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10.1161/CIRCULATIONAHA.123.066485

Safety of Switching from a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients with Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial

Running title: *Joosten et al.; Switching VKA to NOAC in frail patients with AF*

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*This work was presented as an abstract at ESC Congress, August 25-28, 2023

Abstract

Background: There is ambiguity whether frail patients with atrial fibrillation (AF) managed with vitamin K antagonists (VKAs) should be switched to a non-vitamin K oral anticoagulant (NOAC).

Methods: We conducted a pragmatic, multicenter, open-label, randomized controlled superiority trial. Older AF patients living with frailty (age ≥75 years plus a Groningen Frailty Indicator (GFI) score ≥3) were randomized to switch from INR-guided VKA treatment to a NOAC or to continued VKA treatment. Patients with a glomerular filtration rate <30 mL/min/1.73 m^2 or with valvular AF were excluded. Follow-up was 12 months. The cause-specific hazard ratio (HR) was calculated for occurrence of the primary outcome which was a major or clinically relevant non-major bleeding complication, whichever came first, accounting for death as a competing risk. Analyses followed the intention-to-treat principle. Secondary outcomes included thromboembolic events.

Results: Between January 2018 and June 2022, a total of 2,621 patients were screened for eligibility and 1,330 patients were randomized (mean age 83 years, median GFI 4). After randomization 6 patients in the switch to NOAC arm and 1 patient in the continue with VKA arm were excluded due to the presence of exclusion criteria, leaving 662 patients switched from a VKA to a NOAC and 661 patients continued VKAs in the intention-to-treat population. After 163 primary outcome events (101 in the switch arm, 62 in the continue arm), the trial was stopped for futility according to a prespecified futility analysis. The HR for our primary outcome was 1.69 (95% CI 1.23-2.32). The HR for thromboembolic events was 1.26 (95% CI 0.60 to 2.61).

Conclusions: Switching INR-guided VKA treatment to a NOAC in frail older patients with AF was associated with more bleeding complications compared to continuing VKA treatment, without an associated reduction in thromboembolic complications.

Clinical Trial Registration: EudraCT (2017-000393-11) and The Netherlands Trial Registry: 6721 (FRAIL-AF study).

Keywords: atrial fibrillation, non-vitamin K oral anticoagulants, anticoagulants, frail older patients

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Clinical Perspective

What is new?

- In this pragmatic randomized trial in older patients with atrial fibrillation (AF), living with frailty, more major and/or clinically relevant non-major bleeding complications were observed when switching from vitamin K antagonist (VKA) treatment to a non-VKA oral anticoagulant (NOAC), compared to continuing VKA treatment.
- This higher bleeding risk with NOACs was not off-set by a reduction in thrombo-embolic events, albeit the risk of thrombo-embolic events was low in both treatment arms.

What are the clinical implications?

- Without a clear indication, switching from VKA treatment to NOAC treatment should not be considered in older AF patients living with frailty.

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Non-standard Abbreviations and Acronyms

AF	Aatrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
CI	Confidence interval
COMBINE AF	a Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation
CRNM	Clinically relevant non-major
DSMB	Data safety monitoring board
eGFR	Estimated glomerular filtration rate
ENGAGE AF-TIME 48	Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48
FRAIL-AF	Frail atrial fibrillation
GFI	Groningen Frailty Indicator
HR	Hazard ratio
INR	International normalized ratio
IQR	Interquartile range
ITT	Intention-to-treat
NOAC	Non-vitamin K antagonist oral anticoagulant
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SD	Standard deviation
TE	Thromboembolic
TIA	Transient ischemic attack
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

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Introduction

Atrial fibrillation (AF) is associated with an increase in many adverse outcomes including stroke, heart failure, renal failure, cognitive decline, and all-cause mortality.[1] The risk of developing AF is strongly related to age and comorbidity.

Stroke prevention is the corner stone of AF management. Hereto, patients are prescribed anticoagulants, either a vitamin K antagonist (VKA) or a non-vitamin K antagonist oral anticoagulant (NOAC). In newly diagnosed non-frail AF patients, NOACs are preferred over VKAs because in landmark trials NOAC treatment was associated with a lower risk of (major) bleeding at similar efficacy regarding stroke prevention, compared to VKAs.[2] However, there is a large population of older AF patients who are (still) on VKAs; around 30-40% of all AF patients.[3,4] Many of these patients suffer from the frailty syndrome, a clinical entity of accumulating comorbidities and polypharmacy and defined by a high biological vulnerability, dependency on significant others and a reduced capacity to resist stressors.[5–7] These AF patients living with frailty, currently on VKA-treatment, are managed mainly in an outpatient setting, close to the communities where they live, by family medicine specialists, cardiologists, or internists.

The high proportion of older AF patients that are prescribed VKAs Instead of NOACs is a least partly attributable to the lack of convincing trial evidence on superiority of NOACs in older individuals with AF living with frailty. Indeed, previous studies on the impact of frailty on bleeding outcomes in AF were mainly observational as frail patients were underrepresented in the landmark trials.[8–10] However, observational studies on efficacy and side effects of drugs are sensitive to confounding bias. In daily practice, physicians will implicitly weigh multiple factors when deciding on the optimal anticoagulant treatment, which is very difficult to adjust for in observational studies.[5,11] Certainly, monitoring via International Normalized Ratio (INR) testing allows for intervening at an early stage by

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titrating the VKA dose to the most optimal range, which may be beneficial in older patients living with frailty given their larger volatility in anticoagulant status. Consequently, it is uncertain whether the superiority of NOACs over VKAs in AF patients observed also holds for *frail* AF patients and the question whether these AF patients on VKA should be switched to a NOAC remains heavily debated. We therefore performed the FRAIL-AF study, a pragmatic randomized multicenter open-label clinical trial in older AF patients living with frailty.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Trial design and oversight

FRAIL-AF was a pragmatic, investigator-initiated, multi-center, open-label, randomized superiority trial. The protocol has been described earlier.[12] The trial was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht. The trial was conducted in accordance with the Declaration of Helsinki, Dutch law, and regulations related to clinical research. Written informed consent was provided by all study participants. The trial was registered at EudraCT (2017-000393-11) and The Netherlands Trial Registry: 6721 (FRAIL-AF study).

Funding for the trial came from the Dutch government (ZonMw, grant number 848015004) with additional and unrestricted educational grants from Boehringer-Ingelheim, BMS-Pfizer, Bayer, and Daiichi-Sankyo. A patient representative was part of the steering committee. The full scientific committee whose membership did not include representatives of financial contributors, had final responsibility for the interpretation of the data, the preparation of the manuscript, and the decision to submit for publication.

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An independent data safety monitoring board (DSMB; one cardiologist, one internal medicine specialist, one biostatistician) had full access to accumulating study data and – to fully assess patient safety in this frail population – was deliberately left unblinded to randomization status. The protocol allowed the DSMB to advice the trial steering committee on halting or modifying the trial if, in their view, the randomized comparison provided 'proof beyond reasonable doubt' that one particular treatment strategy (NOAC or VKA) was clearly indicated or clearly contra-indicated in terms of a net difference in the primary outcome (this is a difference of at least three standard deviations; P-value ~ 0.002). Following observations in the trial, an interim analysis was planned after having observed at least 160 primary outcome events, at which time point the DSMB could also advice the trial steering committee to halt the trial for futility if at that stage the hazard ratio (HR) for the primary outcome of NOACs versus VKAs exceeded 0.9925.

The last author (GJG) vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

In order to be eligible, patients needed to meet all of the following criteria: age ≥75 years; currently managed on INR-guided VKA treatment for AF by one of the eight participating Dutch thrombosis services; a Groningen Frailty Indicator (GFI) ≥3; and willingness to switch from VKA management to a NOAC-based treatment strategy. The GFI is a validated questionnaire that assesses frailty from a functional perspective on several domains (see S1 Groningen Frailty Indicator).[13] A potential subject who met any of the following criteria was excluded from randomization: valvular AF (this is AF in the presence of a mechanical heart valve and/or severe mitral valve stenosis); an eGFR below 30 ml/min/1.73 m^2; taking part in another medical scientific research program; and/or unwilling or unable to provide written informed consent.

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Randomization, procedures, and follow-up

Patients were randomized to either the index group – switch to a NOAC-based treatment strategy (stop VKA and start NOAC if INR is below 1.3) – or to the control group (continue with INR-guided VKA management – either 1 mg acenocoumarol or 3 mg phenprocoumon – targeting INR levels between 2.0 and 3.0). Computerized block randomization was used, stratified by thrombosis service and renal function at baseline (two strata: an eGFR of 30 to 50 ml/min/1.73m^2 and an eGFR ≥50 ml/min/1.73m^2).

Initially patients randomized to a NOAC-based treatment strategy started NOAC therapy when the INR was <2.0 after stopping VKA therapy. However, shortly after the trial was initiated the DSMB observed a tendency of more bleedings during the switching period. Accordingly, in July 2019, after having included 102 patients in the intervention arm, an INR level <1.3 was used to prevent too high anticoagulation during the switching period.

The decision on the type of NOAC was at the discretion of the treating physician, if needed in collaboration with the study team. The study team had no preference for one NOAC of the other, yet when asked to help making a NOAC choice aimed to balance the different prescribed NOACs as much as possible during patient accrual. NOAC dosing and dose adjustments in principle followed the summary of product characteristics guidelines, unless the treating physician deliberately opted for a different dose (typically off-label dose reduction), which was then accepted.

All patients were followed-up after 1, 3, 6, 9 and 12 months by telephone interviews, and when the occurrence of any of our predefined outcomes was suspected, additional medical information was retrieved.

Outcomes

The primary outcome was the occurrence of a major or clinically relevant non-major (CRNM) bleeding complication (whichever came first). For bleeding complications, we used the

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definitions of the International Society of Thrombosis and Hemostasis.[14,15] A major bleeding complication was defined as: a fatal bleeding; and/or any bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular leading to a compartment syndrome); and/or bleeding leading to a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more; and/or bleeding leading to a transfusion of 2 or more units of whole blood or red cells. A CRNM bleeding complication was defined as any bleeding not being major but including at least one of the following items: prompting a face-to-face consultation; requiring a medical intervention by a healthcare professional; leading to hospitalization or increased level of care.

Secondary endpoints included all-cause mortality, major bleeding complications (separate from CRNM bleeding complications); CRNM bleeding complications (separate from major bleeding complications); the occurrence of all-cause thromboembolic (TE) events (ischemic stroke; transient ischemic attack (TIA); peripheral arterial thromboembolism), the composite of TE events and major or CRNM bleeding, and the composite of ischemic and hemorrhagic stroke.

Statistical analysis

The yearly incidence of major and CRNM bleeding complications was assumed to be 10%–15% in frail older patients with AF using a VKA.[16] A relative reduction of 20%–30% was expected on the occurrence of these bleeding complications when switching to a NOAC. At a two-sided alpha level of 0.05, a 1:1 allocation ratio and 1,250 patients in each treatment arm, the power was at least 0.80 if the incidence of major or CRNM bleeding complications on VKA-treatment was between 11% (with an incidence of our composite outcome on NOAC-treatment of 7%) and 15% (with an incidence of our composite outcome on NOAC- treatment of 11.2%).

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All analyses were performed on an intention-to-treat (ITT) basis. In patients randomized to the intervention group, a variable amount of time occurred between the moment of randomization and the actual start of the NOAC. In line with the ITT analysis, this time was assumed to be part of the 'switch to NOAC treatment' strategy and therefore any outcome events observed during this period were included in the analyses. The primary outcome was compared between the trial arms (switching to a NOAC versus continuing VKAs) using a cause-specific Cox regression analysis with death from causes other than major bleeding considered a competing event. The renal function stratum used to stratify randomisation was included as independent variable in the Cox model. Thrombosis services were included as stratification factor, allowing separate baseline hazard function for each service. Patients without major or CRNM bleeding complications who did not experience the competing event were censored at the last day of follow-up. Proportional hazard assumption was assessed visually using log-log survival plots and a time-dependent coefficient for treatment arm would be added into the model in case of non-proportionality. HRs are reported as effect sizes with 95% confidence intervals (CI). The Aalen-Johansen cumulative incidence estimator was used for visualization of time to first major or CRNM bleeding complication. The following subgroup analyses were proposed a posteriori: sex, age, type of prescribed NOAC in the intervention-arm, different levels of GFI, and strata of renal function. For each subgroup the primary analysis was followed. Analyses of secondary endpoints followed the primary analysis.

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Results

From January 10, 2018, through April 25, 2022, a total of 2,621 patients were screened for eligibility. The majority of these patients were not included as they were considered non-frail. A total of 1,396 patients provided informed consent. In these patients – prior to randomization

– renal function was assessed, and an additional 66 patients were excluded from randomization because of an eGFR below 30 ml/min/1.73 m^2. Thus, a total of 1,330 underwent randomization (Fig. 1). After randomization, 7 patients (0.5% of the trial population) were excluded from analysis as in 5 patients they were in hindsight wrongly registered as having AF by the participating thrombosis service, in 1 patient the eGFR was below 30 ml/min/1.73 m^2 and in 1 patient valvular AF was present; these were all a priori defined exclusion criteria for participating in our trial. Thus, the ITT population included 662 patients that switched from a VKA to a NOAC and 661 patients that continued with INR-guided VKA management. This ITT population was used for all further analyses, both for our primary and secondary outcomes. Of note, all ITT analyses were also repeated including these 7 excluded patients, yielding similar findings (data not shown). Mean age was 83 (standard deviation [SD] 5.1) years and the median score on the GFI was 4. Other characteristics of these patients, comorbidities and renal function are presented in Table 1. The median duration from randomization to start with the NOAC in the intervention arm was 52 days (interquartile range [IQR] 35 to 72 days). A total of 22 patients did not switch to a NOAC despite allocated to switching (3.3%), 57 (8.6%) patients were switched to dabigatran, 332 (50.2%) to rivaroxaban, 115 (17.4%) to apixaban, and 109 (16.5%) to edoxaban; in the remaining 3 patients (0.5%), information on the prescribed NOAC was missing. In patients randomized to switch from a VKA to a NOAC, dosing followed the market authorized dosing in most patients, except for 44 patients (6.6%) in whom off-label dose reduction occurred. The mean duration of follow-up was 344 days and 90 patients died during follow-up (44 in the intervention arm (6.6%) and 46 in the control arm (7.0%). Of those patients that died, a total number of 31 deaths were cardiovascular related deaths: in the intervention arm 12 cardiovascular deaths (1.8%; 8 terminal heart failure, 4 fatal myocardial infarction), and in the control arm 19 cardiovascular deaths (2.9%; 14 terminal heart failure , 5 fatal myocardial

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infarction). A total of 10 deaths were 5 fetal bleedings in both the intervention (0.8%) and control arm (0.8%). In total 8 patients were lost to follow up (3 patients in the VKA group and 5 patients in the NOAC group), in the remaining 1269 patients who did not withdrew consent (99.4%) occurrence of the primary outcomes was ascertained.

Primary outcome

After having observed 163 primary outcome events (101 in the NOAC arm (15.3%) and 62 (9.4%) in the VKA-arm), this superiority trial, with the hypothesis that switching to NOAC treatment would lead to fewer major and/or CRNM bleeding, was halted for futility following the advice of the DSMB and in accordance with our prespecified protocol. It was decided to stop inclusion and complete follow-up for all participants in the study. After complete follow-up, the hazard ratio (HR) for our primary outcome was 1.69 for switching to a NOAC relative to continuing INR-guided VKA treatment (95% CI, 1.23 to 2.32; P=0.00112) (Fig. 2, Table 2). The location of bleeding sites differed per treatment arm (Table 3). Numerically, more gastrointestinal and urogenital bleedings were observed in the intervention arm compared to the control arm; 17 (2.6%) versus 4 (0.6%) gastrointestinal bleedings and 20 (3.0%) versus 11 (1.7%) urogenital bleedings, respectively. Hemorrhagic stroke was seen in 7 (1.1%) patients switched to NOAC versus 6 (0.9%) patients in those continuing with VKAs. Visual inspection of the cumulative incidence curve revealed the potential of non-proportionality related to the switch period, namely from day 1 to day 100, with lines only diverging after day 100 (in fact, the time point after which all patients would have been switched from a VKA to a NOAC in our intervention arm). Following the statistical analysis plan in such circumstances we introduced a step-function using a time-period interaction term should be introduced in the Cox model. This sensitivity analyses showed a hazard ratio (HR) for the first 100 days of 1.17 (95% confidence interval (CI) 0.70-1.96), and a HR of 2.10 (95% 1.40-3.16) for days 100 to 365 (see S2 Sensitivity analysis).

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Subgroup analyses yielded no apparent differences in subgroups based on age, sex, GFI score, or renal function (Fig. 3). Some differences were observed in relation to the prescribed NOAC. The HR for our primary outcome was similar for the two most prescribed NOACs in our trial, rivaroxaban and apixaban (HR 1.95, 95% CI 1.36 to 2.79, and HR 2.17, 95% CI 1.28 to 3.68), yet appeared to be lower notably for edoxaban (HR 1.10, 95% CI 0.57 to 2.13). Nevertheless, these analyses should be interpreted with caution as they were post-hoc and non-randomized.

Secondary outcomes

In the analysis where the two components of our primary outcome were assessed separately, the observed difference between both treatment arms seemed mainly driven by an increase in CRNM bleeding (Table 2); HR for major bleeding was 1.52 (95% CI 0.81 to 2.87), and for CRNM bleeding 1.77 (95% CI 1.24 to 2.52).

The occurrence of all-cause thromboembolic events was similar in the intervention arm compared to the control arm; (HR 1.26; 95% CI, 0.60 to 2.61). The HR of switching from a VKA to a NOAC for the composite outcome ischemic and/or hemorrhagic stroke was 1.30 (95% CI 0.59 to 2.87), and for the outcome all-cause mortality 0.96 (95% CI 0.64 to 1.45).

Discussion

In our pragmatic randomized controlled trial among frail older AF patients, switching INR-guided VKA-management to a NOAC based treatment strategy was associated with a 69% increase in major and/or CRNM bleeding complications. Event rates for thrombo-embolic events, major bleeding in isolation, hemorrhagic stroke, or the composite of hemorrhagic and ischemic stroke were low in both treatment arms, withholding us from drawing firm conclusions on these also clinically relevant outcomes. Importantly, there was no clear signal

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for either a reduced or improved efficacy for these outcomes in patients switching from a VKA to a NOAC.

Our trial strengthens the evidence by studying at the complete domain of frailty (surpassing individual domains) in a large pragmatic trial in older AF patients, accounting for the downfalls of observational studies such as confounding bias. Even more so, we aimed to extend (i.e., 'stretch the tails' of) the trial evidence to the most vulnerable (and increasing) AF population, a population that previously was largely excluded in clinical trials.

To elaborate on this, prior to our trail, trial evidence on the impact of ageing and frailty on clinical outcomes in NOAC- or VKA-treated individuals with AF was limited to subgroup analyses from either individual or aggregated data from the pivotal four NOAC trials.[17–20] However, it is difficult to compare these studies with our trial, given that frail older patients were underrepresented in the four NOAC trials, because these patients were either not eligible (e.g., due to a high anticipated bleeding risk) or physicians were hesitant to include these vulnerable older patients into clinical trials. Moreover, in these subgroup analyses, apart from the impact of ageing, frailty was predominantly quantified as a cumulative deficit of an increasing number of comorbidities and/or increasing polypharmacy. Albeit ageing, multimorbidity and polypharmacy are important drivers of the concept of frailty, this clinical syndrome is broader including for instance weight loss, communication difficulties, loneliness, dependency on others, cognition, mental condition and overall physical fitness, all items that are likely related to drug availability in the human body, and thus bleeding and thromboembolic risk. Nevertheless, some interesting comparisons with our findings can be drawn to put our trial into perspective.

First, data from the COMBINE-AF consortium that pooled individual patient data from all four pivotal NOAC trials (n=71,683 patients) revealed that, compared with warfarin, NOAC treatment was associated with a lower risk of major or clinically relevant non-major

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bleeding in patients regardless of age: overall HR for standard-dose NOAC treatment was 0.87 (95% CI 0.75 to 1.02) and for reduced-dose NOAC treatment 0.70 (95% CI 0.59 to 0.82).[21,22] Although overall effects remained similar, the authors showed that the better efficacy of standard-dose NOAC treatment over VKA treatment was mainly driven by the results in patients who are VKA naïve. Moreover, an interaction of ageing on safety outcomes was observed: for standard-dose NOAC-treatment every 10-year increase in age led to a 10.2% increase in HR for major bleeding (P-value for interaction 0.02) and for reduced-dose NOAC-treatment every 10-year increase in age led to a 17.6% increase in the HR for major bleeding (P-value for interaction 0.01). In addition to these results of the COMBINE-AF study, the ROCKET-AF trial and the ARISTOTLE trial both found a statistically significant interaction for the impact of polypharmacy on major bleeding with a waning (and in some analyses a reversed) advantage of NOACs over VKAs on this safety outcome when using more drugs.[22,23] Finally, in the ENGAGE AF-TIMI 48 trial, edoxaban was associated with a significant lower rate of bleeding compared with warfarin, at different levels of frailty, except in those at the most severe end of the frailty spectrum. Here, the HR for major bleeding no longer reached statistical significance; HR for edoxaban 30 mg 0.74 (95% CI 0.36 to 1.52), and for edoxaban 60 mg 0.60 (95% CI 0.29 to 1.26).[24] Hence, given that at the current end of the trial tails from the pivotal NOAC trials already a waning (and in some analyses a reversed) advantage of NOACs over VKAs in the oldest and most comorbid trial participants was observed, our findings of an increased risk of major or clinically relevant non-major bleeding associated with *switching* VKA treatment to a NOAC in a trial with patients who are even older and more frail may be less unexpected than a priori foreseen.

In addition to this trial evidence, observational studies looked at the impact of ageing and frailty in real-world patients with AF treated with a VKA or a NOAC. With respect to ageing, findings from these observational studies are largely in line with the above-described

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trial evidence. For instance, a systematic review in 444,281 included older AF patients found that the HR for hemorrhagic stroke was lower in older patients treated with a NOAC compared to VKAs; HR 0.61 (95% 0.48 to 0.79).[25] Similar as what we observed in our trial, the HR for gastrointestinal bleeding was higher in NOAC recipients compared to INR-guided VKA; HR 1.46 (95% CI 1.30 to 1.65). It is important to note, however, that observational studies exploring the impact of frailty are more scarce and also more difficult to perform given that in the context of frailty residual confounding bias remains problematic.[26]

For full appreciation, a number of topics need to be discussed. First, our population included patients who were tolerant to VKA-treatment. Switching from a treatment that most patients tolerate to a newer drug (NOAC) could have resulted in a higher tendency to report bleeding complications in the group that switched. Indeed, previous reports using both aggregated or pooled individual patient data from the pivotal NOAC trials also revealed that the efficacy and safety differences favored NOACs over warfarin most strongly in AF patients that where VKA-naïve.[2,21] However, including patients that currently use INR-guided VKA was the clinically relevant population for the research question addressed in this trial, which was to study whether these patients, provided they were old and frail, should *switch* from a VKA to a NOAC. Also, inherent to this switching design, slightly more cross-over was observed in the 'switch to NOAC' arm of our trial (n=73), compared to the 'continue with VKA' arm (n=51). Nevertheless, adherence to the protocol was still relatively high, certainly for this older frail population: 89% adherence in the intervention arm versus 92% adherence in the control arm of our trial.

Second, one could postulate that the infrastructure of INR-guided VKA management is adequate in the Netherlands, which may positively affect the time in therapeutic range (TTR) positively in the VKA-arm of our trial. Levels of TTR were not an inclusion criterium in our trial nor were individual participants' TTR levels registered. Monitoring of the INR levels at

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the eight study sites in FRAIL-AF was done according to current Dutch clinical practice in this pragmatic trial. The range of TTR levels in Dutch clinical practice for the participating thrombosis services in this trial, specifically for the older individuals that are visited at home for their INR measurements (thus the frailest individuals), during the study years of our FRAIL-AF trial, was between 65.3% and 74.0% (measured as part of yearly quality reports, see https://www.fnt.nl/algemeen/jaarverslagen). As a comparison, the impact of TTR on efficacy and safety of apixaban versus warfarin was studied in the ARISTOTLE trial population and resulted in a TTR from patients recruited from the Netherlands around the median study average of 66.4%, which is similar to countries like e.g., the United States of America, the United Kingdom, Italy, Germany, and Canada[27]. At that TTR level, apixaban still was associated with a lower rate of major bleeding, compared to warfarin, in a non-frail population with a median age of 70 years. Hence, we believe levels of TTR did not influence our findings significantly nor hamper generalizability to the substantial population of older patients living with frailty in many countries, and we consider our findings to be generalizable to patients currently receiving adequate INR-guided VKA management. Our findings should lead to a careful consideration whether or not to switch a patient, who is stable on INR-guided VKA management (TTR around 70%) to a NOAC, given our finding of a higher risk of major or clinically relevant non-major bleeding. Our trial does not allow to draw conclusions for patients with a low TTR, for whom switching to a NOAC may certainly be considered appropriate.

Third, the choice of the NOAC was at the discretion of treating physicians. Albeit this would mimic (future) clinical practice, it could have impacted our results. In observational studies rivaroxaban (the most prescribed NOAC in our trial) is associated with more bleeding complications than other NOAC-types, notably gastro-intestinal bleeding, with apixaban having the best safety profile in older.[28–31] In our trial, a post-hoc analysis per NOAC-type

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showed that rivaroxaban and apixaban had a similar HR for our primary outcome. Nevertheless, as the type of NOAC prescribed was non-randomized, our trial cannot answer whether one NOAC should be preferred over the other in this frail population.

Fourth, our trial was not powered to show differences in clinical outcomes in isolation such as hemorrhagic stroke. Due to the small numbers of events, we cannot draw any conclusions on possible differences between treatment arms.

Finally, rather than comparing two types of anticoagulant *molecules*, it is important to acknowledge that our open-label pragmatic trial allows to draw conclusions from the comparison of two healthcare anticoagulation *strategies* in older patients living with frailty, namely switching from INR-guided VKA therapy to a NOAC or continue with VKAs. This was done deliberately, as it answers the clinically relevant question on whether this particular AF patient living with frailty should switch from a VKA to a NOAC or not. For this pragmatic clinical question, we decided an open-label design was most appropriate, as this would mimic future clinical care as much as possible. Nevertheless, by design, study procedures were not blinded and moreover some bleeding events in the NOAC-group occurred while the patient was (still) on a VKA, and vice versa. However, the proportion of these bleeding events occurring not on the anticoagulant strategy they were randomly allocated to was small in both treatment arms: 7/101 (6.9%) bleeding events in the NOAC arm and 5/62 (8.1%) bleeding events in the VKA arm (see Supplemental Table 1).

In conclusion, our FRAIL-AF pragmatic trial showed that switching INR-guided VKA treatment to a NOAC in frail older patients with non-valvular atrial fibrillation is associated with more bleeding complications compared to continuing INR-guided VKA treatment. Albeit our trial was not powered to demonstrate differences in thrombo-embolic events, major bleeding in isolation, hemorrhagic stroke, or the composite of hemorrhagic and ischemic stroke, there was no clear signal that switching results in reduction of these outcomes in our

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trial population. Hence, we believe our trial indicates that careful consideration should be applied when choosing between continuing VKA or switch from a VKA to a NOAC in older patients living with frailty.

Sources of Funding

Dutch government (ZonMw, grant number 848015004) with additional and unrestricted educational grants from Boehringer-Ingelheim, BMS-Pfizer, Bayer, and Daiichi-Sankyo.

Disclosures

Martin E.W. Hemels reports payment for educational lectures from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. Menno V. Huisman reports payment to institution from Dutch Healthcare Fund, Dutch Heart Foundation, Bayer Health Care, Pfizer, Leo Pharma. Marieke Kruip reports payment to institution of unrestricted grants from Sobi, payment to institution of research grants from The Netherlands Organisation for Health Research and Development and The Netherlands Thrombosis Foundation, and payment to institution of speaker fees from Sobi, Roche, BMS. G.J. Geersing reports payment to institution of unrestricted grants from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer and Daiichi Sankyo. F.H. Rutten reports payment to institution of unrestricted grants from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer and Daiichi Sankyo.

Supplemental Materials

Supplemental Materials 1-2

Supplemental Table 1

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References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42:373–498.
2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet*. 2014;383:955–962.
3. Grymonprez M, Simoens C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: A systematic review and meta-analysis. *Europace*. 2022;24:887–898.
4. Joosten LPT, de Boer AR, van Eerde EJB, van Doorn S, Hoes AW, Bots ML, Rutten FH, Geersing GJ. Atrial fibrillation: Trends in prevalence and antithrombotic prescriptions in the community. *Netherlands Heart Journal*. 2022;30:459–465.
5. Savelieva I, Fumagalli S, Kenny RA, Anker S, Benetos A, Boriani G, Bunch J, Dagres N, Dubner S, Fauchier L, et al. EHRA expert consensus document on the management of arrhythmias in frailty syndrome, endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace*. 2023;25:1249–1276.
6. Proietti M, Romiti GF, Raparelli V, Diemberger I, Boriani G, Vecchia LAD, Bellelli G, Marzetti E, Lip GY, Cesari M. Frailty prevalence and impact on outcomes in patients with atrial fibrillation: A systematic review and meta-analysis of 1,187,000 patients. *Ageing Res Rev.* 2022;79:101652.
7. Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: A systematic review and meta-analysis. *Age Ageing*. 2019;48:196–204.
8. He L, He R, Huang J, Zou C, Fan Y. Impact of frailty on all-cause mortality and major bleeding in patients with atrial fibrillation: A meta-analysis. *Ageing Res Rev*. 2022;73: 101527.
9. Kim DH, Pawar A, Gagne JJ, Bessette LG, Lee H, Glynn RJ, Schneeweiss S. Frailty and clinical outcomes of direct oral anticoagulants versus warfarin in older adults with atrial fibrillation: A cohort study. *Ann Intern Med*. 2021;174:1214–1223.
10. van den Dries CJ, van Doorn S, Souverein P, Pajouheshnia R, Moons KGM, Hoes AW, Geersing G-J, van den Ham HA. The number of concomitant drugs and the safety of direct oral anticoagulants in routine care patients with atrial fibrillation. *TH Open*. 2020;4:e417–e426.
11. Bul M, Shaikh F, McDonagh J, Ferguson C. Frailty and oral anticoagulant prescription in adults with atrial fibrillation: A systematic review. Aging Medicine. 2023;6:195–206.
12. Joosten LPT, Van Doorn S, Hoes AW, Nierman MC, Wiersma NM, Koek HL, Hemels MEW, Huisman M V., Roes KC, Van Den Bor RM, et al. Safety of switching from vitamin K antagonist to non-vitamin K antagonist oral anticoagulant in frail elderly with atrial fibrillation: Rationale and design of the FRAIL-AF randomised controlled trial. *BMJ Open*. 2019;9:e032488.
13. Steverink N, Slaets J, Schuurmans H, van Lis M. Measuring frailty: Developing and testing the GFI (Groningen Frailty Indicator). *Gerontologist*. 2001;41:236–237.
14. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*. 2005;3:692–694.

Downloaded from http://ahajournals.org by on October 17, 2023

15. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: Communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*. 2015;13:2119–2126.
16. Kooistra HA, Calf AH, Piersma-Wichers M, Kluin-Nelemans HC, Izaks GJ, Veeger NJ, Meijer K. Risk of bleeding and thrombosis in patients 70 Years or older using vitamin K antagonists. *JAMA Intern Med*. 2016;176:1176–1183.
17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
18. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
19. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
20. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104.
21. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, Patel MR, Wallentin L, Alexander JH, Cecilia Bahit M, et al. Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: Patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. *Circulation*. 2022;145:242–255.
22. Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt G, Berkowitz SD, Halperin JL, Hankey GJ, Hacke W, Mahaffey KW, et al. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation. *Circulation*. 2016;133:352–360.
23. Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, Lanas F, Xavier D, Husted S, Wallentin L, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: Post hoc analysis of the ARISTOTLE trial. *Br Med J*. 2016;353:i2868.
24. Wilkinson C, Wu J, Searle SD, Todd O, Hall M, Kunadian V, Clegg A, Rockwood K, Gale CP. Clinical outcomes in patients with atrial fibrillation and frailty: Insights from the ENGAGE AF-TIMI 48 trial. *BMC Med*. 2020;18:1–12.
25. Silverio A, Di Maio M, Prota C, De Angelis E, Radano I, Citro R, Carrizzo A, Ciccarelli M, Vecchione C, Capodanno D, et al. Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: Systematic review and meta-analysis of 22 studies and 440 281 patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:F20–F29.
26. Menichelli D, Sole F Del, Rocco A Di, Farcomeni A, Vestri A, Violi F, Pignatelli P, Lip GYH, Pastori D. Real-world safety and efficacy of direct oral anticoagulants in atrial fibrillation: A systematic review and meta-analysis of 605 771 patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:F11–F19.
27. Wallentin L, Lopes RD, Hanna M, Thomas L, Hellkamp A, Nepal S, Hylek EM, Al-Khatib SM, Alexander JH, Alings M, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation*. 2013;127:2166–2176.
28. Menichelli D, Del Sole F, Di Rocco A, Farcomeni A, Vestri A, Violi F, Pignatelli P, Lip GYH, Pastori D. Real-world safety and efficacy of direct oral anticoagulants in atrial

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fibrillation: A systematic review and meta-analysis of 605 771 patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:F11–F19.
29. Xu W, Lv M, Wu S, Jiang S, Zeng Z, Fang Z, Qian J, Chen M, Chen J, Zhang J. Severe bleeding risk of direct oral anticoagulants versus vitamin K antagonists for stroke prevention and treatment in patients with atrial fibrillation: A systematic review and network meta-analysis. *Cardiovasc Drugs Ther* [Internet]. 2023;37:363–377. Available from: https://doi.org/10.1007/s10557-021-07232-9
30. Mamas MA, Batson S, Pollock KG, Grundy S, Matthew A, Chapman C, Manuel JA, Farooqui U, Mitchell SA. Meta-analysis comparing apixaban versus rivaroxaban for management of patients with nonvalvular atrial fibrillation. *American Journal of Cardiology*. 2022;166:58–64.
31. Grymonprez M, Petrovic M, De Backer TL, Steurbaut S, Lahousse L. Impact of frailty on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J Qual Care Clin Outcomes*. 2023;1–11.

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Table 1. Patient Characteristics

Characteristic*	Switch to NOAC (n=662)	Continue with VKA (n=661)
Age – yr. (SD)	83.0 (5.1)	82.8 (5.1)
Female sex – no. (%)	274 (41.4%)	239 (36.2%)
Type of atrial fibrillation		
Paroxysmal atrial fibrillation – no. (%)	170 (25.7%)	201 (30.4%)
Persistent atrial fibrillation – no. (%)	63 (9.5%)	57 (8.6%)
Permanent atrial fibrillation – no. (%)	340 (52.7%)	335 (50.7%)
Unknown – no. (%)	89 (13.4%)	68 (10.3%)
Duration of atrial fibrillation – yr. (SD)	12.0 (9.2)	13.0 (9.9)
Groningen Frailty Indicator – score (IQR)	4 (3-6)	4 (3-6)
Groningen Frailty Indicator 3 (%)	170 (25.7%)	171 (25.9%)
Groningen Frailty Indicator ≥4	492 (74.3%)	490 (74.0%)
Groningen Frailty Indicator domain		
Use of ≥4 different types of medication	589 (89%)	581 (87.9)
Complaints of memory	237 (35.8%)	261 (39.5%)
Unable to walk around the house	112 (16.9%)	112 (16.9%)
Problems due to of impaired vision	297 (44.9%)	279 (42.2%)
Problems due to of impaired hearing	380 (57.4%)	353 (53.4%)
CHA_2DS_2-VASc score (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)
Heart failure – no. (%)	129 (19.5%)	150 (22.7%)
Hypertension – no. (%)	365 (55.1%)	336 (50.8%)
Diabetes – no. (%)	140 (21.1%)	140 (21.2%)
History of major bleeding – no. (%)	105 (15.9%)	88 (13.3%)
History of thromboembolic event – no. (%)	139 (21.0%)	117 (17.7%)
Active cancer – no. (%)	44 (6.6%)	35 (5.3%)
Liver cirrhosis – no. (%)	3 (0.5%)	5 (0.8%)
Body-mass index (SD)	27.4 (6.0)	27.4 (11.7)
eGFR mL/min/1.73 m^2 (SD)	62.5 (15.8)	62.7 (15.6)
Off-label reduced NOAC dose (%)	44 (6.6%)	-
Concurrent platelet inhibitor use – no. (%)	16 (2.4)	13 (2.0)

VKA = vitamin K antagonist; NOAC = non-vitamin K antagonist oral anticoagulant; SD = standard deviation; IQR = interquartile range; eGFR = estimated glomerular filtration rate.
*For continuous variables a mean is presented, except for the Groningen Frailty Indicator and the CHA_2DS_2-VASc score where a median is presented.

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Table 2. Primary and Secondary Outcomes

Variable	Switch to NOAC		Continue with VKA		
	No. (%)	No. of events / 100 patient-yr (95% CI)	No. (%)	No. of events / 100 patient-yr (95% CI)	Hazard Ratio (95% CI)
Primary outcome					
Major or CRNM bleeding	101 (15.3%)	17.8 (14.5-21.6)	62 (9.4%)	10.5 (8.0-13.4)	1.69 (1.23-2.32)
Secondary outcomes					
Bleeding outcomes separately					
Major bleeding	24 (3.6%)	3.9 (2.5-5.9)	16 (2.4%)	2.6 (1.5-4.2)	1.52 (0.81-2.87)
CRNM bleeding	84 (12.7%)	14.6 (11.7-18.1)	49 (7.4%)	8.2 (6.1-10.9)	1.77 (1.24-2.52)
TE events	16 (2.4%)	2.6 (1.5-4.3)	13 (2.0%)	2.1 (1.1-3.6)	1.26 (0.60-2.61)
Composite of TE events plus major or CRNM bleeding	115 (17.4%)	20.6 (17.0-24.7)	73 (11.0%)	12.4 (9.8-15.6)	1.65 (1.23-2.21)
Composite of ischemic and hemorrhagic stroke	14 (2.1%)	2.3 (1.3-3.8)	11 (1.7%)	1.8 (0.9-3.2)	1.30 (0.59-2.87)
All-cause mortality	44 (6.7%)	7.1 (5.2-9.5)	46 (7.0%)	7.4 (5.4-9.8)	0.96 (0.64-1.45)

CI = confidence interval; CRNM = clinically relevant non-major; No. = number; NOAC = non vitamin-K antagonist oral anticoagulant; TE = thromboembolic; VKA = vitamin K antagonist.

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Table 3. First Major or Clinically Relevant Non-major Bleeding* Location per Treatment Arm

Bleeding location	Switch to NOAC	Continue with VKA	Switch to NOAC	Continue with VKA
	Major bleedings		CRNM bleedings	
Skin – no. (%)			23 (3.5%)	10 (1.5%)
Oropharyngeal – no. (%)		1 (0.2%)	19 (2.9%)	16 (2.3%)
Gastrointestinal – no. (%)	9 (1.4%)	1 (0.2%)	8 (1.2%)	3 (0.5%)
Urogenital – no. (%)			20 (3.0%)	11 (1.7%)
Brain† – no. (%)	7 (1.1%)	6 (0.9%)		
Ophthalmic – no. (%)		1 (0.2%)	3 (0.5%)	2 (0.3%)
Musculoskeletal – no. (%)	1 (0.2%)		1 (0.2%)	4 (0.6%)
Lung – no. (%)		1 (0.2%)		
Other – no. (%)	2 (0.3%)	3 (0.5%)	8 (1.2%)	3 (0.5%)

CRNM = clinically relevant non-major; no. = number; NOAC = non vitamin-K antagonist oral anticoagulant; VKA = vitamin K antagonist.
* This Table includes only detailed information of the 163 primary endpoint bleeding events.
† Included intracranial bleeding, subarachnoid haemorrhage, and sub- and epidural bleeding, together haemorrhagic stroke.

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Figure Legends

Fig. 1: Flowchart of Included Study Participants

Fig. 2: Cumulative Incidence Curve of First (Major or Clinically Relevant Non-major) Bleeding Event

Fig. 3: Forest Plot of Subgroup Analyses

IR = incidence rate

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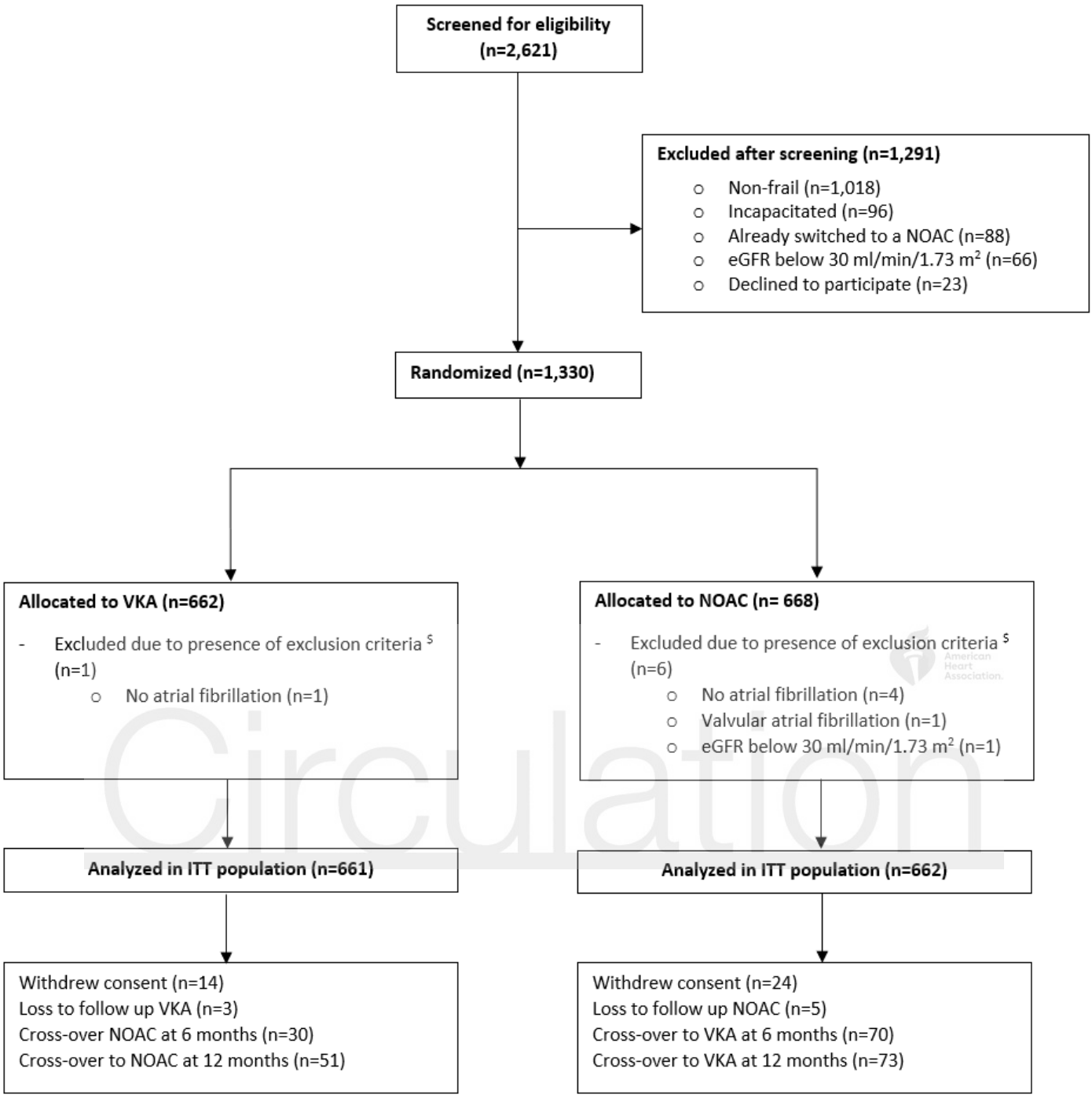

$ These patients did not receive the allocated treatment and were not analyzed in the ITT population as directly after randomization exclusion criteria were found to be present.

ITT = intention to treat; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

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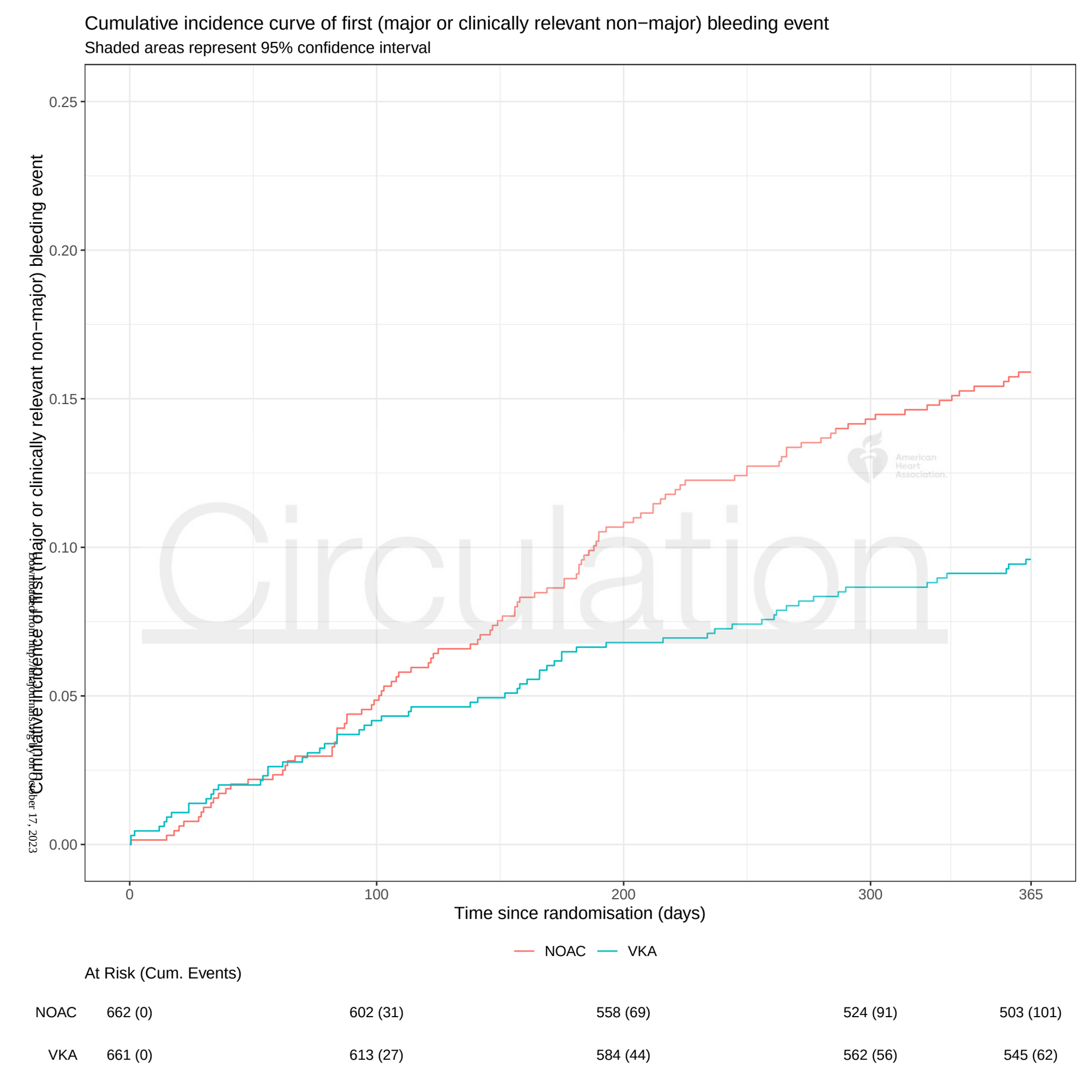

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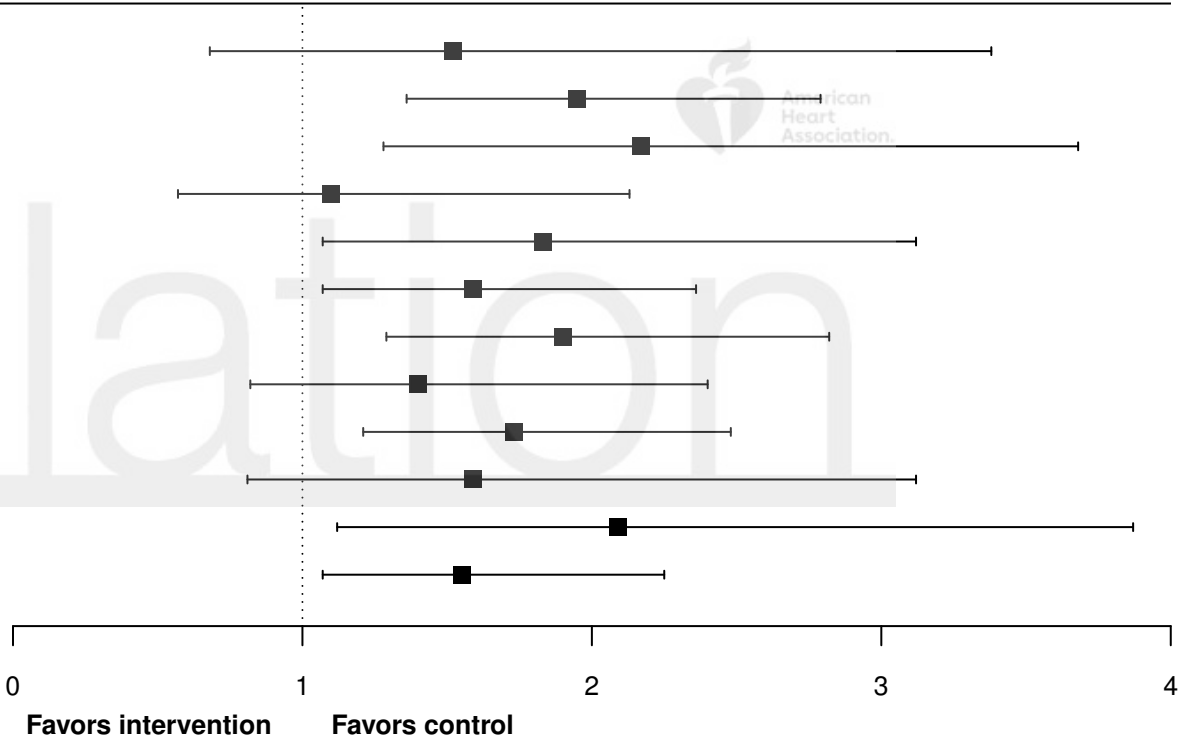
	NOAC n	IR (no. of events)	VKA n	IR (no. of events)	HR (95% CI)
Dabigatran	57	13.6 (7)	661	10.5 (62)	1.52 (0.68 – 3.38)
Rivaroxaban	332	20.8 (61)	661	10.5 (62)	1.95 (1.36 – 2.79)
Apixaban	115	19.5 (20)	661	10.5 (62)	2.17 (1.28 – 3.68)
Edoxaban	109	11.1 (11)	661	10.5 (62)	1.10 (0.57 – 2.13)
Age ...85	233	20.3 (39)	217	10.9 (21)	1.83 (1.07 – 3.12)
Age ...84	429	16.5 (62)	444	10.2 (41)	1.59 (1.07 – 2.36)
Males	388	20.4 (67)	422	10.5 (40)	1.90 (1.29 – 2.82)
Females	274	14.2 (34)	239	10.3 (22)	1.40 (0.82 – 2.40)
eGFR ...50	518	18.1 (80)	519	10.3 (48)	1.73 (1.21 – 2.48)
eGFR ...49	144	16.5 (21)	142	10.9 (14)	1.59 (0.81 – 3.12)
GFI 3	170	21.2 (31)	171	9.7 (15)	2.09 (1.12 – 3.87)
GFI ...4	492	16.6 (70)	490	10.7 (47)	1.55 (1.07 – 2.25)



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