Data Supplement to
Anticoagulation with edoxaban in patients with long Atrial High-Rate Episodes ≥24 hours

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Short Title: Anticoagulation in patients with AHRE≥24 hrs

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Data Supplement to
Efficacy and safety of anticoagulation with edoxaban in patients with Atrial High-Rate Episodes ≥24 hours. The NOAH-AFNET 6 trial.

Table S1. Demographic, clinical, and AHRE characteristics at baseline by AHRE duration

	AHRE duration <24 hours (N=2130)	**AHRE duration ≥24 hours (N=259)**	**p-value**
Demographics			
Age, mean ± SD	78 ± 6.6	78 ± 7.1	0.99
Age ≥ 75 years, N	1443 (68%)	169 (65.3%)	0.42
Female Sex, N (%)	803 (38%)	72 (27.8%)	0.002
Clinical			
BMI [kg/m^2], median (IQR)	27.7 (25.0, 31.1)	27.8 (25.4, 31.6)	0.045
CHA_2DS_2-VASc score, median (IQR)	4 (3, 5)	4 (3, 5)	0.84
Modified CHA_2DS_2-VASc score, median (IQR)	3 (3, 4)	3 (3, 4)	0.30
Modified HAS-BLED Score, median (IQR)	3 (3, 4)	3 (3, 4)	0.30
Acetylsalicylic acid indication at randomization, N (%)	1174 (55%)	139 (54%)	0.66
Comorbidities			
Heart failure[a], N (%)	575 (27%)	77 (30%)	0.35
Hypertension[b], N (%)	1836 (86%)	232 (90%)	0.13
Diabetes mellitus, N (%)	564 (27%)	79 (31%)	0.17
Prior stroke or TIA, N (%)	213 (10%)	25 (10%)	0.86
Prior myocardial infarction, PCI, or CABG, N (%)	567 (27%)	70 (27%)	0.89
eGFR (CKD-EPI) [ml/min/1.73m^2]	64.5 ± 17.5	61.1 ± 16.6	0.003
AHRE characteristics			
AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration)	2060 (97%)	251 (97%)	0.87
Number of total AHRE at baseline, median (IQR)	4 (1, 14)	9 (2, 27)	< 0.001
Maximum duration of AHRE at baseline [min], median (IQR)	132 (38, 355)	3186 (1937, 5760)	
Time from first adequate AHRE to baseline in [days], median (IQR)	121 (46, 249)	139.5 (46, 258)	0.63
Maximum atrial rate during AHRE episodes [bpm]			
Mean ± SD	427.6 ± 136.5	470.2 ± 122.5	< 0.001
Median, IQR	400 (320, 545)	400 (400, 600)	
Time between last AHRE to baseline [days]			
Median, IQR	65 (23, 157)	43.0 (12, 108)	0.002
≤ 3 months	487/829 (59%)	104/148 (70%)	0.008
> 3 months	342/829 (41%)	44/148 (30%)	

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

Table S2. Primary outcome (composite of stroke, systemic embolism and cardiovascular death) in two patient groups split by the median maximal duration of the longest atrial high-rate episode (AHRE).

	Edoxaban	Placebo	Edoxaban vs. Placebo		
Maximum AHRE duration split by median	**Events/patient-years (incidence per patient-years %)**	**Events/patient-years (incidence per patient-years %)**	**Adjusted HR (95% CI)**	**p-value**	**p-value interaction**
≤2.82 hours	34/1289.3 (2.64)	46/1246.42 (3.69)	0.72 (0.46, 1.12)	0.15	0.41
>2.82 hours	45/1138.5 (3.95)	48/1120.8 (4.28)	0.94 (0.62, 1.42)	0.77	

AHRE, atrial high-rate episodes; CI, confidence interval; HR, hazard ratio

Table S3: Results of sensitivity analyses for efficacy and safety outcomes by randomized 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[§]							
Safety population	82/2501 (3.3)	94/2419 (3.9)	0.84 (0.63, 1.14)	13/280 (4.6)	17/245 (6.9)	0.69 (0.33, 1.43)	0.6198
Per-protocol population	42/1448 (2.9)	47/1520 (3.1)	0.94 (0.62, 1.43)	3/135 (2.2)	9/142 (6.3)	0.36 (0.10, 1.33)	0.2071
Without censoring at unblinding or development of ECG documented AF	82/2497 (3.3)	93/2414 (3.9)	0.85 (0.63, 1.15)	13/275 (4.7)	17/245 (6.9)	0.70 (0.34, 1.45)	0.6322
Primary Safety outcomes[§§]							
Safety population	153/2481 (6.2)	123/2422 (5.1)	1.21 (0.96, 1.54)	26/273 (9.5)	18/248 (7.3)	1.30 (0.71, 2.39)	0.8472
Per-protocol population	73/1441 (5.1)	48/1528 (3.1)	1.63 (1.13, 2.35)	10/133 (7.5)	8/144 (5.6)	1.42 (0.56, 3.61)	0.8283
Without censoring at unblinding or development of ECG documented AF	153/2478 (6.2)	123/2416 (5.1)	1.21 (0.96, 1.54)	26/268 (9.7)	18/248 (7.3)	1.33 (0.72, 2.43)	0.7931

§ composite of first occurrence of stroke, systemic embolism or cardiovascular death
§§ composite of all-cause death or major bleeding
All numbers indicate patients with a first occurrence of an event.
CI, confidence interval; HR, hazard ratio

Figure S1. Cumulative incidence of the primary outcome and secondary outcomes in patients split by the median of the longest AHRE duration (2.82 hours). Aalen-Johansen cumulative incidence curves used in case of competing events (maximum AHRE duration categorized as median). **A:** For primary outcome **(**stroke, systemic embolism and cardiovascular death) **B:** All-cause death and major bleeding **C:** Ischemic stroke **D:** Stroke and systemic embolism

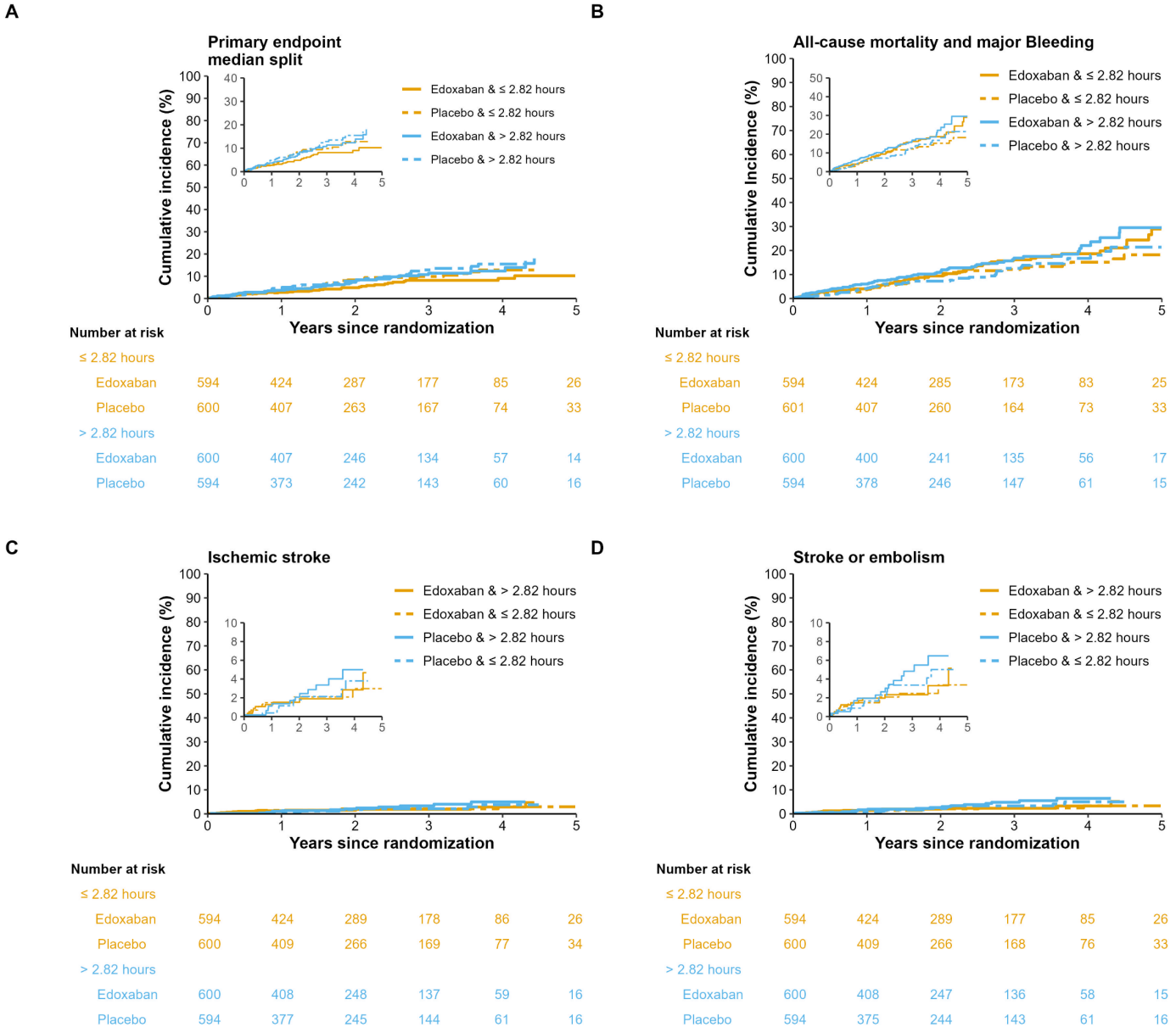
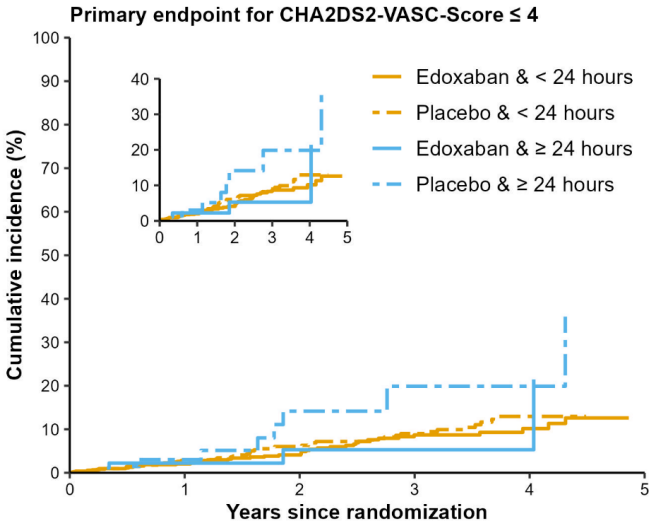
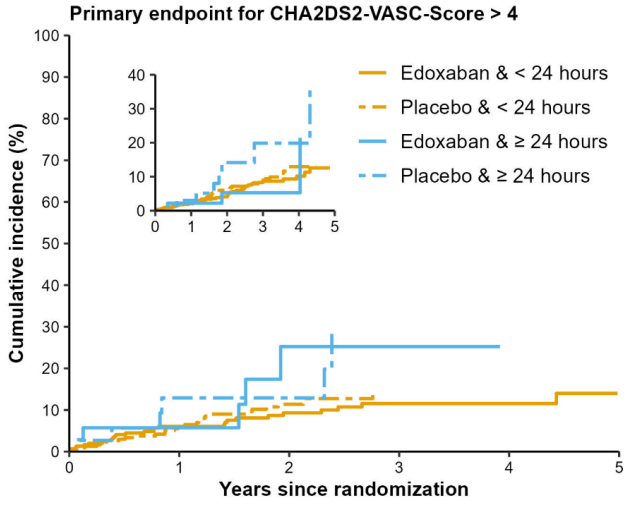


Figure S2: Three-way interaction analysis for the CHA_2DS_2-VASC-Score adjusted for the maximum AHRE duration (categorical). Shown are Aalen-Johansen curves for patients with AHRE < 24 hours and AHRE ≥24 hours for each random group. Upper panel: Primary efficacy outcome, a composite of stroke, systemic embolism, and cardiovascular death, for patients with a CHA_2DS_2VASc score ≤4. Lower panel: Primary efficacy outcome for patients with a CHA_2DS_2VASc score > 4.



Number at risk						
< 24 hours						
Edoxaban	754	541	360	213	89	28
Placebo	744	512	330	211	101	38
≥ 24 hours						
Edoxaban	97	63	28	16	7	1
Placebo	90	50	27	13	5	90



Number at risk						
< 24 hours						
Edoxaban	308	207	137	79	45	11
Placebo	323	197	134	78	25	9
≥ 24 hours						
Edoxaban	35	20	8	3	1	35
Placebo	37	21	14	8	3	2