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ORIGINAL RESEARCH

Anticoagulation in Patients With Device-Detected Atrial Fibrillation With and Without a Prior Stroke or Transient Ischemic Attack: The NOAH-AFNET 6 Trial

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BACKGROUND: Short and rare episodes of atrial fibrillation (AF) are commonly detected using implanted devices (device-detected AF) in patients with prior stroke or transient ischemic attack (TIA). The effectiveness and safety of oral anticoagulation in patients with prior stroke or TIA and device-detected AF but with no ECG-documented AF is unclear.

METHODS AND RESULTS: This prespecified analysis of the NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) trial with post hoc elements assessed the effect of oral anticoagulation in patients with device-detected AF with and without a prior stroke or TIA in the randomized, double-blind, double-dummy NOAH-AFNET 6 trial. Outcomes were stroke, systemic embolism, and cardiovascular death (primary outcome) and major bleeding and death (safety outcome). A prior stroke or TIA was found in 253 patients with device-detected AF randomized in the NOAH-AFNET 6 (mean age, 78 years; 36.4% women). There was no treatment interaction with prior stroke or TIA for any of the primary and secondary time-to-event outcomes. In patients with a prior stroke or TIA, 14 out of 122 patients experienced a primary outcome event with anticoagulation (5.7% per patient-year). Without anticoagulation, there were 16 out of 131 patients with an event (6.3% per patient-year). The rate of stroke was lower than expected (anticoagulation: 4 out of 122 [1.6% per patient-year]; no anticoagulation: 6 out of 131 [2.3% per patient-year]). Numerically, there were more major bleeding events with anticoagulation in patients with prior stroke or TIA (8 out of 122 patients) than without anticoagulation (2 out of 131 patients).

CONCLUSIONS: Anticoagulation appears to have ambiguous effects in patients with device-detected AF and a prior stroke or TIA in this hypothesis-generating analysis of the NOAH-AFNET 6 in the absence of ECG-documented AF, partially due to a low rate of stroke without anticoagulation.

Key Words: anticoagulation ■ atrial fibrillation ■ CHA_2DS_2-VASc score ■ device-detected atrial fibrillation ■ NOAH-AFNET 6 ■ recurrent stroke

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Nonstandard Abbreviations and Acronyms

DDAF	device-detected atrial fibrillation
NOAH-AFNET 6	Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes

CLINICAL PERSPECTIVE

What Is New?

- Patients with device-detected atrial fibrillation (AF) and a prior stroke or transient ischemic attack only have a modestly increased risk of stroke compared with patients with device-detected AF without a prior stroke in the NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) trial.
- Anticoagulation appears to prevent some thromboembolic events, but also appears to increase major bleeding and death in patients with device-detected AF and a prior stroke or transient ischemic attack.

What Are the Clinical Implications?

- Based on these results, anticoagulation should be carefully discussed in a shared decision-making process in patients with device-detected AF and a prior stroke.
- More research is needed to identify patients with device-detected AF at sufficient risk for stroke to justify anticoagulation.

Oral anticoagulation reduces the risk of ischemic stroke in patients with ECG-documented atrial fibrillation (AF).[1,2] Anticoagulation is particularly effective in patients with AF and a prior stroke or transient ischemic attack (TIA)[3] due to the high risk of recurrent stroke in these patients.[4] In patients with a prior stroke without ECG-documented AF, including those with embolic stroke of unknown source[5–7] and patients with atrial cardiomyopathy,[8] oral anticoagulants mainly increase bleeding with only a weak effect on ischemic stroke. Detection of AF to guide initiation of oral anticoagulation has, therefore, been a priority in patients with a prior stroke or TIA.[9,10] Two randomized outcome trials, NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) and Apixaban for stroke prevention in subclinical atrial fibrillation (ARTESIA), recently reported low rates of ischemic stroke in patients with device-detected AF (DDAF) (stroke rate 1.1%–1.2% per year without anticoagulation).[11,12] Due to the low stroke rate, the effect of anticoagulation on stroke using edoxaban (NOAH-AFNET 6) or apixaban (ARTESIA) was small; overall, anticoagulation prevented approximately 0.3 strokes per 100 patient-years and induced 0.7 to 1.6 major bleeding events per 100 patient-years.[13] Screening for DDAF using implanted long-term ECG monitors and subsequent initiation of oral anticoagulation in the Implantable loop recorder detection of atrial fibrillation to prevent stroke (Loop) study did not significantly reduce the rate of stroke,[14] but there was a signal that detection of DDAF and subsequent initiation of anticoagulation could be effective in patients with a prior stroke.[15] Given these results, this prespecified subanalysis of the NOAH-AFNET 6 trial assessed the effectiveness and safety of oral anticoagulation in patients with DDAF and a prior stroke or TIA.

METHODS

Data will be available from the Atrial Fibrillation Network on reasonable request. Please contact info@kompetenznetz-vorhofflimmern.de.

This is a prespecified subgroup analysis of the NOAH-AFNET 6 trial data set comparing outcomes and the effect of oral anticoagulation in patients with and without a prior stroke or TIA. The direction of the effect in patients with a prior stroke or TIA has been reported in a forest plot in the supplement of the main article results. The analysis is enriched with post hoc regression analyses of kidney function and DDAF episodes ≥24 hours and their association with thromboembolic and bleeding events.

Trial Design

Details of the NOAH-AFNET 6 trial[11,16] and the methods for prespecified secondary analyses[17] have been reported. In brief, 206 sites in 18 European countries randomized 2608 patients aged ≥65 years with DDAF, but without ECG-documented AF, and with at least 1 additional stroke risk factor, to oral anticoagulation with edoxaban in the dose approved for stroke prevention in AF or to matching placebo. The trial was approved by the ethics committees at all sites. All patients gave written informed consent. Patients randomized to a placebo who had an accepted indication for acetylsalicylic acid (683 out of 1264 patients, 54.0%) received aspirin 100 mg per day with the blind study medication (double-dummy design). The primary analysis population consisted of all patients who were randomized and took at least 1 dose of the study drug. All patients were switched from study medication to open-label anticoagulation upon ECG documentation of AF and censored at that time point. Sensitivity analyses were

performed without censoring. All events were centrally adjudicated by an independent event review committee. All patients were followed up until the end of the trial for the primary outcome of stroke, systemic embolism, or cardiovascular death, and for the safety outcome of major bleeding or all-cause death.

Primary and Secondary Outcomes

The primary efficacy and safety outcomes of this analysis are identical to the outcomes in the main trial.[11,16] The primary efficacy outcome was a composite of ischemic stroke, systemic embolism, and cardiovascular death. Secondary outcomes included ischemic stroke, systemic embolism, a composite of stroke and systemic embolism, and cardiovascular death. A secondary post hoc outcome included a composite of ischemic stroke (including transient events with matching lesions on cerebral imaging) and systemic embolism excluding pulmonary embolism and myocardial infarction.[17]

Quality of life was assessed using the EQ-5D-5L and Karnofsky index at baseline and at 12 months.[16] The EQ-5D-5L is an accepted score quantifying quality of life (details can be accessed on euroqol.org). Cognitive function was assessed using the Montreal Cognitive Assessment test at baseline and 12 months.[16]

Safety outcomes were a composite of major bleeding according to the International Society of Thrombosis and Hemostasis definition and all-cause death, and each of the 2 components of this outcome.[11,16]

Statistical Analysis

Categorical data are summarized by frequencies and percentages. Continuous data are summarized by mean±SD or median with first and third quartile (interquartile range). The primary analysis population consisted of all randomized patients receiving at least 1 dose of the study drug (ie, a modified intention-to-treat population). For all time-to-event analyses, patients were censored when they developed ECG-documented AF, were unblinded, lost to follow-up, or withdrew consent. Furthermore, all Ukrainian patients were censored on February 24, 2022, the day of the start of the Russian invasion. Deaths of unknown cause were classified as cardiovascular death. No other imputation was made. All analyses are exploratory, and thus no adjustment was made for multiple testing.

Sample size calculation for the primary study has been previously published.[11,16]

For all time-to-event analyses, cause-specific Cox proportional hazards models using the Breslow method to handle tied failures were conducted, with frailty for trial site and the randomization strata indication for acetylsalicylic acid as a covariate. To examine the extent to which prior stroke or TIA had an impact on the treatment effect, the interaction term between treatment and an indicator of prior stroke or TIA and the corresponding main effects were added to the model.

The primary efficacy outcome and the safety outcome were also analyzed for the per-protocol population, a population that was not censored for AF onset or unblinding and a population with censoring at discontinuation of study medication.

The outcome results are reported as group-specific event rates in percentage per patient-years and as adjusted estimated cause-specific hazard ratios (HRs) with a 2-sided 95% 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.

Quality of life and cognitive function continuous outcomes were based on the differences between baseline values and the follow-up values at 12 months. Mean differences were estimated with the use of a linear mixed-effects regression model with the baseline value and randomization strata indication for acetylsalicylic acid as a covariate and trial site as random effect. The probabilities of at least moderate problems of the single EQ-5D-5L items as well as mild cognitive impairment (Montreal Cognitive Assessment test score<26) at 12 months were analyzed with a logistic mixed-effects regression model with the respective baseline value and randomization strata indication for acetylsalicylic acid as covariates and trial site as random effect.

A sensitivity analysis considering only patients with a prior stroke was conducted, and HRs for the primary outcome and for the safety outcome were calculated.

The modified Rankin Scale was presented separately by treatment for patients who suffered a stroke during the study.

All the analyses were conducted with the use of Stata software version 18.0 (StataCorp), and R software version 4.2.3 (R Project for Statistical Computing).

RESULTS

Of the 2534 patients randomized and treated in the NOAH-AFNET 6, 253 patients (10%) had a prior stroke (n=130), TIA (n=107), or both (n=16). Of these 253 patients with prior stroke or TIA, 122 patients were randomized to edoxaban, and 131 patients were randomized to no anticoagulation (placebo or aspirin) (Figure 1). Of the 2281 patients without a prior stroke or TIA, 1148 were randomized to edoxaban and 1133 to placebo.

Demographic and Baseline Characteristics

Patient distribution was comparable between randomized groups in patients with a prior stroke or TIA and in patients without a prior stroke or TIA (Table 1). Age and sex hardly differed between patients with a

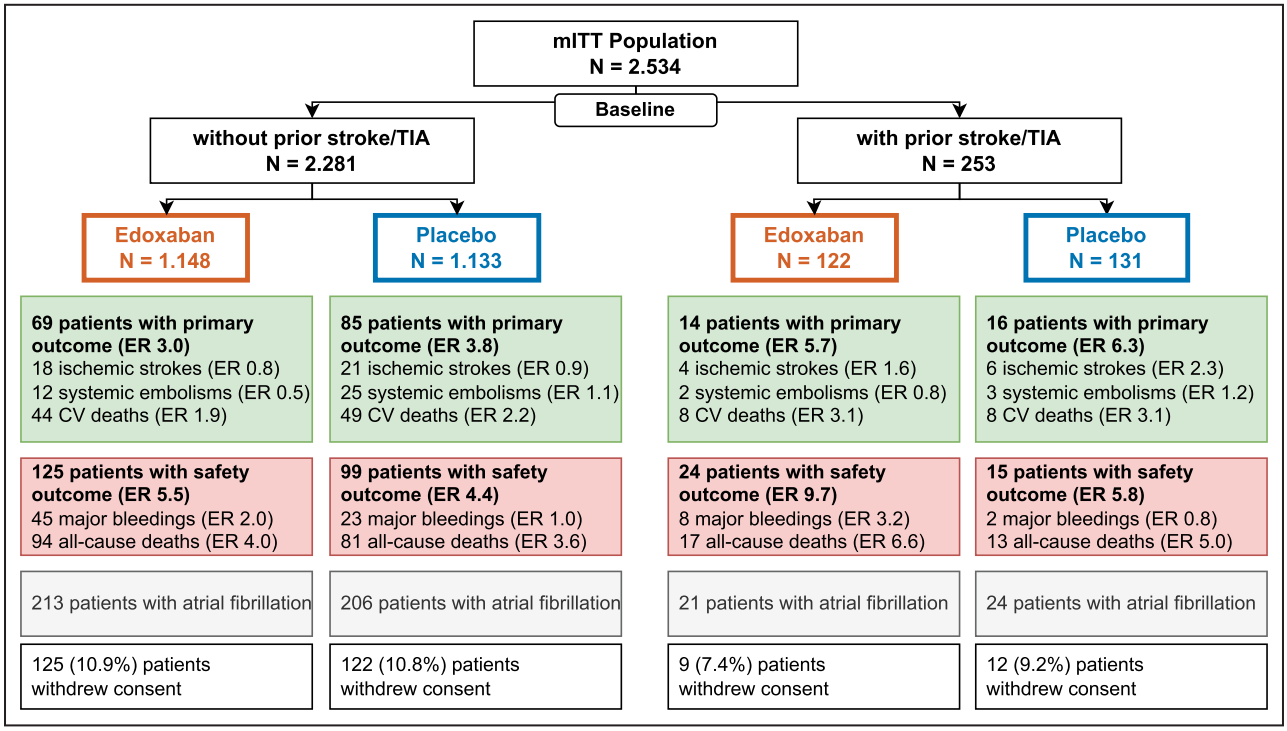

Figure 1. CONSORT flow diagram of this analysis of the NOAH-AFNET 6 trial in patients with a prior stroke or transient ischemic attack.

ER, event rate (% per patient-year); CONSORT, Consolidated Standards of Reporting Trials; CV indicates cardiovascular; mITT, modified intention-to-treat population (the primary analysis population in NOAH-AFNET 6); NOAH-AFNET 6, Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; and TIA, transient ischemic attack.

prior stroke or TIA compared with patients without a prior stroke or TIA. Patients with prior stroke or TIA had a higher CHA_2DS_2-VASc score (median CHA_2DS_2-VASc 6) compared with patients without a prior stroke or TIA (median CHA_2DS_2-VASc 4). More patients with a prior stroke or TIA had diabetes, valvular heart disease, carotid stenosis, or peripheral vascular disease (Table 1).

Primary Outcome

Patients with prior stroke or TIA showed a high risk of primary outcome events: 30 out of 253 (11.9% [95% CI. 8.4%–16.5%]) compared with 154 out of 2281 (6.8% [95% CI, 5.8%–7.9%]) in patients without a prior stroke or TIA. Anticoagulation did not interact with the presence of a prior stroke (*P*-interaction=0.763; Table 2). Among patients with prior stroke or TIA, 14 out of 122 (5.7% per patient-year[95% CI, 3.4%–9.6%] per patient-year) patients randomized to anticoagulation had a primary outcome event compared with 16 out of 131 (6.3% per patient-year [95% CI, 3.9%–10.3%] per patient-year) patients with prior stroke or TIA randomized to no anticoagulation (Figure 2A). In patients without prior stroke or TIA, 69 patients (3.0% per patient-year [95% CI, 2.4%–3.8%] per patient-year) experienced a primary outcome event with anticoagulation, and 85 patients (3.8% per patient-year [95% CI, 3.1%–4.7%] per patient-year) experienced a primary outcome event without anticoagulation.

The rate of recurrent stroke was not different between treatment groups in patients with a prior stroke or TIA (anticoagulation: 4 out of 122 [1.6% per patient-year {95% CI, 0.6%–4.3%} per patient-year], no anticoagulation: 6 out of 131 [2.3% per patient-year {95% CI, 1.1%–5.2%} per patient-year]; Figure 2B).

Safety Outcome

The safety outcome, a composite of major bleeding or all-cause death, occurred more often in patients with a prior stroke or TIA, namely in 24 out of 122 patients (9.7% per patient-year [95% CI, 6.5%–14.4%] per patient-year) with anticoagulation and 15 out of 131 patients (5.8% per patient-year [95% CI, 3.5%–9.6%] per patient-year) without anticoagulation (Figure 3A, Table 3). In patients without prior stroke or TIA, a safety outcome occurred in 125 out of 1148 patients (5.5% per patient-year [95% CI, 4.6%–6.5%] per patient-year) with anticoagulation and 99 out of 1133 patients (4.4% per patient-year [95% CI, 3.6%–5.4%] per patient-year) without anticoagulation. There was no interaction of the randomized treatment with prior stroke or TIA (*P*-interaction=0.4; Table 3). Major bleeding occurred more

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline by Randomized Group and With and Without Prior Stroke or TIA

Characteristic	No prior stroke/TIA		Prior stroke/TIA		Total
	Edoxaban	Placebo	Edoxaban	Placebo	
	(N=1148)	(N=1133)	(N=122)	(N=131)	(N=2534)
Demographics					
Age, y, mean±SD	77.4±6.5	77.4±6.7	77.5±6.7	78.5±7.0	77.5±6.7
Women, n (%)	426 (37.1%)	429 (37.9%)	43 (35.2%)	49 (37.4%)	947 (37.4%)
Clinical					
BMI, kg/m^2, mean±SD	28.6±4.8	28.2±4.8	28.2±4.6	27.9±4.1	28.4±4.8
Time since stroke, y, median (Q1–Q3)	…	…	6.1 (2.4–15.2)	5.6 (2.4–10.4)	
Min–Max	…	…	52 d–43.9 y	33 d–43.2 y	
CHA_2DS_2-VASc score, median (Q1–Q3)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	4.0 (3.0–5.0)
Modified HAS-BLED score, median (Q1–Q3)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	3.0 (3.0–4.0)
Acetylsalicylic acid indication as dispensed, n (%)	584 (50.9%)	572 (50.5%)	100 (82.0%)	111 (84.7%)	1367 (53.9%)
Comorbidities					
Heart failure, n (%)	326 (28.4%)	300 (26.5%)	35 (28.7%)	35 (26.7%)	696 (27.5%)
Arterial hypertension, n (%)	994 (86.6%)	991 (87.5%)	102 (83.6%)	116 (88.5%)	2203 (86.9%)
Diabetes, n (%)	303 (26.4%)	287 (25.3%)	47 (38.5%)	44 (33.6%)	681 (26.9%)
Dyslipidemia, n (%)	572 (49.8%)	539 (47.6%)	65 (53.3%)	69 (52.7%)	1245 (49.1%)
eGFR, mean±SD	64.2±17.4	64.5±17.6	61.1±18.0	61.7±16.4	64.0±17.5
Valvular heart disease, n (%)	115 (10.0%)	104 (9.2%)	17 (13.9%)	22 (16.8%)	258 (10.2%)
Coronary artery disease, n (%)	422 (36.8%)	376 (33.2%)	42 (34.4%)	43 (32.8%)	883 (34.8%)
History of PCI, CABG, or myocardial infarction, n (%)	312 (27.2%)	286 (25.2%)	41 (33.6%)	30 (22.9%)	669 (26.4%)
Carotid stenosis, >50% lumen reduction, n (%)	25 (2.2%)	24 (2.1%)	8 (6.6%)	10 (7.6%)	67 (2.6%)
Peripheral arterial vascular disease, n (%)	72 (6.3%)	69 (6.1%)	14 (11.5%)	19 (14.5%)	174 (6.9%)
Patient-reported outcomes and functional status					
MoCA score, valid n (%)	1103 (96.1%)	1082 (95.5%)	118 (96.7%)	121 (92.4%)	2424 (95.7%)
Median (Q1–Q3)	25.0 (22.0–27.0)	25.0 (21.0–27.0)	25.0 (21.0–26.8)	23.0 (20.0–26.0)	25.0 (21.0–27.0)
Mild cognitive impairment (MoCA<26), n (%)	620/1103 (56.2%)	625 /1082 (57.8%)	73/118 (61.9%)	81/ 121 (66.9%)	1399/2424 (57.7%)
EQ-5D-5L UK index, valid n (%)	1053 (91.7%)	1028 (90.7%)	113 (92.6%)	124 (94.7%)	2318 (91.5%)
Median (Q1, Q3)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.8 (0.7–0.9)
EQ-5D-5L VAS, valid n (%)	1060 (92.3%)	1019 (89.9%)	109 (89.3%)	124 (94.7%)	2312 (91.2%)
Median (Q1–Q3)	75.0 (60.0–85.0)	75.0 (60.0–85.0)	65.0 (50.0–80.0)	70.0 (50.0–80.0)	71.0 (60.0–85.0)
Karnofsky performance score, valid n (%)	1126 (98.1%)	1113 (98.2%)	122 (100%)	128 (97.7%)	2489 (98.2%)
Median (Q1–Q3)	90.0 (80.0–100.0)	90.0 (80.0–100.0)	90.0 (80.0–100.0)	90.0 (80.0–100.0)	90.0 (80.0–100.0)
DDAF characteristics					
DDAF, ≥ 170 bpm atrial rate and ≥6 min duration, n (%)	1103 (96.1%)	1100 (97.1%)	116 (95.1%)	125 (95.4%)	2444 (96.4%)
Number of DDAF episodes, valid n (%)	1087 (94.7%)	1062 (93.7%)	114 (93.4%)	126 (96.2%)	2389 (94.3%)
Median (Q1–Q3)	4.0 (1.0–16.0)	4.0 (1.0–15.0)	7.5 (1.0–32.0)	4.0 (2.0–14.0)	4.0 (1.0–16.0)
Maximum duration of DDAF episodes, h, valid n (%)	1082 (94.3%)	1067 (94.2%)	112 (91.8%)	126 (96.2%)	2387 (94.2%)
Median (Q1–Q3)	2.8 (0.8–9.0)	2.8 (0.8–9.6)	3.1 (1.0–10.9)	2.9 (0.6–8.8)	2.8 (0.8–9.4)
Min–Max	6 min–167* h	6 min–167* h	6 min–167* h	6 min–120 h	6 min–167* h

(*Continued*)

Table 1. Continued

Characteristic	No prior stroke/TIA		Prior stroke/TIA		Total
	Edoxaban	Placebo	Edoxaban	Placebo	
	(N=1148)	(N=1133)	(N=122)	(N=131)	(N=2534)
Time between first adequate DDAF episode and randomization, d, valid n (%)	804 (70.0%)	811 (71.6%)	82 (67.2%)	99 (75.6%)	1796 (70.9%)
Median (Q1, Q3)	124 (47–254)	123 (46–249)	93 (44–228)	136 (59–298)	122 (47–250)
Time between last adequate DDAF episode and randomization, d, valid n (%)	460 (40.1%)	425 (37.5%)	42 (34.4%)	62 (47.3%)	989 (39.0%)
Median (Q1–Q3)	60 (20–146)	57 (17–158)	45 (14–107)	72 (31–165)	58 (20–148)

Indications for acetylsalicylic acid include prior myocardial infarction, PCI, or CABG, and secondary prevention of stroke. CHA_2DS_2-VASc score range 2 to 9 means the higher score indicates greater stroke risk in patients with atrial fibrillation. BMI indicates body mass index; CABG, coronary artery bypass graft; DDAF, device-detected atrial fibrillation; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQoL 5 dimensions; EQ-5D-5L VAS indicates EuroQoL visual analog scale (full health [score=100] or worst imaginable health state [score=0]); HAS-BLED score, modified hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, elderly, drugs/alcohol; MoCA, Montreal Cognitive Assessment (total possible score is 30 points, and a score ≥26 is considered normal); PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*Recording limit.

often in patients receiving anticoagulation. In patients without prior stroke or TIA, major bleeding occurred in 45 out of 1148 patients (2.0% per patient-year [95% CI, 1.5%–2.6%] per patient-year) with anticoagulation and in 23 out of 1133 patients (1.0% per patient-year [95% CI, 0.7%–1.5%] per patient-year) without anticoagulation (HR, 1.9 [95% CI, 1.2–3.2]; *P*=0.011; Figure 3C, Table 3). Major bleeding occurred in 8 out of 122 patients (3.2% per patient-year [95% CI, 1.6%–6.4%] per patient-year) with a prior stroke or TIA randomized to anticoagulation and in 2 out of 131 patients with a prior stroke randomized to no anticoagulation (0.8% per patient-year [95% CI, 0.2%–3.1%] per patient-year; HR, 4.3 [95% CI, 0.9–20.1]; *P*=0.068; Figure 3C, Table 3).

Sensitivity Analysis Excluding Patients With a Prior TIA

A sensitivity analysis considering only patients with a prior stroke yielded similar hazard ratios for the primary outcome (HR, 0.8 [95% CI, 0.4–2.0]) and for the safety outcome (HR, 4.9 [95% CI, 0.6–42.2]). This analysis, based on 146 patients with a prior stroke excluding patients with a prior TIA, found 73 patients randomized

Table 2. Primary and Secondary Efficacy Outcomes in Patients With and Without Prior Stroke or TIA

Outcome	No prior stroke or TIA			Prior stroke or TIA			*P*-interaction value
	Edoxaban	Placebo	Edoxaban vs placebo	Edoxaban	Placebo	Edoxaban vs placebo	
	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	
Primary efficacy outcome	69/2310 (3.0)	85/2240 (3.8)	0.8 (0.6–1.1)	14/246 (5.7)	16/254 (6.3)	0.9 (0.4–1.8)	0.76
Secondary efficacy outcomes							
Ischemic stroke	18/2323 (0.8)	21/2263 (0.9)	0.8 (0.4–1.6)	4/250 (1.6)	6/255 (2.3)	0.7 (0.2–2.4)	0.82
Systemic embolism	12/2324 (0.5)	25/2255 (1.1)	0.5† (0.2–1.0)	2/254 (0.8)	3/259 (1.2)	0.7 (0.1–4.1)	0.71
Myocardial infarction	9/2331 (0.4)	14/2263 (0.6)		1/257 (0.4)	2/259 (0.8)		
Pulmonary embolism	3/2331 (0.1)	8/2272 (0.4)		0/257	1/260 (0.4)		
Peripheral limb	0/2337	3/2274 (0.1)		1/254 (0.4)	0/260		
Abdominal embolism	0/2337	1/2278 (0.0)		0/257	0/260		
Stroke or systemic arterial embolism	21/2316 (0.9)	31/2253 (1.4)	0.7 (0.4–1.2)	4/250 (1.6)	7/255 (2.7)	0.6 (0.2–2.0)	0.89
Post hoc outcome stroke and systemic embolism*	59/2323 (2.5)	68/2258 (3.0)	0.8 (0.6–1.2)	13/246 (5.3)	13/255 (5.1)	1.0 (0.5–2.2)	0.64
Cardiovascular death	44/2337 (1.9)	49/2278 (2.2)	0.9 (0.6–1.3)	8/257 (3.1)	8/260 (3.1)	1.0 (0.4–2.7)	0.78

All numbers indicate patients with a first occurrence of an event. HR indicates hazard ratio; and TIA, transient ischemic attack.

*Post hoc outcome included a composite of ischemic stroke (including transient events with matching lesions on cerebral imaging) and systemic embolism excluding pulmonary embolism and thrombotic events without clear origin.

†*P*=0.040.

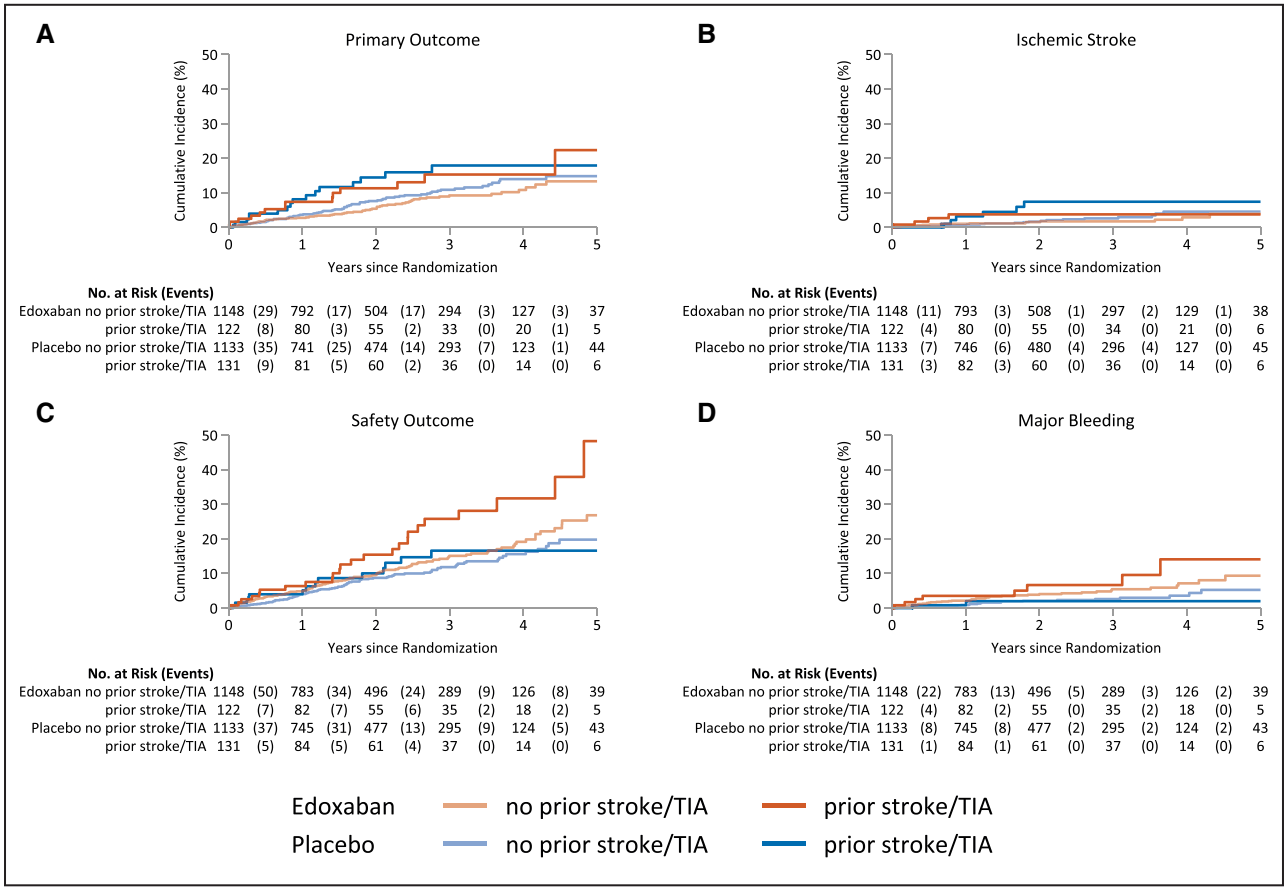

Figure 2. Efficacy outcomes in this subanalysis.
Shown are time-to-event Aalen-Johansen curves in patients with (dark colors) and without (light colors) a prior stroke by randomized group. Orange curves show time-to-event curves in patients randomized to edoxaban, blue curves show time-to-event curves in patients randomized to no anticoagulation (placebo, containing aspirin in most patients with a prior stroke). **A**, Primary outcome, a composite of stroke, systemic embolism, and cardiovascular death. **B** through **D**, Components of the primary outcome, namely ischemic stroke (**B**), systemic embolism (**C**), and cardiovascular death (**D**). TIA indicates transient ischemic attack.

to anticoagulation and 73 patients randomized to no anticoagulation. Without anticoagulation, 11 out of 73 patients experienced a primary outcome event (event rate 8.5%, 5 strokes). With anticoagulation, 10 out of 73 patients experienced a primary outcome event (event rate 7.2%, 4 strokes). With anticoagulation, 14 patients had a safety outcome (9.8% event rate, 5 major bleedings). Without anticoagulation, 11 patients had a safety outcome (8.3% event rate, 1 major bleeding). ECG-documented AF developed in 15 out of 73 patients with anticoagulation and in 14 out of 73 patients without anticoagulation.

Secondary Outcomes

There was no difference in the rate of occurrence of ECG-documented AF between patients with or without prior stroke or TIA. In patients with prior stroke or TIA, ECG-documented AF occurred in 21 out of 122 (7.8% per patient-year) randomized to anticoagulation and in 24 out of 131 (8.8% per patient-year) without anticoagulation (HR, 0.8 [95% CI, 0.5–1.5]). The rate of ECG-documented AF was not different in patients without prior stroke or TIA (*P*-interaction=0.53). Cognitive function and quality of life were not different between treatment groups (Table 4).

The severity of subsequent stroke, estimated by the modified Rankin scale, was not different between patients experiencing a stroke on anticoagulation and patients experiencing a stroke without anticoagulation (Figure 4).

DISCUSSION

Main Findings

This prespecified analysis of the NOAH AFNET 6 trial did not detect an effect of anticoagulation on stroke, systemic embolism, or cardiovascular death in patients with device-detected AF and prior stroke or TIA. Severity of strokes occurring during the trial was not different with or without anticoagulation. As expected,

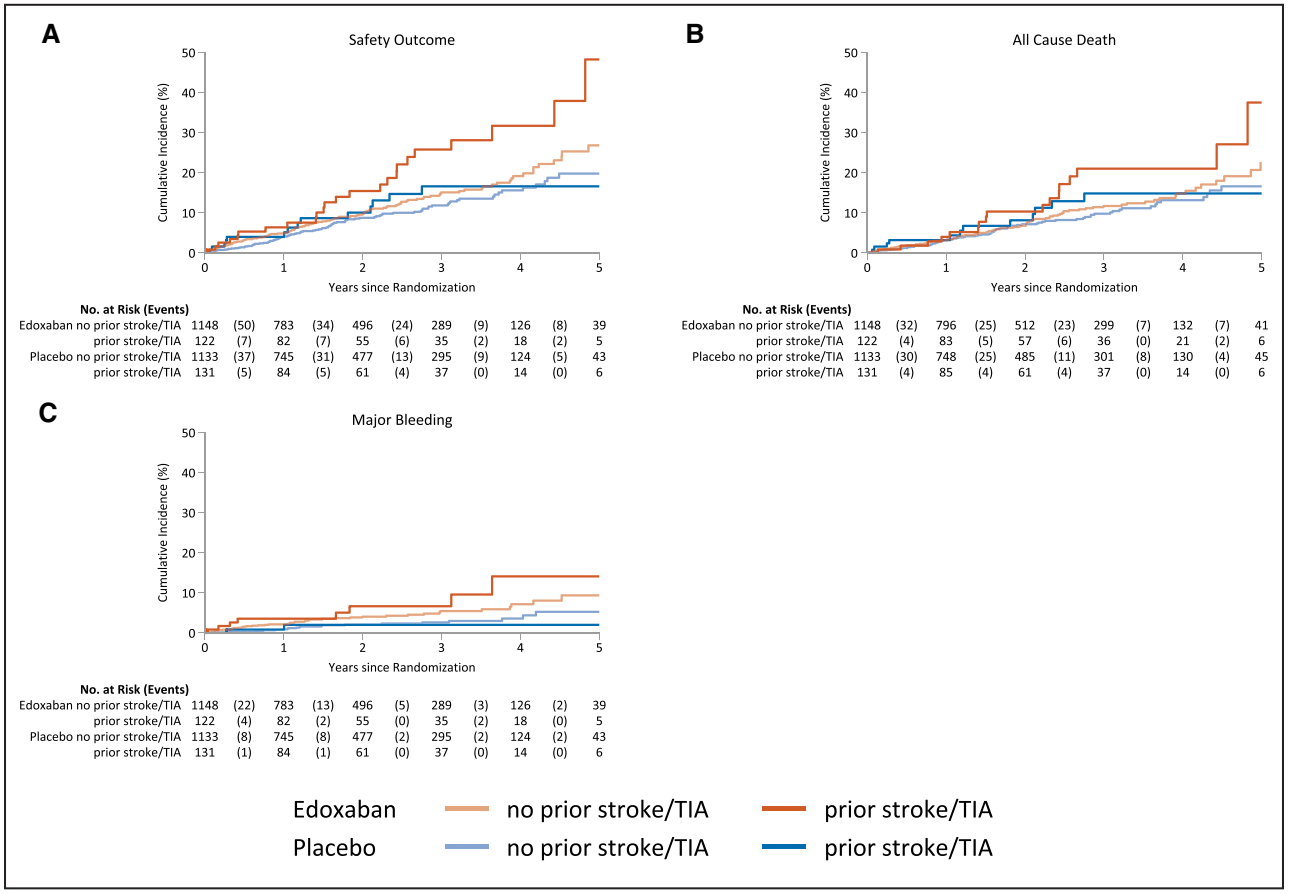

Figure 3. Safety outcomes in this subanalysis.
Shown are time-to-event Aalen-Johansen curves in patients with (dark colors) and without (light colors) a prior stroke by randomized group. Orange curves show time-to-event curves in patients randomized to edoxaban, blue curves show time-to-event curves in patients randomized to no anticoagulation (placebo, containing aspirin in most patients with a prior stroke). **A**, Primary safety outcome, a composite of death or major ISTH bleeding. **B** and **C**, Components of the safety outcome, namely death (**B**) and major ISTH bleeding (**C**). ISTH indicates International Society of Thrombosis and Hemostasis; and TIA, transient ischemic attack.

anticoagulation led to more safety events, including a numerical increase in major bleeding events. Anticoagulation appeared to increase the rate of major bleeding events in patients with a prior stroke or TIA. Within the limitations of a subanalysis relying on 253 patients, these hypothesis-generating results suggest

Table 3. Safety Outcomes in Patients With and Without Prior Stroke or TIA

Outcome	No prior stroke or TIA			Prior stroke or TIA			*P*-interaction value
	Edoxaban	Placebo	Edoxaban vs Placebo	Edoxaban	Placebo	Edoxaban vs placebo	
	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	
Safety outcomes							
All-cause death	94/2337 (4.0)	81/2278 (3.6)	1.1 (0.8, 1.5)	17/257 (6.6)	13/260 (5.0)	1.3 (0.6, 2.7)	0.69
Major bleeding (ISTH)	45/2285 (2.0)	23/2249 (1.0)	1.9* (1.2, 3.2)	8/248 (3.2)	2/259 (0.8)	4.3† (0.9, 20.1)	0.34
Hemorrhagic Stroke	6/2285 (0.3)	7/2249 (0.3)		0/248	0/259		
All-cause death and major bleeding	125/2285 (5.5)	99/2249 (4.4)	1.3‡ (1.0, 1.6)	24/248 (9.7)	15/259 (5.8)	1.7 (0.9, 3.2)	0.40

All numbers indicate patients with a first occurrence of an event. HR indicates hazard ratio; ISTH, International Society of Thrombosis and Hemostasis; and TIA transient ischemic attack.
*P=0.011.
†P=0.068.
‡P=0.094.

Table 4. Secondary Outcomes: Change in Quality of Life and Cognitive Function at 12Months

Outcome	No prior stroke or TIA			Prior stroke or TIA			*P*-interaction value
	Edoxaban	Placebo	Edoxaban vs placebo	Edoxaban	Placebo	Edoxaban vs placebo	
	Adjusted change from baseline (95% CI)		Treatment effect (95% CI)	Adjusted change from baseline (95% CI)		Treatment effect (95% CI)	
Difference from baseline at 12mo FU in							
MoCA score	−0.04 (−0.36 to 0.29)	0.02 (−0.32 to 0.35)	Diff: −0.05 (−0.40 to 0.29)	−0.75 (−1.55 to 0.04)	−0.55 (−1.33 to 0.23)	Diff: −0.20 (−1.25 to 0.84)	0.167
Probability of mild cognitive impairment (MoCA <26)	56.9% (53.2% to 60.6%)	57.7% (53.9% to 61.5%)	OR: 0.95 (0.71 to 1.27)	65.9% (55.9% to 75.8%)	55.4% (45.0% to 65.7%)	OR: 2.03 (0.80 to 5.16)	0.369
Karnofsky performance score	−0.79 (−1.63 to 0.05)	−1.24 (−2.09 to −0.39)	Diff: 0.45 (−0.47 to 1.38)	−2.78 (−4.91 to −0.66)	−2.62 (−4.71 to −0.52)	Diff: −0.17 (−3.00 to 2.66)	0.137
EQ-5D-5L UK index	−0.01 (−0.02 to 0.01)	−0.01 (−0.02 to 0.01)	Diff: −0.00 (−0.02 to 0.02)	−0.02 (−0.07 to 0.02)	−0.00 (−0.04 to 0.04)	Diff: −0.02 (−0.08 to 0.03)	0.834
EQ-5D-5L VAS	0.09 (−1.34 to 1.52)	−0.86 (−2.32 to 0.61)	Diff: 0.95 (−0.79 to 2.68)	−2.44 (−6.32 to 1.44)	−1.59 (−5.41 to 2.23)	Diff: −0.85 (−6.09 to 4.39)	0.474
Probability of at least moderate problems at 12mo FU in EQ-5D-5L items							
Mobility	33.1% (29.5% to 36.7%)	29.8% (26.3% to 33.3%)	OR: 1.25 (0.92 to 1.69)	29.6% (20.3% to 38.9%)	31.5% (22.5% to 40.6%)	OR: 0.87 (0.36 to 2.09)	0.518
Self-care	9.3% (7.4% to 11.3%)	9.8% (7.7% to 11.9%)	OR: 0.93 (0.58 to 1.48)	11.5% (5.8% to 17.3%)	11.0% (5.2% to 16.7%)	OR: 1.09 (0.35 to 3.40)	0.856
Usual activities	18.7% (15.5% to 22.0%)	18.3% (15.1% to 21.6%)	OR: 1.04 (0.73 to 1.48)	25.9% (16.4% to 35.4%)	17.9% (10.0% to 25.8%)	OR: 1.91 (0.74 to 4.93)	0.389
Pain/discomfort	27.8% (24.4% to 31.2%)	27.1% (23.6% to 30.5%)	OR: 1.05 (0.78 to 1.40)	28.7% (19.1% to 38.3%)	27.8% (18.6% to 37.1%)	OR: 1.06 (0.46 to 2.41)	0.984
Anxiety/depression	11.2% (8.8% to 13.6%)	12.1% (9.6% to 14.6%)	OR: 0.90 (0.61 to 1.34)	18.7% (10.0% to 27.5%)	11.2% (4.8% to 17.7%)	OR: 2.08 (0.73 to 5.91)	0.299

Diff indicates difference; EQ-5D-5L, EuroQoL 5 dimensions; EQ-5D-5L VAS indicates EuroQoL visual analog scale (full health [score=100] or worst imaginable health state [score=0]); FU, follow-up; MoCA, Montreal Cognitive Assessment (total possible score is 30 points, and a score of 26 or above is considered normal); OR, odds ratio; and TIA, transient ischemic attack.

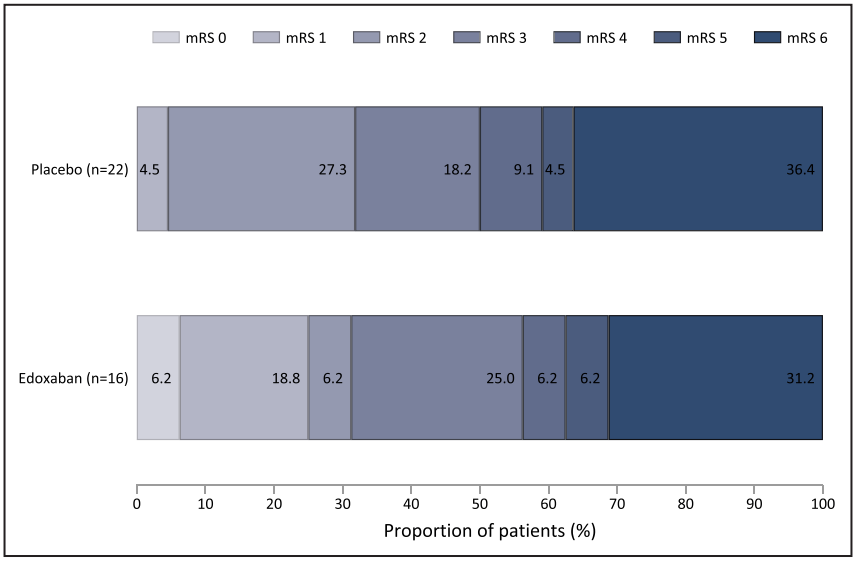

Figure 4. Stroke severity in the NOAH-AFNET 6 trial.
Shown is the distribution of mRS scores after a stroke experienced during the trial. The mRS estimates stroke severity on an ordinal scale from 0 (no residual deficit or symptoms) to 6 (patient died). mRS indicates modified Rankin Scale.

that initiating oral anticoagulation in patients with DDAF and prior stroke or TIA may have weaker effects on stroke prevention than implied, based on earlier observational data sets, while inducing an expected increase in major bleeding events.

Low Effectiveness of Anticoagulation in Patients With DDAF and Prior Stroke

Patients with a prior stroke or TIA have a high risk of a second stroke,[18] with potentially severe effects on quality of life and disability. Diagnosing DDAF by implanting a loop recorder and initiation of anticoagulation upon DDAF detection did not prevent strokes in the LOOP study.[14] In the subgroup of patients with a prior stroke, this strategy appeared to have a stronger effect.[15] The present subanalysis of the NOAH-AFNET 6 trial did not find that anticoagulation reduced cardiovascular events (primary outcome) in patients with DDAF and a prior stroke or TIA (Figure 2). Anticoagulation may have a small effect on ischemic stroke[12] that could not be detected in this analysis. Patients with embolic stroke of unknown source have a higher rate of recurrent stroke (3%–6% per year[19]) than the stroke rate observed without anticoagulation in this subanalysis (Table 2). Even at this high stroke rate, anticoagulation did not reduce recurrent stroke in patients with embolic stroke of undetermined source (ESUS) but without ECG-documented AF[5,6] or in patients with atrial cardiomyopathy without ECG-documented AF.[8] Competing causes probably contribute to the lack of effectiveness of anticoagulants in these patients, including stroke due to arteriosclerotic disease, hypertension, and strokes of unknown source.[19] Furthermore, a sizeable proportion of patients (8%–9% per year in both randomized groups) switched to oral anticoagulation due to ECG-documented AF, probably including many patients with a high arrhythmia burden.[20] The low average arrhythmia burden of DDAF (0.13% in LOOP[21]) probably contributed to the low rate of stroke in this analysis in a similar way as AF burden-reducing treatments such as early rhythm control therapy reduce cardiovascular events including ischemic stroke.[22,23] The event rates in LOOP are comparable or slightly lower to the event rates in this subanalysis. The primary outcome of this analysis, stroke, systemic embolism, or cardiovascular death, occurred at a rate of 1.6% per year (376 out of 4503 patients) without implantable loop recorder (ILR) detection of DDAF and anticoagulation, and at a rate of 1.4% per year (104 out of 1501 patients) with ILR detection of DDAF and anticoagulation. Stroke or systemic embolus occurred at a rate of 1.1% per year (251 out of 4503 patients) without ILR detection of DDAF and anticoagulation, and at a rate of 0.9% per year (77 out of 1501) patients with ILR detection of DDAF and anticoagulation.[14] The recent ACC/AHA/HRS atrial fibrillation guidelines recognize AF burden reduction as a therapeutic goal in patients with AF.[1] Furthermore, patients were enrolled into NOAH-AFNET 6 several years after their stroke, which is different from studies reporting high detection of DDAF in the first months (up to 3 years) after a stroke[9] or after a stroke with presumed large-artery origin.[24] NOAH-AFNET 6 may have selected patients with a low AF burden or patients with a low risk of stroke for other reasons.

Bleeding and Death With Anticoagulation in Patients With DDAF and Prior Stroke

Randomization to anticoagulation increased the rate of major International Society of Thrombosis and Hemostasis bleeding or death in the present subanalysis (Figure 3, Tables 2 and 3). Most patients with DDAF and prior stroke or TIA randomized to no anticoagulation received aspirin as part of the double-blind study medication, following clinical guidelines[25] and respecting local decisions on indications for aspirin. The high rate of safety events with anticoagulation in patients with DDAF and prior stroke or TIA was unexpected given the almost comparable bleeding risk with aspirin and anticoagulation with apixaban in patients with ECG-documented AF studied in AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment).[26] The absolute number of events is low, and power was not sufficient to detect small effects of anticoagulation in efficacy or safety outcomes, but this observation in a randomized, double-blind trial is a safety signal on the use anticoagulation in patients with DDAF and a prior stroke or TIA. In LOOP, 25% of the patients had a prior stroke, and a subanalysis suggested a possible effectiveness of initiating anticoagulation based on the detection of DDAF.[15] The present analysis suggests that initiation of anticoagulation upon detection of DDAF may also increase harm compared with no anticoagulation in patients with prior stroke or TIA. More data are needed to define the effectiveness and safety of anticoagulation in patients with DDAF and a prior stroke or TIA.

Limitations

The most important limitation of this report is the small number of patients and events. This prespecified subanalysis of NOAH-AFNET 6 included 253 patients with DDAF and a prior stroke or TIA. A total of 30 primary outcome events and 39 safety events in such patients were not sufficient to rule out smaller effects. The results are hypothesis-generating, including the signal for high bleeding risk. Validation in other data sets such as ARTESIA[12] and ideally in a combined data set of both trials will provide additional information. An adequately powered randomized trial would need to randomize between 5000 and 15 000 patients with DDAF and a prior stroke to anticoagulation or no anticoagulations to confirm or refute the estimated effects reported here. Most patients in this analysis had a distant stroke or TIA at enrollment into the trial. The effectiveness and safety of anticoagulation may differ in patients with a more recent stroke or TIA who may be at higher risk of recurrent stroke.[4] One clinical trial found no effect of anticoagulation initiated in patients with AF detected directly after a stroke when systematic Holter electrocardiographic monitoring for AF was compared with usual care.[27] Another trial that includes patients with DDAF detection is ongoing (Intensive Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism - the Find-AF 2 Study) (FIND-AF 2)[28]. This analysis included mainly patients with multiple comorbidities (median CHA_2DS_2VASc score of 6 in patients with a prior stroke or TIA). The safety of anticoagulation may be different in patients with a prior stroke and fewer comorbidities. The NOAH-AFNET 6 trial enrolled a primarily White population in Europe. Thus, this analysis cannot provide information on other races.

CONCLUSIONS

Anticoagulation therapy does not interact with prior stroke or TIA in this subanalysis of the NOAH-AFNET 6 trial comparing anticoagulation with edoxaban to no anticoagulation in patients with device-detected AF. The observed rate of stroke was lower than expected in patients with DDAF and a prior stroke or TIA. The analysis suggested a higher rate of bleeding with anticoagulation in patients with DDAF and a prior stroke or TIA. Further studies are needed to identify patients with DDAF at high risk of stroke, and to determine the effects of anticoagulation on stroke and bleeding more precisely.

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Supplemental Material

Data S1

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