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ORIGINAL ARTICLE

Effects of anticoagulation in patients with device-detected atrial fibrillation and multiple stroke risk factors: a win ratio analysis of the NOAH-AFNET 6 trial

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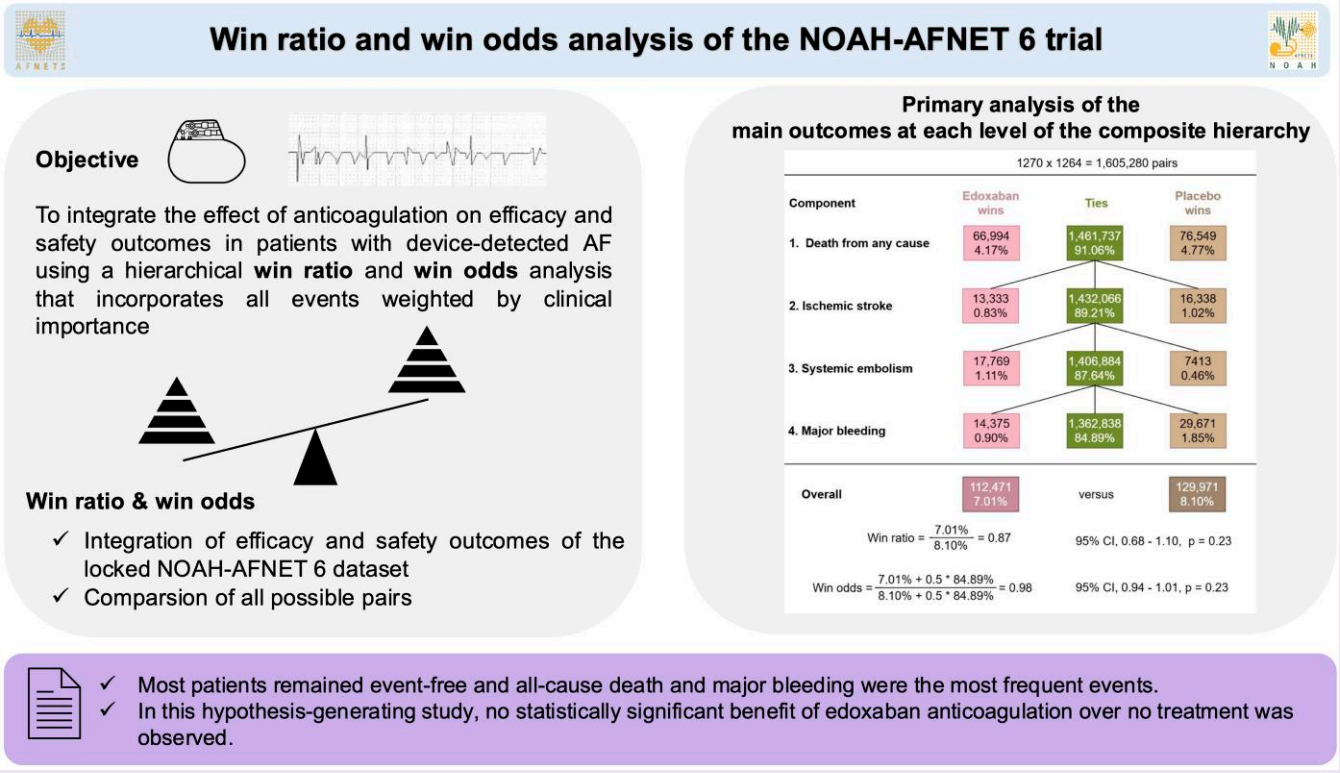
Aims Patients with device-detected atrial fibrillation (DDAF) have a lower stroke risk than those with ECG-diagnosed AF, requiring careful evaluation of oral anticoagulation benefits vs. its inherent bleeding risk.

Methods and results An unmatched win ratio analysis was performed of the NOAH-AFNET 6 trial dataset, using components of the primary efficacy and safety outcomes of the trial. The primary analysis used this hierarchical order: (1) all-cause death, (2) stroke, (3) systemic or pulmonary embolism/myocardial infarction, and (4) major bleeding. Two additional analyses replaced all-cause death with cardiovascular death or included patient-reported outcomes. Win odds were calculated to account for undecided comparisons. Among 2534 patients 77 ± 7 years old, 947 (37%) women, median CHA2DS2-VA score 3 [interquartile range (IQR), 3–4], median follow-up 21 months (IQR, 10–38) 1 605 280 win ratio pairs were analyzed. The win ratio comparing edoxaban to no anticoagulation was 0.87 (95% CI: 0.68–1.10; $P = 0.23$). Most comparisons resulted in no clear winner (undecided pairs 84.9%). In the remaining comparisons, edoxaban won in 46% of the cases, placebo in 54%. Death and major bleeding were the most common events. The win odds was 0.98 (95% CI: 0.94–1.01; $P = 0.23$).

Conclusions This hypothesis-generating win ratio analysis, integrating death, thrombotic events, and major bleeds with and without quality of life, did not find an advantage of anticoagulation with edoxaban over no anticoagulation in patients with DDAF. The most common events were death and major bleeding.

Graphical abstract



Keywords Device-detected atrial fibrillation • NOAH-AFNET 6 • Stroke risk • Win ratio • Major bleeding • Oral anticoagulation

Key Learning Points

- Anticoagulation decisions must balance stroke prevention and increased risk of bleeding in patients with device-detected AF (DDAF).
- This hypothesis-generating win ratio and win odds analysis integrating death or cardiovascular death, thrombotic events and major bleeds with or without patient-reported outcomes in patients with DDAF and stroke risk factors (median CHA_2DS_2VA score 3) found no advantage of anticoagulation with edoxaban compared with no anticoagulation.
- Most patients remained event-free. All-cause death and major bleeding were the most frequent events.

Introduction

Patients with device-detected atrial fibrillation (DDAF) have a lower risk of stroke than patients with electrocardiogram (ECG)-diagnosed AF and the same clinical risk factors.[1–3] Oral anticoagulation is recommended in patients with ECG-diagnosed AF and stroke risk factors with a CHA_2DS_2-VA score ≥2 (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65–74 years).[1] In patients with DDAF, the use of anticoagulation has more ambiguous effects: Anticoagulation slightly reduces the relatively low risk of stroke but also increases the risk of major bleeding.[3] This combination of desirable and undesirable effects, combined with a lower rate of stroke without anticoagulation than anticipated, led to early termination of the NOAH-AFNET 6 (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High-Rate Episodes) trial[2] comparing no anticoagulation to edoxaban in patients with DDAF due to expected safety signals and a trend towards futility. A similar divergence in efficacy and safety outcomes was found in the ARTESIA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) trial[4] comparing apixaban and aspirin.

Traditional reporting of composite endpoints in clinical trials presents efficacy and safety events separately. Most analyses furthermore consider the first-event experienced by a patient, which may not fully capture the overall clinical significance of all events.[5,6] Thus, the win ratio analysis has been proposed as a statistical method to overcome these limitations by hierarchically weighting outcomes according to their clinical importance.[5–7] The win ratio integrates several outcomes in a hierarchical order and considers the most severe event observed in each patient. Due to challenges posed by the high number of ties in win ratio analyses, the win odds—a new method that accounts for ties—has been proposed as a more balanced alternative.[8] Win odds express the difference in the number of wins in context with the number of ties.

To integrate the wanted and unwanted effects of anticoagulation, a hierarchical win ratio and wind odds analysis was performed on the locked NOAH-AFNET 6 trial dataset,[2] which incorporates all events weighted by clinical importance. A clinical win ratio was calculated using the components of the primary efficacy and safety outcome. The primary analysis ranked outcomes in this order: (1) all-cause death, (2) stroke, (3) systemic embolism, pulmonary embolism, or myocardial infarction and (4) major bleeding. Two supplementary analyses were also conducted. The first replaced all-cause death with cardiovascular death to limit the impact of non-cardiovascular deaths on the observed effects, while the second included patient-reported outcomes as a fifth tier in the hierarchical win ratio to better reflect outcomes meaningful to patients and to lower the frequency of ties. In addition, win odds were calculated as a measure that integrates the number of undecided comparisons.

Methods

This post-hoc analysis was conducted using the locked data set from the NOAH-AFNET 6 trial.[2] The analyses were based on the modified intention-to-treat population, the primary analysis population in the trial. The clinical win ratio was calculated based on components of the efficacy and safety outcomes. Components included were all-cause death, cardiovascular death, ischemic stroke, systemic embolism, pulmonary embolism or myocardial infarction, major bleeding and patient-reported outcomes. The components were tested in different hierarchical sequences, with the primary analysis following this order: (1) all-cause death, (2) ischemic stroke, (3) systemic embolism, pulmonary embolism, or myocardial infarction, and (4) major bleeding.

Health-related quality of life was measured using the EuroQol 5-Dimension questionnaire with the United Kingdom (UK) value set [EQ-5D (UK)]. Assessments were performed at 12 months of follow-up (12 m FU) and 24 months of follow-up (24 m FU). Higher EQ-5D scores indicate better health-related quality of life.

Two sensitivity win ratio analyses were performed. In the first analysis, the first hierarchical component was changed from all-cause death to cardiovascular death to reduce dilutions of the therapeutic effects by non-cardiovascular deaths. In the second analysis, quality of life as determined by the EQ-5D was added as a fifth hierarchical component in the win ratio.

We applied the unmatched pair Win Ratio approach, evaluating all possible pairs between treatment groups without requiring exact matches, to provide a robust hierarchical analysis of clinical outcomes. The win ratio was based on survival without an event in each pair. Additionally, win odds were computed to account for the proportion of undecided comparisons. The confidence intervals for the win ratio and odds ratio were calculated using the logarithm of the win ratio and then transformed back to the original scale of the win ratio.

All analyses were conducted using Stata software, version 19.0 (StataCorp), and R software, version 4.2.3 (R Project for Statistical Computing).

Results

Baseline characteristics

Baseline characteristics are shown in *Table 1*. A total of 2534 patients were analysed aged 77 ± 7 years, 947 (37%) women, median CHA2DS2-VA score = 3 [interquartile range (IQR), 3–4], median follow-up time 21 months (IQR, 10–38).

Win ratio and wind odds for the hierarchical order (1) all-cause death, (2) ischemic stroke, (3) systemic embolism, pulmonary embolism or myocardial infarction, and (4) major bleeding.

An overview of events is shown in *Table 2*. The total number of events observed was 374, including 205 (8.1%) all-cause deaths, 49 ischemic strokes (1.9%), 42 (1.7%) systemic embolisms, and 78 (3.1%) major bleeding events (*Table 2*). At least one event occurred in 327 cases (12.9%), 153 (12.1%) in the placebo group and 174 in the edoxaban group (13.7%). Among the patients in the edoxaban group who experienced an event, one event was observed in 151 patients (86.8%). Twenty-one patients (12.0%) experienced two events, while one patient (0.6%) experienced three events, and one patient (0.6%) experienced all four events. Similarly, in the placebo group, one event was observed in 134 patients (87.6%). Seventeen patients (11.1%) experienced two events, two patients (1.3%) experienced three events, and no patient experienced all four events.

Among 1 605 280 possible pairs (1270 edoxaban patients × 1264 placebo patients), the clinical win ratio identified wins for no anticoagulation in 8.10% of the pairs and wins for anticoagulation in 7.01% of the pairs, yielding a Win Ratio of 0.87 (95% CI: 0.68–1.10; $P = 0.23$; *Figure 1* and *Graphical Abstract*) in favour of no anticoagulation. In 84.9% of the comparisons did not yield a clear winner. Among the remaining comparisons, edoxaban was favoured in 46% of cases, while placebo showed a more favourable outcome in 54%. The two most common events were death and major bleeding (*Figure 2*). During the study period, the proportion of wins steadily rose in both groups, showing a slower increase up to day 1500, followed by a more rapid increase thereafter (*Figure 2*).

The data on wins and final undecided comparisons yield a win odds calculated as 0.98 (95% CI: 0.94–1.01; $P = 0.23$) (*Figure 1*).

Win ratio and wind odds for the hierarchical order (1) cardiovascular death, (2) stroke, (3) systemic embolism, pulmonary embolism or myocardial infarction, and (4) major bleeding.

Using a hierarchical endpoint comprising (1) cardiovascular death, (2) stroke, (3) systemic or pulmonary embolism, or myocardial infarction, and (4) major bleeding, the win ratio and win odds were calculated. Among 1 605 280 patient pairs (1270 edoxaban vs. 1264 placebo), wins were observed in 6.27% for no anticoagulation and 5.78% for anticoagulation, yielding a win ratio of 0.92 (95% CI: 0.70–1.21; $P = 0.55$) and a win odds of 0.99.

Win ratio and odds ratio including patient-reported outcomes

The win ratio and win odds were assessed using a hierarchical endpoint comprising: (1) all-cause death, (2) ischemic stroke, (3) systemic or

Table 1 Baseline characteristics

Characteristics	Edoxaban (*N* = 1270)	Placebo (*N* = 1264)	Total (*N* = 2534)
Age, mean ± SD	77.42 ± 6.53	77.50 ± 6.78	77.46 ± 6.65
Female Sex, *n* (%)	469/1270 (36.9%)	478/1264 (37.8%)	947/2534 (37.4%)
BMI (kg/m^2), median (IQR)	27.80 (25.20, 31.30)	27.70 (25.00, 30.90)	27.70 (25.10, 31.18)
CHA_2DS_2-VA Score, median (IQR)	3 (34)	3 (34)	3 (34)
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)
AHRE episode duration [hours], median (IQR), *N* (%)	2.8 (0.8, 9.2) 1194 (94.0%)	2.8 (0.7, 9.5) 1193 (94.4%)	2.8 (0.8, 9.4) 2387 (94.2%)
Heart failure[a], *N* (%)	361/1270 (28.4%)	335/1264 (26.5%)	696/2534 (27.5%)
Arterial hypertension[b], *N* (%)	1096/1270 (86.3%)	1107/1264 (87.6%)	2203/2534 (86.9%)
Diabetes mellitus, *N* (%)	350/1270 (27.6%)	331/1264 (26.2%)	681/2534 (26.9%)
Prior stroke or TIA, *N* (%)	122/1270 (9.6%)	131/1264 (10.4%)	253/2534 (10.0%)
Vascular disease[c], *N* (%)	396/1270 (31.2%)	381/1264 (30.1%)	777/2534 (30.7%)
EQ-5D UK Index, *N* (%), Mean ± SD	1166 (91.8%) 0.8 ± 0.2	1152 (91.1%) 0.7 ± 0.2	2318 (91.5%) 0.8 ± 0.2
EQ-5D VAS, *N* (%), Mean ± SD	1169 (92.0%) 71.0 ± 17.5	1143 (90.4%) 71.0 ± 17.5	2312 (91.2%) 71.0 ± 17.5

[a]Clinically overt or LVEF <45%.
[b]Chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure >145/90 mmHg.
[c]Vascular disease [previous myocardial infarction; peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardiogram (TEE)].
AHRE, Atrial high-rate episode; BMI, body mass index; QR, interquartile range; SD, standard deviation; TIA, transient ischemic attack; VAS, visual analogue scale.

Table 2 Overview of the events

	Placebo (*N* = 1264)	Edoxaban (*N* = 1270)	Overall (*N* = 2534)
Occurrence of composite	153 (12.1%)	174 (13.7%)	327 (12.9%)
All-cause death	94 (7.4%)	111 (8.7%)	205 (8.1%)
Ischemic Stroke	27 (2.1%)	22 (1.7%)	49 (1.9%)
Systemic embolism	28 (2.2%)	14 (1.1%)	42 (1.7%)
Major bleeding	25 (2.0%)	53 (4.2%)	78 (3.1%)

pulmonary embolism, or myocardial infarction, (4) major bleeding, and (5) health-related quality of life (EQ-5D (UK)) at 12- and 24-month follow-up (higher scores indicating better outcomes). In 1 605 280 possible patient pairs (1270 edoxaban vs. 1264 placebo), wins were observed in 19.04% for no anticoagulation and 18.51% for anticoagulation, yielding a win ratio of 0.97 (95% CI: 0.86–1.10; $P = 0.66$) and a win odds of 0.99.

Discussion

The win ratio and win odds analyses of the NOAH-AFNET 6 trial presented here provide a new, integrated perspective onto the efficacy and safety of oral anticoagulation in patients with DDAF and stroke risk factors by integrating all observed events in the trial in a hierarchical order. This new perspective yields three main observations:

(1) The majority of patients do not experience events (84.9% of all win ratio pairs in the primary analysis) over a median follow-up of 21 months.
(2) The most frequent events were death from any cause and major bleeding.
(3) In this hypothesis-generating study, no statistically significant benefit of anticoagulation over no treatment was observed.

In patients with ECG-diagnosed AF and stroke risk factors, estimated as a CHA_2DS_2-VA score >2, anticoagulation reduces stroke and other thrombo-embolic events to a sufficient degree to justify the increase in major bleeding events.[1,9] The 2023 American Heart Association guidelines recommend considering the annual risk of stroke (>2%) in anticoagulation decisions.[9] The rate of stroke is around 1%/year without anticoagulation in patients with DDAF and stroke risk factors.[2,4] Therefore, current guidelines recommend individual decisions that aim towards improving a 'net clinical benefit' considering thrombo-embolic events, bleeding events, and patient preferences.[1] The NOAH-AFNET 6[2] and ARTESIA[4] trials provide helpful results informing that decision. Both trials were designed with a time-to-first-event primary outcome for thrombo-embolic events (ARTESiA: stroke or systemic arterial embolism, NOAH-AFNET 6: cardiovascular death, stroke, or systemic embolism) and a separate reporting of safety events (ARTESiA: major bleeding; NOAH-AFNET 6: major bleeding or death). The present win ratio analysis considers all events that were observed in NOAH-AFNET 6 and integrates the efficacy and safety outcomes of NOAH-AFNET 6[2] into a single analysis.

The win ratio analysis is a statistical method that assigns different priority to events in a hierarchical order.[5,6,10] All outcomes within these prespecified composites are clinically relevant, but some have a higher impact on patients' lives than others. We selected the following hierarchical order of events for the primary analysis: (1) all-cause death, (2) stroke, (3) systemic embolism, pulmonary embolism or myocardial infarction, and (4) major bleeding. This order was considered supporting the greater perceived severity of death, and then ischemic stroke compared with other events.[11,12] Nevertheless, this hierarchy may not fully capture all individual clinical scenarios. The two additional

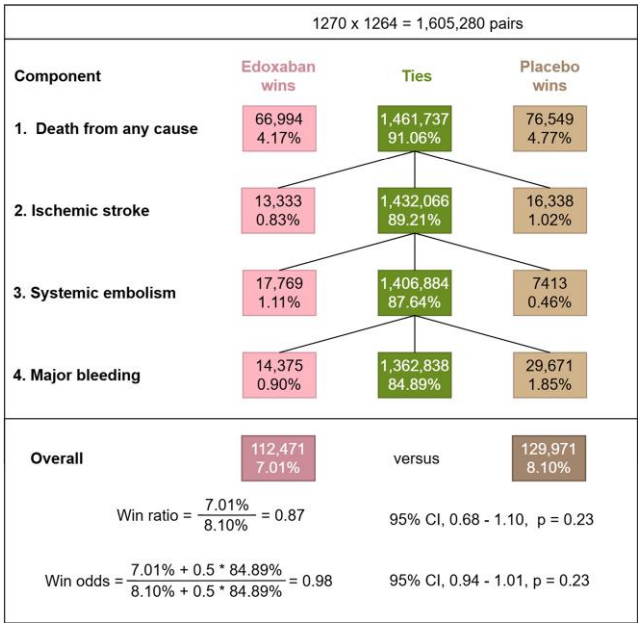


Figure 1 Results of the win ratio and win odds analysis of the main outcomes in NOAH-AFNET 6[2] at each level of the composite hierarchy. The first line shows the number and proportion of wins for edoxaban, ties and wins for placebo for the outcome of death. The second line shows the same information for ischemic stroke, the third line for systemic embolism, and the fourth line for major bleeding. Pairs will become undecided/ties when no patient has an event or when one patient has an event and the comparator was censored before. When both patients have an event, the win goes to the patient who survives longer without experiencing another event.

analyses—one with cardiovascular death at the top of the hierarchy and another including patient-reported outcomes (EQ-5D)—also showed no statistically significant benefit of edoxaban anticoagulation compared with no treatment. Additionally, recurrent events beyond the first were not accounted for in the primary analyses of NOAH-AFNET 6,[2] although they may significantly influence patient outcomes.

A key finding of this study was the high proportion of event-free patients during follow-up, reflected by 85% tied pairwise comparisons and a win odds of 0.98 in the primary analysis. Thus, the chance of a patient on edoxaban achieving a win or a tie is, on average, 2% lower than that of a patient on placebo.[13] Nevertheless, the win ratio overestimates the treatment effect here, as its estimates is greater than the win odds. In this analysis, we could not show significant results in the win ratio and wind odds analyses. However, it is worth noting that the follow-up duration affects both the win ratio and win odds. In the NOAH-AFNET 6 study, the follow-up period was shortened due to early termination, which may have affected the results of this analysis.

In the recently published Markov analysis[14] of the NOAH-AFNET 6 and ARTESIA trial, NOACs treated patients with DDAF were associated with a minimal increase in cumulative quality-adjusted life-years. Using a different mathematical and statistical approach in the Markov approach[14] this study found similarly uncertain benefits of oral anticoagulation, with the overall net effect size unlikely to result in a meaningful clinical benefit.

The lower AF burden in patients with DDAF[15] may have contributed to the lower rate of stroke without anticoagulation in NOAH-AFNET 6 and in ARTESiA and the attenuated efficacy of anticoagulation compared with patients with ECG-documented AF. A low AF burden has also been implicated in the neutral results of anticoagulation in screening-detected AF,[16–18] including in patients with a prior stroke.[19] The hypothesis-generating subanalyses of patients with a prior stroke in NOAH-AFNET 6[20] and in ARTESIA[21] show signals for both a relatively strong stroke-preventing effect and for a relatively high risk of bleeding. The reduction in cardiovascular events, including stroke, with early rhythm control in the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial—Atrial Fibrillation NETwork 4 (EAST-AFNET 4) trial,[22] an intervention that reduces AF burden, is another indication that stroke risk is linked to AF burden. The baseline AF burden in ARTESiA did not influence stroke risk,[23] potentially because all patients with a high AF burden were switched to open-label anticoagulation in NOAH-AFNET 6[2] and ARTESIA,[4] leaving only patients with DDAF and a low AF burden exposed to the study drug. Further research is needed to better characterize AF burden and its impact on stroke risk to inform anticoagulation decisions in patients with DDAF and to estimate AF burden thresholds associated with increases in the risk of stroke. Such research will require the compilation of large databases that combine AF burden information with clinical events.

Individual treatment decisions for anticoagulation in patients with DDAF include patient preferences and views. This analysis did not find a difference in a hierarchical analysis that includes quality of life estimated by the EQ-5D, an overall scale for health-related quality of life. Given the importance of increased bleeding risk on anticoagulation, anticoagulation may be preferable to aspirin in patients with DDAF and a clear need for antiplatelet therapy.[24] Further analyses, also combining the individual patient data from NOAH-AFNET 6[2] and ARTESIA.[4] may help to better define subpopulations of patients with DDAF in whom anticoagulation therapy is sufficiently effective to justify the increased risk of bleeding.

Strengths and limitations

Strengths of the analysis include the use of the locked data set from a randomized, controlled clinical trial. This analysis has several limitations that have to be considered when interpreting the results. One, this is a post-hoc analysis and the findings are hypothesis-generating. Two, even with integration of efficacy and safety outcomes, most patients remained

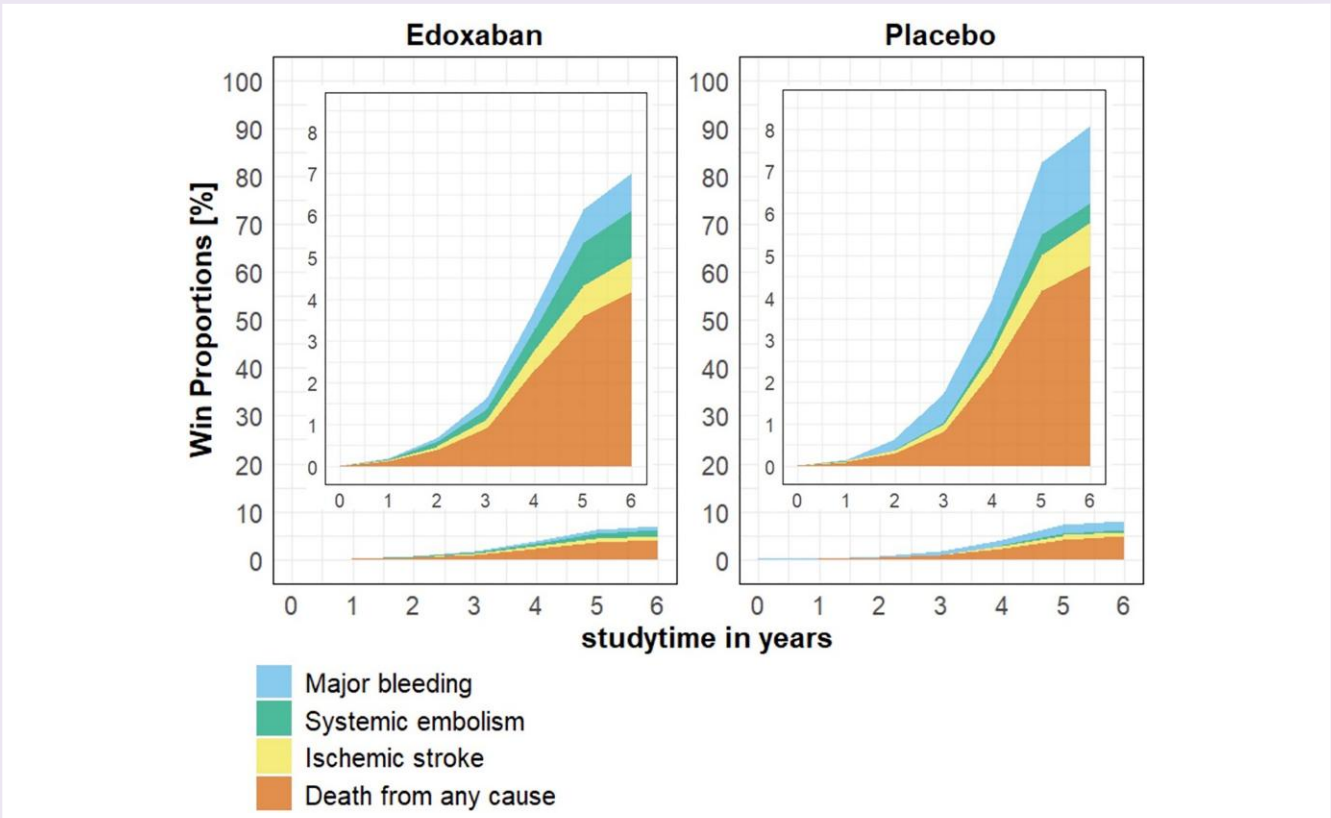


Figure 2 Proportion of wins (time-to-first-event plot) displayed by endpoint components. The proportion of wins for each component of the win ratio analysis is shown for each outcome (death, ischemic stroke, systemic embolism, major bleeding—coloured stacks) after each year of follow-up (*x*-axis).

event-free during follow-up (85% undecided comparisons, win odds 0.98 in the primary analysis), resulting in a high proportion of undecided comparisons. Therefore, and due to the early termination of NOAH-AFNET 6 for expected safety concerns and a trend towards futility, the analysis is not powered to detect or refute small effects. Three, in the hierarchical analysis, only the most severe event was counted in patients who experienced several events, which may underestimate the total burden of multiple events. Four, the analysis integrated events over a follow-up of 21 months. The long-term effects of anticoagulation may be different. Five, AF burden is a likely modulator of stroke risk in patients with AF, including those with DDAF and a high AF burden. Data on AF burden were not available for this analysis. Six, the applicability of the trial findings to settings outside the European context may be limited.

Conclusions

In this hypothesis-generating study, there was no clear advantage of anticoagulation compared with no anticoagulation. Most patients in NOAH-AFNET 6 remained event-free during follow-up, and the most frequently observed events were death and major bleeding. The high proportion of undecided comparisons and the high number of deaths and major bleeds highlight the relatively low risk of stroke in this population, suggesting that the benefit of anticoagulation in this population remains unclear. Further analyses, particularly those combining individual patient data from NOAH-AFNET 6[2] and ARTESIA,[4] may help to quantify small effects and to identify subpopulations of patients with DDAF in whom anticoagulation provides sufficient benefit to outweigh the associated bleeding risk.

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Data availability

The data underlying these analyses will be made available upon reasonable request in accordance with data protection regulations and respecting the individual consent. Please contact info@kompetenznetz-vorhofflimmern.de.

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