risk than patients without AHRE,  
20 although the stroke risk appears lower compared to patients with ECG-diagnosed AF<sup>1</sup>. This  
21 prespecified secondary analysis of the NOAH-AFNET 6 trial did not find that AHRE duration  
22 interacts with the efficacy and safety of oral anticoagulation in a large, randomized, double-blind  
23 trial (**Graphical abstract**). Unexpectedly, the stroke rate appeared low in patients across AHRE  
24 durations, including in patients with AHRE  $\geq 24$  hours not receiving anticoagulation (1%/year).

1 The observed stroke rate in patients with long AHRE durations is comparable to the stroke rate in  
2 large routine care databases of patients with AHRE and stroke risk factors<sup>9, 10</sup>.

3 Small observational data sets, including a subgroup analysis of the ASSERT trial with  
4 similar demographic and clinical characteristics compared to this data set (ASSERT: age 77.2  
5 years, CHA<sub>2</sub>DS<sub>2</sub>-VASc score 4), suggested a higher rate of stroke<sup>4, 5</sup>. Patients randomized in  
6 NOAH-AFNET 6 had an ECG recorded every six months and received anticoagulation upon ECG  
7 documentation of AF, in accordance with current guidelines on the initiation of anticoagulation in  
8 patients with ECG-documented AF<sup>11</sup>. In patients with AHRE  $\geq 24$  hours, these ECGs found AF in  
9 17%/year, and in 29% of the patients during the duration of the trial. It is unclear how many patients  
10 received anticoagulation after ECG documentation of AF in ASSERT<sup>5</sup>. Timely detection of ECG-  
11 documented AF and initiation of open-label anticoagulation is a likely contributor to the lower rate  
12 of stroke in NOAH-AFNET 6. There was a numerical signal for more ischemic events in patients  
13 with AHRE  $\geq 24$  hours, and the point estimates for thrombotic events were higher in patients with  
14 long AHRE randomized to no anticoagulation compared to patients with long AHRE randomized  
15 to anticoagulation. Within the limitations of this analysis, our results do not identify an interaction  
16 between AHRE duration and the efficacy and safety of oral anticoagulation in patients with AHRE  
17 and stroke risk factors.

### 18 19 **What Differentiates AHRE from ECG-diagnosed Atrial Fibrillation?**

20 The overwhelming majority of AHRE recorded in NOAH-AFNET 6 show features  
21 consistent with AF during episodes, including a high atrial rate ( $>200$  bpm) and irregular RR  
22 intervals. NOAH-AFNET 6 enrolled patients without an upper limit for AHRE duration and  
23 therefore included patients with very long AHRE. Despite several approaches to analysing AHRE  
24 duration at baseline, including a cut-off of  $\geq 24$  hours, a split by median duration, and integrating

1 AHRE duration as a continuous parameter, no subgroup of patients was identified that had a  
2 substantially higher stroke risk than the overall population. The main finding in the overall trial, a  
3 low rate of stroke, extends to the population with long AHRE durations in this analysis. Overall,  
4 this hypothesis-generating analysis suggests that the arrhythmia burden in patients with AHRE may  
5 be too low to create a stroke risk that is comparable to the stroke risk in paroxysmal atrial  
6 fibrillation<sup>12-16</sup>. The neutral outcome of the intervention tested in the LOOP study, initiation of oral  
7 anticoagulation upon AHRE detection by an implanted loop recorder, may support the concept that  
8 device-detected AHRE are only associated with a relatively small increase in stroke risk. In LOOP,  
9 the overall arrhythmia burden was low (mean estimate 0.13%<sup>17, 18</sup>). The arrhythmia burden in a  
10 patient with ECG-diagnosed AF not undergoing rhythm control is likely to be higher (estimated at  
11 11%<sup>19</sup>). Early rhythm control therapy reduced cardiovascular events in the EAST-AFNET 4 trial<sup>20</sup>.  
12 This outcome-reducing effect was mediated by attaining sinus rhythm<sup>21</sup>. In view of the low AF  
13 burden on rhythm control therapy (0.2% AF burden after AF ablation, 2% AF burden on  
14 antiarrhythmic drugs)<sup>22</sup>, a lower arrhythmia burden on rhythm control therapy is a likely driver of  
15 reduced outcomes with early rhythm control. Further research on the interaction of stroke risk and  
16 arrhythmia burden is needed. Such research would become much easier if reliable methods for  
17 atrial arrhythmia quantification and a uniform definition of atrial arrhythmia burden across devices  
18 were available<sup>23</sup>. In the view of the authors, a higher arrhythmia burden is a likely contributor to  
19 the higher rate of stroke between the population studied here and patients with paroxysmal AF  
20 enrolled in anticoagulation trials<sup>14</sup>.

21

## 22 **Arrhythmia Detection by Wearable Electronic Devices**

23 The detection rate of atrial arrhythmias resembling AF by wearables<sup>24, 25</sup> is lower than the  
24 AHRE rate detected by implanted devices<sup>1, 24, 26</sup>. This is probably due to at least three factors, first

1 the younger age and lower comorbidity burden in the populations studied using wearables, second  
2 the shorter monitoring duration limited to the time during which the devices are worn, and third  
3 the incomplete detection of arrhythmias by algorithms and systems used in wearable electronics.  
4 Given the low stroke rate in patients with long AHRE durations found here (1%/year), there is a  
5 need for randomized trials comparing oral anticoagulation to no anticoagulation in patients with  
6 rare atrial arrhythmia episodes. The design of such trials can be improved by including methods to  
7 detect patients with rare atrial arrhythmias who are at a high risk of stroke. In addition to clinical  
8 stroke risk factors, quantitative proxies for stroke risk obtained from imaging or from circulating  
9 biomolecules<sup>27, 28</sup> may be helpful to identify patients with AHRE at high risk of stroke.

#### 11 Limitations

12 This analysis is not sufficient to rule out interaction effects between anticoagulation and  
13 AHRE duration on thromboembolic events. The findings were consistent whether analysing AHRE  
14 duration categorically split by 24 hour episode duration, by median, or as a continuous variable.  
15 The findings need validation in independent and larger cohorts. An individual patient-meta-  
16 analysis of the data collected in NOAH-AFNET 6 and ARTESiA<sup>29</sup> can help to identify subgroups  
17 of patients at high risk of stroke. Due to the exclusion of patients with AHRE  $\geq 24$  hours in  
18 ARTESiA, such an effort will not generate more data in patients with very long AHRE durations.  
19 Most of the analyses presented here were prespecified in the analysis plan, but some of the outcome  
20 definitions were defined post-hoc. This analysis found a numerically higher event rate in patients  
21 with long AHRE randomized to no anticoagulation. This illustrates the need for adequately  
22 powered randomized trials of anticoagulation therapy in patients with long device-detected atrial  
23 arrhythmias. NOAH-AFNET 6 only tested anticoagulation with edoxaban. Efficacy and safety of  
24 anticoagulation with other anticoagulants can only be inferred. NOAH-AFNET 6 was conducted

1 in Europe, and most patients had access to evidence-based management of cardiovascular  
2 conditions to reduce stroke risk, including blood pressure control, treatment of dyslipidemias and  
3 diabetes, and heart failure therapy. Furthermore, an ECG every six months was used to detect AF,  
4 triggering treatment with open-label anticoagulation. This may have contributed to the low event  
5 rates. Effects in other ethnicities and effects of other anticoagulants can only be deduced from the  
6 present data. Furthermore, the enrolment bias inherent in randomized trials may have affected event  
7 rates. All devices captured AHRE characteristics, but the methods to quantify the total duration of  
8 AHRE and to estimate the monitored time differ between devices and manufactures. Therefore,  
9 quantification of the arrhythmia burden at baseline, a candidate predictor of stroke risk<sup>30, 31</sup>, was  
10 not possible in this analysis. Further analyses may enable quantification of the effect of baseline  
11 arrhythmia burden on the efficacy and safety of oral anticoagulation.

## 13 **Conclusions**

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

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7

ACCEPTED MANUSCRIPT

## 1 **Figure Legends**

2

### 3 **Graphical Abstract. Anticoagulation with edoxaban in patients with long AHRE $\geq 24$ hours.**

4 AHRE, atrial high-rate episodes; CI, confidence interval; ECG, electrocardiogram; HR, hazard  
5 ratio

6

7 **Figure 1: CONSORT flow chart of this secondary prespecified subanalysis.** Shown is the  
8 analysis population, the number of patients with a primary efficacy outcome, the number of patients  
9 with a safety outcome, and the number of patients who developed ECG-diagnosed atrial fibrillation  
10 in each group.

11

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

21

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

24 **3 A:** Primary outcome, a composite of stroke, systemic embolism and cardiovascular death

1 **3B:** All-cause death and major bleeding.

2 **3C:** Ischemic stroke

3 **3D:** Ischemic stroke or systemic embolism

4

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

9

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1 **Table 1.** Demographic variable, clinical parameters, and AHRE characteristics at baseline by maximal AHRE duration <24 hours and  
 2 ≥24 hours and by randomized treatment group.

|  | AHRE duration at baseline <24 hours |                   | AHRE duration at baseline ≥24 hours |                   | Total<br>(N=2389) |
|--|-------------------------------------|-------------------|-------------------------------------|-------------------|-------------------|
|  | Edoxaban (N=1062)                   | Placebo (N=1068)  | Edoxaban (N=132)                    | Placebo (N=127)   |                   |
| <b>Demographics</b>  |                                     |                   |                                     |                   |                   |
| 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%)         |
| <b>Clinical</b>  |                                     |                   |                                     |                   |                   |
| BMI [kg/m <sup>2</sup> ], 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 <sub>2</sub> DS <sub>2</sub> -VAsC-score, median (IQR) | 4 (3, 5)                            | 4 (3, 5)          | 4 (3, 5)                            | 4.0 (3, 5)        | 4 (3, 5)          |
| CHA <sub>2</sub> DS <sub>2</sub> -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)          |
| <b>Comorbidities</b>                                       |                                     |                   |                                     |                   |                   |
| Heart failure <sup>a</sup> , N (%)                         | 292 (28%)                           | 283 (27%)         | 45 (34%)                            | 32 (25%)          | 652 (27%)         |
| Hypertension <sup>b</sup> , 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)<br>[ml/min/1.73m <sup>2</sup> ]                          | 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<br>and ≥ 6 min duration)                    | 1023 (96%)           | 1037 (97%)           | 128 (97%)            | 123 (97%)            | 2311 (97%)           |
| Number of total AHRE at<br>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<br>at baseline [h], median<br>(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<br>AHRE to baseline in [days],<br>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%)        |

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

3 <sup>a</sup> clinically overt or LVEF < 45%.

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

1 The HASBLED score was modified for this analysis of a population exposed to NOAC. The point for labile INR values was not considered.  
2 Information about major bleeding was limited to the assessment available at the baseline visit of the trial. All patients were considered suitable for  
3 NOAC therapy by the site investigators.

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1 **Table 2:** Efficacy and safety outcomes for the primary and secondary outcomes by AHRE duration <24 hours and ≥24 hours and by  
 2 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 <sup>§</sup>         | 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<br>(5.72) | 95/2165.7<br>(4.39) | 1.32<br>(1.01, 1.73) <sup>§</sup>  | 16/204.4<br>(7.83) | 13/206.1<br>(6.31) | 1.30<br>(0.62, 2.71) | 0.96 |
| All cause death                    | 92/2255.4<br>(4.08)  | 78/2193.6<br>(3.56) | 1.16<br>(0.85, 1.57)               | 12/211.0<br>(5.69) | 11/209.4<br>(5.25) | 1.15<br>(0.50, 2.61) | 0.97 |
| Major bleeding                     | 45/2201.0<br>(2.04)  | 20/2165.7<br>(0.92) | 2.22<br>(1.31, 3.76) <sup>§§</sup> | 7/204.4<br>(3.43)  | 4/206.1<br>(1.94)  | 1.78<br>(0.52, 6.12) | 0.69 |

1 § p = 0.04

2 §§ p=0.003

3

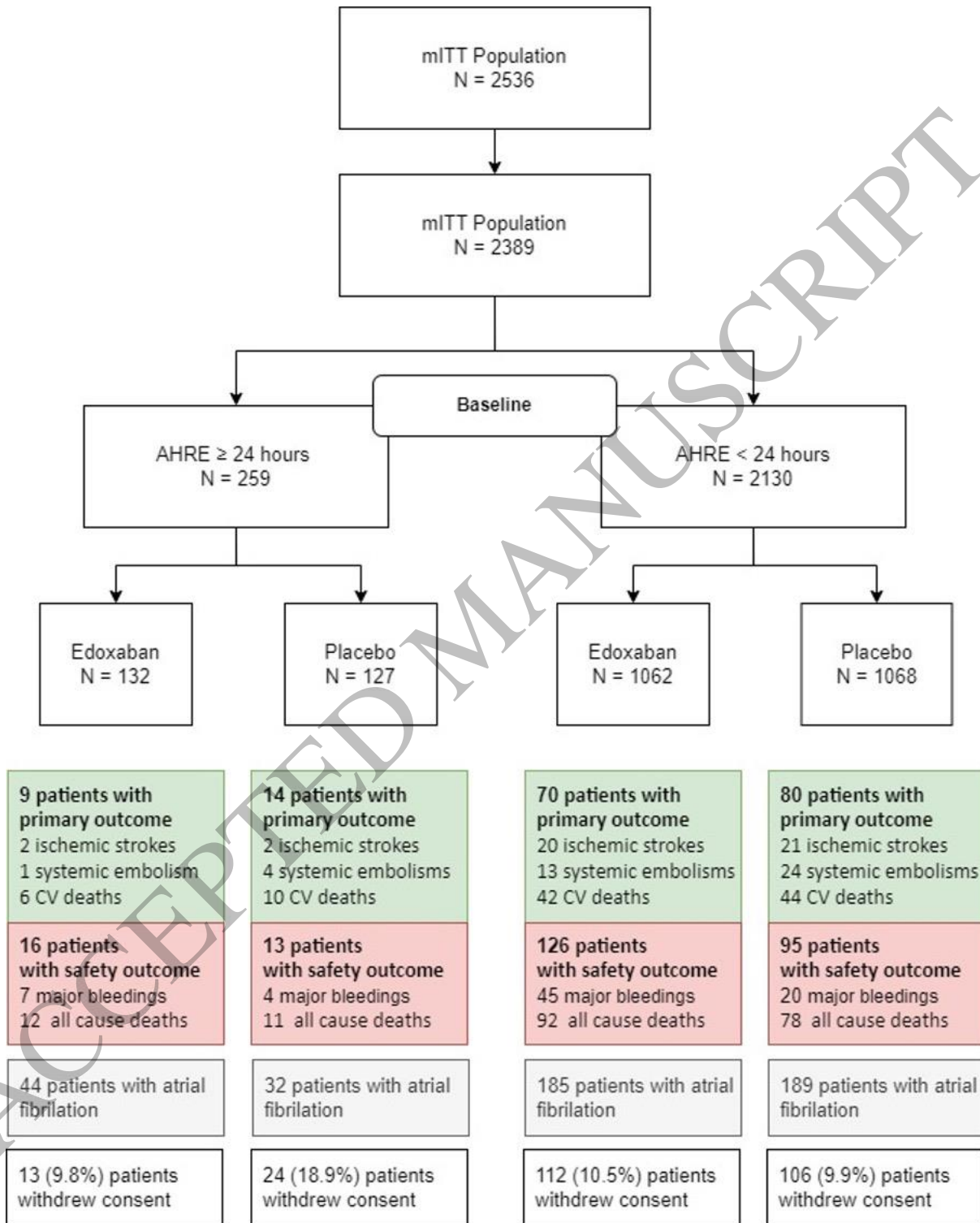


Figure 1  
160x199 mm ( x DPI)

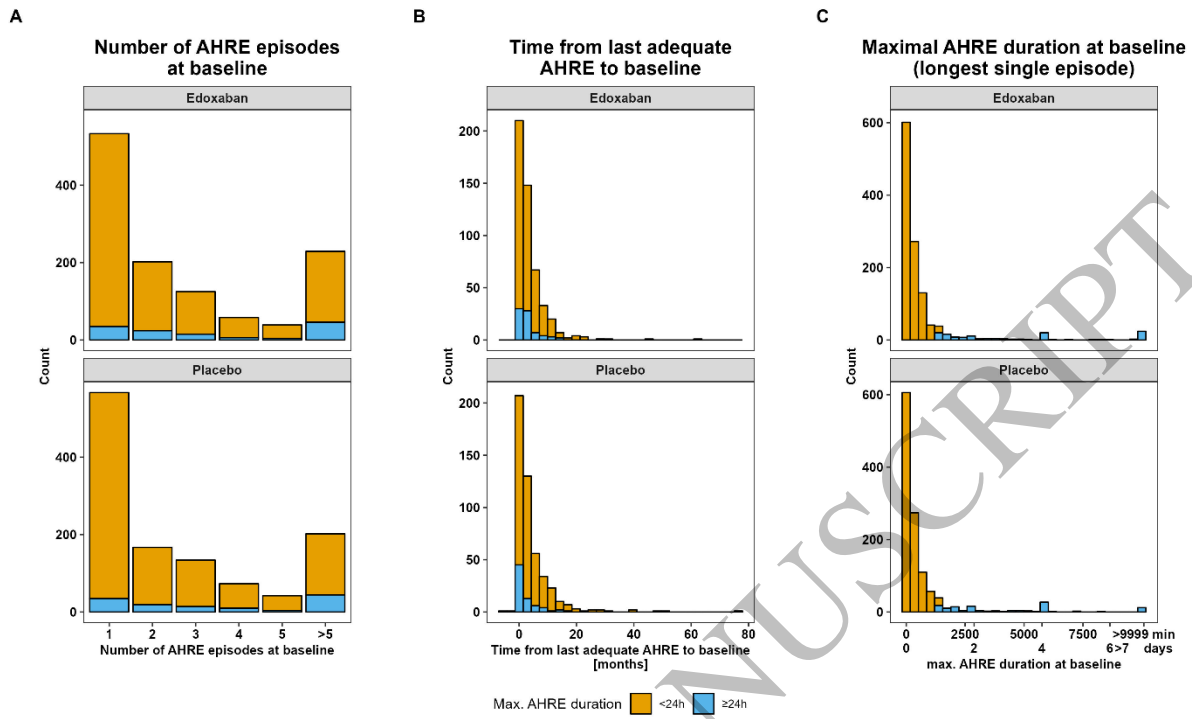


Figure 2  
160x98 mm (x DPI)

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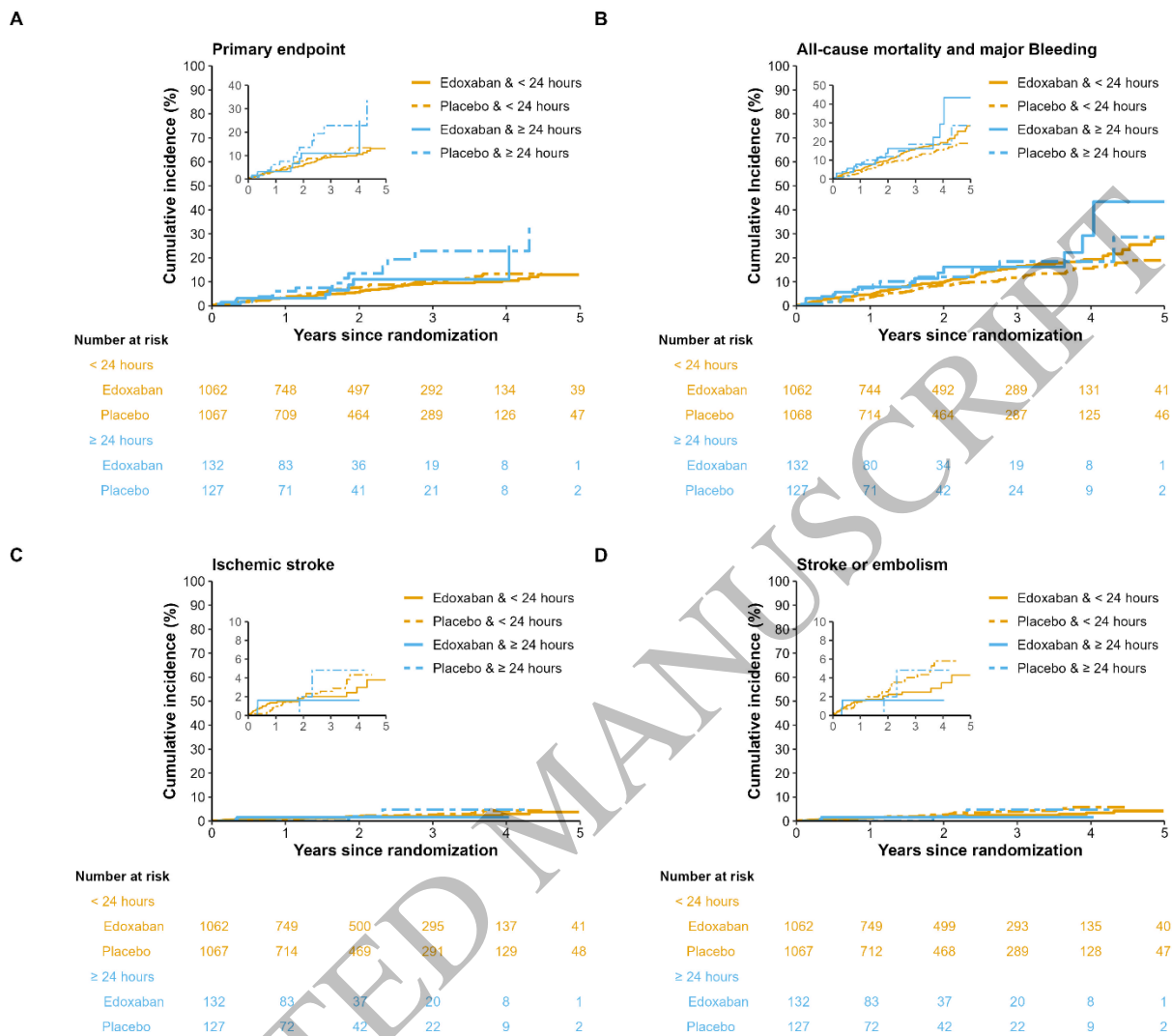
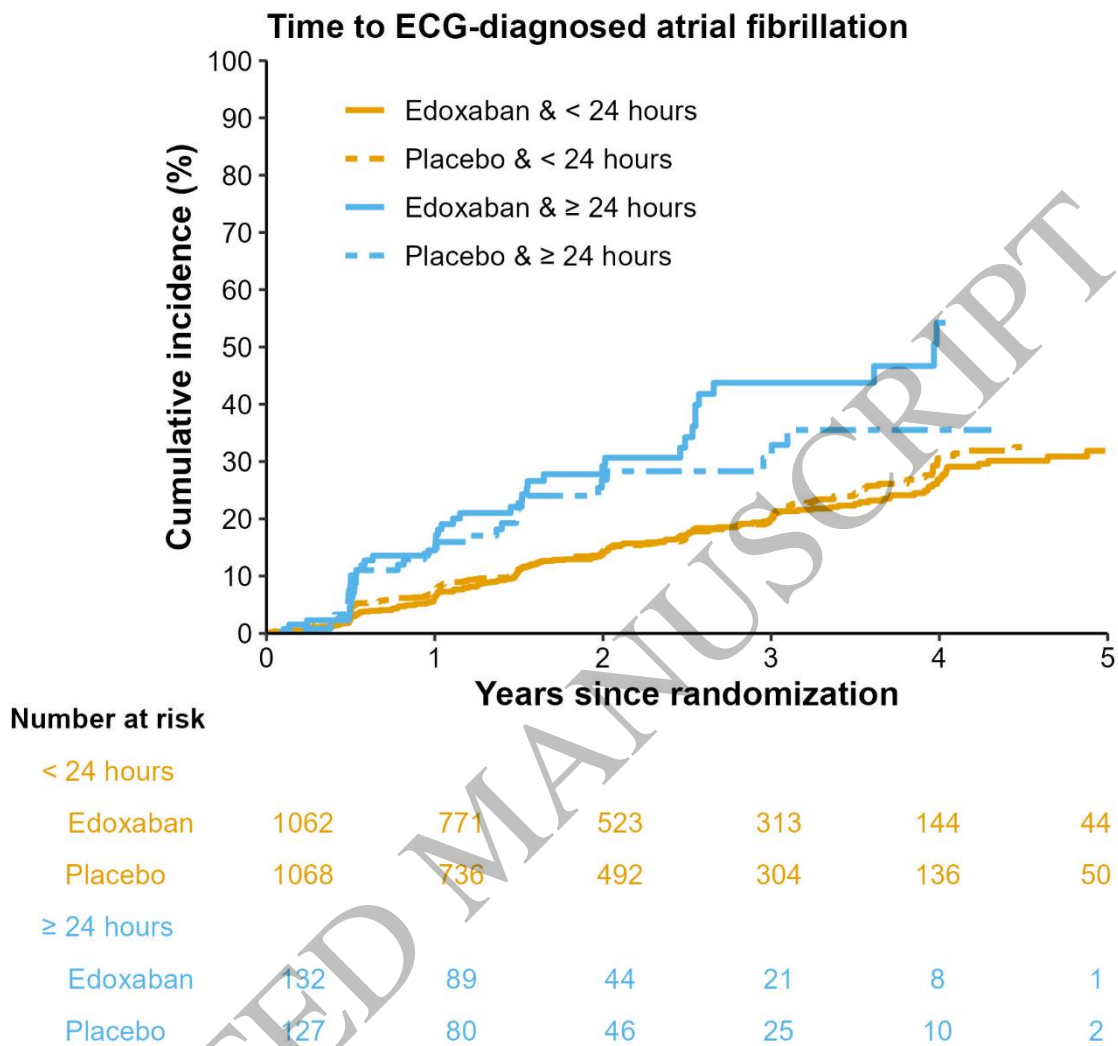


Figure 3  
160x147 mm ( x DPI)

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*Figure 4*  
160x160 mm ( x DPI)

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**Permission information file**

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