

BMJ Open 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

Linda P T Joosten ,¹ Sander van Doorn ,¹ Arno W Hoes,¹ Melchior C Nierman,² Nynke M Wiersma,³ Huiberdina L Koek,⁴ Martin E W Hemels,^{5,6} Menno V Huisman,⁷ Kit C Roes,¹ Rutger M van den Bor,¹ Wim F Buding,⁸ Frans H Rutten,¹ Geert-Jan Geersing¹

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For numbered affiliations see end of article.

Correspondence to

Linda P T Joosten;
l.p.t.joosten-3@umcutrecht.nl

ABSTRACT

Introduction Clinical guidelines recommend non-vitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists (VKAs) for stroke prevention in most patients with atrial fibrillation (AF). Frail elderly were under-represented in the landmark NOAC-trials, leaving a knowledge gap on the optimal anticoagulant management (VKA or NOAC) in this increasing population. The aim of the Frail-AF (FRAIL-AF) study is to assess whether switching from international normalised ratio (INR)-guided VKA-management to a NOAC-based treatment strategy compared with continuing VKA-management is safe in frail elderly patients with AF.

Methods and analysis The FRAIL-AF study is a pragmatic, multicentre, open-label, randomised controlled clinical trial. Frail elderly (age ≥ 75 years plus a Groningen Frailty Indicator score ≥ 3) who receive VKA-treatment for AF in the absence of a mechanical heart valve or severe mitral valve stenosis will be randomised to switch to a NOAC-based treatment strategy or to continue INR-guided VKA-management. Patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m²) will be excluded from randomisation. Based on existing trial evidence in non-frail patients, we will aim to explore whether NOAC-treatment is superior to VKA-therapy in reducing major or clinically relevant non-major bleeding events. Secondary outcomes include minor bleeding, the composite of ischaemic and haemorrhagic stroke, health-related quality of life and cost-effectiveness. The follow-up period for all subjects is 12 months.

Ethics and dissemination The protocol was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht, the Netherlands and by the Central Committee on Research Involving Human Subjects, the Netherlands. All patients are asked written informed consent. Results are expected in 2022 and will be disseminated through peer-reviewed journals as well as presentations at national and international conferences.

Strengths and limitations of this study

- This is the first randomised controlled trial that will demonstrate whether it is safe to switch from vitamin K antagonist (VKA) to non-VKA oral anticoagulant in frail elderly patients with atrial fibrillation.
- In addition to major or clinically relevant non-major (CRNM) bleeding events (primary outcome), thromboembolic events, quality of life and cost-effectiveness will be examined.
- An interim analysis in this superiority trial will be performed after having observed 160 major or CRNM bleeding events so that the study can be halted if necessary for futility or efficacy reasons.
- Due to the open-label pragmatic design of this study, reporting bias might be an important factor that needs to be taken into account during the interim and final analysis.

Trial registration number EudraCT: 2017-000393-11; The Netherlands Trial Registry: 6721 (FRAIL-AF study).

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a prevalence rising to above 15% in the elderly.^{1,2} The most feared complication of AF is a thromboembolic event, notably ischaemic stroke.³ Anticoagulants are prescribed to reduce this risk, with vitamin K antagonists (VKAs) long being the cornerstone of stroke prevention. Although highly effective, VKAs are well known for their multiple food and drug interactions as well as changes in anticoagulation levels due to intercurrent diseases, both leading to the need for frequent international

normalised ratio (INR)-monitoring and subsequent dose adjustments. Despite intensive INR-monitoring, we know from clinical practice that thromboembolic and bleeding complications still occur in patients with AF treated with VKA. This is notably problematic in frail elderly, that is, those that due to a combination of components such as multimorbidity, social isolation, mood disorders, insufficient food and variable vitamin K intake, and/or cognitive decline are more susceptible for the side effects of anticoagulants, in particular VKAs.⁴

Treatment with a non-VKA oral anticoagulant (NOAC) is considered a convenient alternative for VKAs, also for the elderly. Monitoring of anticoagulation status is no longer needed and the standard daily dosage, where possible combined with the use of a medicine sachet system, makes it easier to use, which may result in increased treatment persistence and compliance.^{5 6} Importantly, large randomised trials and postmarketing surveillance studies in non-frail patients demonstrated that NOACs, compared with VKAs, were at least non-inferior in preventing ischaemic stroke with an overall better safety profile, notably a markedly decreased risk of intracranial haemorrhage (about 50% risk reduction), also among older (usually above 75 years) patients included in these studies.⁷⁻¹² Because of these advantages, NOACs are now recommended as the first choice anticoagulants for most patients with AF when initiating antithrombotic treatment. Moreover, guidelines even recommend to consider switching from VKA- to NOAC-treatment, especially if time in therapeutic range is not well-controlled despite good drug adherence.¹³

Importantly, frail elderly were not included in the landmark NOAC-randomised controlled trials. The evidence on the efficacy and safety of NOACs may not be generalisable to frail elderly with AF for a variety of reasons.^{14 15} To summarise, in frail elderly the dynamic pharmacokinetics have changed and as such this may be more 'fragile'. It is likely that drug distribution is generally different due to altered body composition with relatively less muscle and more fatty tissue, and prolonged availability of drugs and their remnants because of lower 'elimination' capacities of liver and kidney. In addition, cognitive impairment and interacting polypharmacy may negatively influence treatment adherence and persistence. NOACs lack control of anticoagulant status, as in VKAs with INR-monitoring, which is a disadvantage if anticoagulant status is very volatile as may be the case in the large majority of frail elderly. Finally, notably in frail elderly due to changed pharmacokinetics, switching from VKA- to NOAC-treatment possibly induces a time frame in which patients are not yet fully eliminated of VKAs while NOACs are already initiated, thereby probably (temporarily) increasing bleeding risk.

Altogether, there is currently clinical equipoise on which oral anticoagulant to use—VKAs or NOACs—in frail elderly patients who already comprise ~25% of all patients with AF, and this group is likely to increase in the near future.¹³ Importantly, there is even more uncertainty on whether or not frail elderly patients on

VKA-treatment should switch to a NOAC-based regimen, given that general clinical practice data on safety and effectiveness of switching anticoagulant treatment is confounded by the reason to switch.¹⁶ Thus, there is an urgent need for evidence from randomised studies to assess whether frail elderly should switch from VKA- to NOAC-treatment. Therefore, we designed the Frail-AF (FRAIL-AF) study. The primary objective of the FRAIL-AF study is to determine whether switching from INR-guided VKA-management to a NOAC-based treatment strategy reduces the risk of major or clinically relevant non-major (CRNM) bleeding complications compared with continuing INR-guided VKA-management in frail elderly patients with AF.

METHODS AND ANALYSIS

Study design

FRAIL-AF is a pragmatic, multicentre, open-label, randomised controlled clinical trial with a superiority design. Because studies showed non-inferior efficacy of NOACs compared with VKAs,⁷⁻¹⁰ we powered primarily on the composite safety endpoint of major or CRNM bleeding complications, where a clinically relevant reduction in bleeding complications in favour of NOACs may be expected if results of existing trial evidence in non-frail patients could be generalised to this patient category. During the planning, conduction and reporting of this protocol, we closely followed the Standard Protocol Items: Recommendations for Interventional Trials statement.¹⁷

Setting

In the Netherlands, VKA-therapy is monitored by thrombosis services. We will use existing registries of several of these thrombosis services spread over the Netherlands to select and invite eligible patients with AF on VKA-treatment, typically acenocoumarol or phenprocoumon. Randomisation and follow-up will be coordinated at the study coordinating site (University Medical Center (UMC) Utrecht, the Netherlands). All four available NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) are registered for stroke prevention in the Netherlands and can be prescribed in this study. Enrolment started in January 2018.

Patient population

Eligible subjects are (1) frail persons, (2) aged 75 years or more, (3) diagnosed with AF, (4) receiving VKA-treatment and monitoring by one of the participating thrombosis services and (5) willing to consider switching from VKA to NOAC. Frailty will be assessed with the Groningen Frailty Indicator (GFI) questionnaire (see online supplementary file S1).¹⁸ We set the threshold for frailty at ≥ 3 instead of the 'traditional' cut-off ≥ 4 on a scale from 0 to 15, because the GFI is a generic questionnaire that insufficiently takes into account that patients with AF are more vulnerable than other elderly without AF because of the need for antithrombotic medication known for their rather small

therapeutic range and risk of bleeding. Lowering the threshold in the GFI for patients with specific vulnerable diseases is a strategy that is also often applied in, for example, cancer research.¹⁹ Exclusion criteria are (1) valvular AF, that is, AF in the presence of a mechanical heart valve or severe mitral valve stenosis, (2) participation in other medical scientific drug research and (3) unwilling or unable to provide written informed consent. In addition, patients with severe renal impairment (that is, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²) will not be randomised, but will be followed observationally in parallel to the trial in order to obtain additional information about risk factors for bleeding.

Sample size calculation

There is uncertainty regarding the estimates of the yearly incidences of our composite endpoint major or CRNM bleeding complications in frail elderly patients with AF treated with VKAs^{7–10 20} as well as the effect size of reducing the occurrence of this composite endpoint when switching to a NOAC. Based on a Dutch study²¹ with an aged population we anticipate that the yearly incidence of major and CRNM bleeding complications is 10%–15% in our frail elderly using a VKA. A relative reduction of 20%–30% on the occurrence of these bleeding complications when switching to a NOAC can be expected on the basis of large-scale NOAC-trials and postmarketing observational studies, although studies specifically in frail elderly patients are lacking.^{7–10} Assuming a two-sided alpha level of 0.05, a 1:1 allocation ratio and 1250 patients in each treatment arm, power will be at least 0.80 if the incidence of major or CRNM bleeding complications on VKA-treatment is 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%). Given that power will drop below 0.50, only if the incidence of our composite outcome on VKA-treatment is on the lower margin of our expected estimation (namely at 10%) and if at least 7.7% of patients on NOAC-treatment experience major or CRNM bleeding complications (see [table 1](#)), we consider 1250 patients per group to be sufficient.

Interim analysis plan

Given the uncertainty on the ability to demonstrate a reduction in bleeding events in this frail population, a preplanned interim analysis will be performed to compare the hazard ratio (HR) on major or CRNM bleeding complications between both treatment arms, in order to anticipate futile or negative trends at a relatively early stage. The bounds for this analysis are determined based on a two-sided, asymmetric, beta-spending group sequential design with a non-binding lower bound, with an O'Brien-Fleming-type boundary (Hwang-Shih-DeCani spending function with $\gamma=-4$) for futility and a highly conservative boundary (Hwang-Shih-DeCani spending function with $\gamma=-40$) for efficacy. It is assumed that, after 12 months, the proportion

Table 1 Sample size considerations

VKA: yearly incidence of bleeding complications (%)	Assumed relative reduction (%)	NOAC: yearly incidence of bleeding complications (%)	Power*
15	30	10.5	0.92
15	25	11.25	0.79
15	20	12	0.59
10	30	7	0.77
10	25	7.5	0.60
10	20	8	0.42

*Power calculated assuming a two-sided alpha level of 0.05, a 1:1 allocation ratio, and n=1250 per arm.

NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

of bleeding events in the experimental and control arm equal 10.5% and 15%, respectively (as explained above). If we assume the survival curves are exponential, the hazard in the control arm equals 0.0135 and the hazard in the experimental arm equals 0.0092. The assumed HR, therefore, equals 0.683. Using a one-sided alpha of 0.025 and a maximum sample size of 2500 subjects (each being followed for 12 months), a power of 0.9209 is obtained for the design in which an interim analysis is performed after having observed 160 events. If, at that stage, the estimated HR exceeds 0.9925, the trial may be halted for futility, in collaboration with advice from the independent data safety monitoring board. Only if the HR then is estimated to be lower than 0.3592 (that is, an extremely large difference in favour of the experimental treatment), the trial is halted for efficacy. If the trial continues, then the final analysis is performed after having observed 319 events. If the estimated HR at that point exceeds 0.8028, futility is concluded. If not, efficacy is considered demonstrated.

Study procedures

The flow chart of the FRAIL-AF study is shown in [figure 1](#). Recruitment and enrolment will be done by the participating thrombosis services using their own patient registries. Patients will only be contacted if the patient's treating physician (usually general practitioner or cardiologist) has no objection to the patient's participation in the study, notably because for ethical reasons this study does not allow the inclusion of patients who do not understand an informed consent conversation due to, for example, severe cognitive impairment. After obtaining informed consent and before the start of the study, patients and treating physicians will be asked to provide baseline data and renal function will be measured. Subjects with severe renal impairment (that is, eGFR <30 mL/min/1.73 m²) will not be randomised, but will be followed observationally to retrieve additional information about risk factors for bleeding. Subjects with an eGFR ≥30 mL/min/1.73 m² either receive care as usual

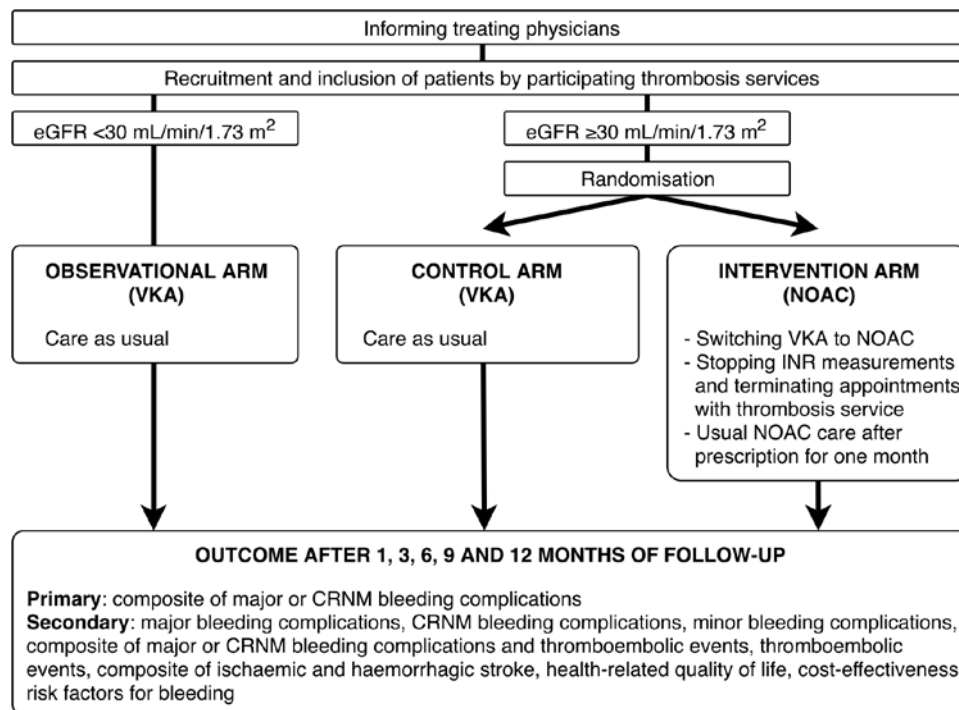


Figure 1 Flow chart of the FRAIL-AF study. CRNM, clinically relevant non-major; eGFR, estimated glomerular filtration rate; FRAIL-AF, Frail-atrial fibrillation; INR, international normalised ratio; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

(that is, continuation of VKA-treatment) (control arm) or switch to a NOAC-based treatment strategy (intervention arm), based on the random allocation of patients. Those randomised to NOAC-treatment receive their first prescription for 1 month by the research team. After 1 month, the treating physician will take over the NOAC-prescription. This strategy exemplifies the pragmatic ‘real-life’ setting of this trial.

Baseline data collection

Baseline data are collected by means of a patient questionnaire and a questionnaire for the treating physician on disease-specific information. We collect (1) patient characteristics (sex, age and body weight), (2) all 15 items of the GFI questionnaire (see online supplementary file S1), (3) all clinical items of the CHA₂DS₂-VASc rule, a commonly used rule to calculate stroke risk in patients with atrial fibrillation, consisting of the following items: history of ‘congestive’ heart failure, hypertension, age ≥75 years (two points), diabetes, stroke/transient ischaemic attack (TIA)/thromboembolism (two points), vascular disease (for example, peripheral artery disease or myocardial infarction), age 64–74 years and female sex, (4) other relevant clinical information (for example, type and duration of AF, time in therapeutic INR-range of the last year, past bleeding and thromboembolic complications, active curative or palliative malignancy), (5) concomitant medication use, (6) eGFR and (7) 5-level EuroQol 5-dimension (EQ-5D-5L) items to measure health-related quality of life.

Randomisation

Subjects are randomised to the intervention or control arm, following a computerised block randomisation with a 1:1 allocation ratio, and stratified by thrombosis service and renal function at baseline. For renal function, two strata are defined: patients with an eGFR of 30 to 50 mL/min/1.73 m² and patients with an eGFR ≥50 mL/min/1.73 m². Allocation using the randomisation results will be executed by the researchers at the study coordinating site. As this is a pragmatic randomised trial, neither patients nor treating physicians will be blinded to the allocated therapy.

Intervention under study

Patients randomised to the intervention switch from VKA-therapy to a NOAC-based treatment strategy. Because of the pragmatic design of the study and the lack of direct comparative research between NOACs that have evaluated which NOAC is the best, we feel it is not appropriate to prescribe only one type of NOAC. Therefore, treating physicians (usually general practitioners or cardiologists) of patients randomised to the intervention arm are asked which of the four available NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) they want to continue after the initial month. If preferred by the physician, this allocation will be accomplished in collaboration with local cardiologists, the thrombosis service or in shared decision making between treating physician and one of the senior researchers, and based on the summary of product characteristics (SPCs)^{22–25} and current guidelines. In

case the treating physician's chosen NOAC-dosage for an individual patient does not correspond to the recommendation in the SPC, consultation takes place between the researchers and the treating physician. However, we explicitly follow any deliberately chosen prescription regimen of the treating physician, also if the treating physician willingly chooses a higher or (more likely) lower NOAC-dose, again to mimic general clinical practice conditions as much as possible. In summary, the decision which NOAC is prescribed is tailored to the specific patients' and physicians' preferences; as such this study does not aim to compare different NOACs with each other. After all, this comparison would be highly affected by confounding by indication.

The switching itself is carried out by the thrombosis services. Initially, the study protocol allowed patients to start the NOAC after the VKA was stopped for 48 hours if the previous INR-measurement was within the therapeutic range for patients using acenocoumarol, or if a scheduled INR-measurement was below 2.0 for patients on phenprocoumon. Following patient accrual into the study, the protocol of switching VKA-treatment to NOAC-treatment was adapted to best fit the frail population. With this adjustment a NOAC is only initiated the subsequent day after an INR-measurement (performed 72 hours after stopping VKA-treatment) is below 1.3. If the INR is still above 1.3, a subsequent INR will be performed the next day to check if INR-levels have fallen below 1.3.

After 1 month, the intervention itself (that is, switching treatment from VKA to NOAC) will be completed, and NOAC-treatment will be taken over by the treating physician as part of usual care, given the pragmatic setting of this trial.

Control arm and observational arm

Subjects randomised to the control arm and those in the observational arm continue to receive care as usual, that is, VKA-treatment (in the Netherlands either acenocoumarol or phenprocoumon) aiming at an INR-target value between 2.0 and 3.0, with monitoring by the Dutch thrombosis services. Outcomes of patients in the observational arm are not included in the primary comparison of outcomes between both randomised treatment arms, but will be included in a secondary analysis exploring potential predictors of bleeding, as explained below in the section on data analysis.

Neither switch to NOAC-treatment in the control or observational arm, nor switch back to VKA-treatment in the intervention arm are contraindicated. Hence, it is likely that some form of crossover (that is, patients randomised to a NOAC who switch back to a VKA, and vice versa) between both randomised treatment arms will occur; this will probably also happen in general clinical practice, and is therefore permitted in this pragmatic trial.

Study outcome assessment

Endpoints are collected after 1, 3, 6, 9 and 12 months of follow-up using a standardised questionnaire administered to the patient by telephone (see online supplementary file S2 for a description of primary and secondary outcomes). If necessary, additional information on endpoints is obtained from the patient's treating physician. Data are collected on medication use and on the primary composite endpoint of major or CRNM bleeding complications, based on the definition of the International Society on Thrombosis and Haemostasis (ISTH).^{26 27} Accordingly, major bleeding is defined as fatal bleeding, and/or bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells. CRNM bleeding is defined as any sign or symptom of haemorrhage (for example, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH-definition of major bleeding but does meet at least one of the following criteria: bleeding requiring medical intervention by a healthcare professional, and/or leading to hospitalisation or increased level of care, and/or prompting a face-to-face (that is, not just a telephone or electronic communication) evaluation. Secondary outcomes are (1) major bleeding complications (separate from CRNM bleeding complications), (2) CRNM bleeding complications (separate from major bleeding complications), (3) minor bleeding complications (that is, all bleeding complications that are not classified as major or CRNM bleeding complication according to the definition of the ISTH), (4) composite of major or CRNM bleeding complications and thromboembolic events (where thromboembolic events are defined as ischaemic stroke, TIA and peripheral arterial thromboembolism), (5) thromboembolic events, (6) composite of ischaemic and haemorrhagic stroke, (7) health-related quality of life (measured after 6 and 12 months from baseline), (8) cost-effectiveness and (9) identification of risk factors for bleeding. Cost-effectiveness will be calculated on the basis of the EQ-5D-5L questionnaire (to calculate quality-adjusted life years (QALYs)), and on details of healthcare utilisation (hospitalisation (for example, duration and intensive care admission), doctor visits and other additional care).

An independent committee, consisting of several different physicians and blinded for the randomisation allocation, will first adjudicate all fatal outcomes, both in the intervention and in the control (and observational) arm, using all available patient data. Further adjudication of other outcomes may be warranted following observations made in the trial.

Data analysis

The primary analysis of this randomised controlled trial will be based on the intention-to-treat principle



in a Cox proportional hazards model, after checking for the proportional hazards assumption. Model estimates are used to calculate the hazard of the occurrence of a major or CRNM bleeding complication, whichever comes first. Treatment-specific Kaplan-Meier survival curves will be plotted to graphically illustrate the results. For total incidence of events, where recurrent events within the same patient are accounted for, Poisson regression and/or negative binomial regression will be applied, accounting for overdispersion as appropriate. For some bleeding complications, it may not be possible to obtain the exact occurrence dates, resulting in interval censoring. We expect that ignoring interval censoring, and using midpoint imputation, will not have a substantial impact on the results as telephone assessors are instructed to reduce the length of the time interval as much as possible. However, to assess the robustness of the results, we will perform additional sensitivity analyses that formally address the issue of interval censoring.

Analyses of the secondary endpoints will follow the primary analysis, where appropriate. Cost-effectiveness will be assessed by means of the incremental cost-effectiveness ratio, that is, the difference in average costs between the intervention and the control arm, divided by the difference in QALYs between both arms. Unit prices will be based on Dutch standard prices for economic evaluations in healthcare in order to facilitate comparisons with other economic evaluations.²⁸ A Cox regression model will be used for the identification of risk factors for bleeding in frail elderly patients with AF treated with either VKA or NOAC. For this, also data in the observational arm (that is, subjects with an eGFR <30 mL/min/1.73 m²) will be used.

Patient and public involvement

A patient representative is part of the study board of the FRAIL-AF trial (WFB). He was not explicitly involved in the initial conception of the study, which was investigator initiated, but played an important role in the writing and further conceptualisation of the study protocol, particularly related to how to inform patients on consent and study procedures, including an assessment of the burden of the intervention. He also plays an important part in monitoring the progress of patients in the study and is actively involved in all study board progress meetings. Results will be disseminated to all study participants and their care givers after study completion.

ETHICS AND DISSEMINATION

The FRAIL-AF study will be conducted according to the principles of the Declaration of Helsinki²⁹ and in accordance with Dutch law (the Medical Research Involving Human Subjects Act (WMO)).³⁰ The protocol was approved by the Medical Research Ethics Committee of the UMC Utrecht, the Netherlands (reviewing

committee), and by the Central Committee on Research Involving Human Subjects, the Netherlands (competent authority). All patients are asked written informed consent before being randomised or followed observationally. Patients' personal data will be saved separate from baseline and follow-up data, and their privacy will be guaranteed throughout the entire study. The progress of the study, the occurrence of (serious) adverse events and finally the overall safety of the frail elderly participating in this trial will be assessed on a frequent basis by an independent data safety monitoring board. In addition, quality assurance will be guaranteed by monitoring. Results are expected in 2022 and will be disseminated through peer-reviewed publications and presentations at national and international conferences.

DISCUSSION

The FRAIL-AF open-label pragmatic randomised trial will be the first study to evaluate whether switching from INR-guided VKA-management to a NOAC-based treatment strategy is a safe alternative for continuing INR-guided VKA-management in frail elderly patients with AF. A recent randomised pilot study confirmed the safety and effectiveness of switching VKA-treatment to a NOAC (n=121) compared with continuing VKAs (n=120), although in a different study population namely those with a time in therapeutic INR-range of 70% or higher and a mean age of 73.0 years in those switching from VKA-treatment to a NOAC.³¹

Hence, frail elderly patients with AF are under-represented in the existing trial evidence on the safety and efficacy of NOAC-treatment for stroke prevention, compared with VKA-therapy. If — what might be expected from existing trial results and postmarketing observational studies in non-frail patients with AF — switching from INR-guided VKA-management to a NOAC-based treatment strategy compared with continuing INR-guided VKA-management is superior in terms of less bleeding in frail elderly, this would be a breakthrough in managing stroke risk in these vulnerable patients with AF. Clinicians caring for these patients know that despite frequent INR-monitoring in this patient group, it is often challenging to achieve a sufficient time in therapeutic range when treated with VKAs. The clinical consequence might be the occurrence of thromboembolic or bleeding complications.³² Elderly patients on VKA showed they are willing to switch to an alternative anticoagulant drug, provided it is safe and effective,^{33 34} which exactly is what we aim to evaluate in this trial. If the opposite is true and switching to NOACs is unsafe in frail elderly, we should reconsider switching from VKA to NOAC in frail elderly patients with AF.

For full appreciation of this ongoing trial, several topics deserve attention. First, this trial will provide evidence on the question whether switching from VKA to NOAC reduces the risk of bleeding complications compared with continuing VKA-treatment. Findings should, thus,

be considered in that light and are not directly applicable to anticoagulant naïve frail elderly patients. Second, only patients willing to switch to a NOAC participate in our study. This is related to giving informed consent and could, to a certain extent, lead to patient selection. As with any randomised study, this may affect generalisability. However, this does not lead to selection bias, because selection in this study is the same for both groups due to randomisation after giving informed consent. Third, in our pragmatic study, patients are not blinded for randomisation allocation, as is common in studies evaluating VKAs in a non-explanatory trial. If patients would be blinded, mock INR-blood samples from patients in the NOAC-arm would have been needed, thereby increasing patient burden and influencing the estimation of two of our secondary outcomes (health related quality of life and cost-effectiveness). In addition, our primary outcome is major or CRNM bleeding complications, which we consider to be an objective measurement. The adjudication of all fatal outcomes will, however, be carried out blindly by an independent adjudication committee, which minimises the risk of information bias (for example, misclassification). Fourth, this study relies on patient reported outcome measures, collected at regular intervals at 1, 3, 6, 9 and 12 months. This might lead to reporting bias (reporting difference between the intervention and the control arm). Though, given the nature of the events collected (notably for our primary outcome major or CRNM bleeding complications) we believe missing events and reporting bias is unlikely. Additionally, when events are suspected based on our patient contacts, all routinely collected data will be scrutinised to enable accurate classification of outcome events.

CONCLUSION

This will be the first study to determine whether switching from INR-guided VKA-management to a NOAC-based treatment strategy is a safe alternative for continuing INR-guided VKA-management in frail elderly patients with AF.

Author affiliations

¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

²Department of Thrombosis and Anticoagulation, Atalmedial Medical Diagnostics Centers, Amsterdam, The Netherlands

³Department of Thrombosis and Anticoagulation, Diagnostic Center Salto, Utrecht, The Netherlands

⁴Department of Geriatrics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

⁵Department of Cardiology, Rijnstate Hospital, Arnhem, The Netherlands

⁶Department of Cardiology, Radboud University Medical Center, Radboud University, Nijmegen, The Netherlands

⁷Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden University, Leiden, The Netherlands

⁸Member of the Dutch Organisation for patients using anticoagulant medication, CTD Nederland, Leiden, The Netherlands

Twitter Geert-Jan Geersing @gjeersing

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Contributors G-JG, FHR and AWH conceived and initiated the study. LPTJ, SvD, MCN, NMW, HLK, MVH, MEWH and WFB provided input on the study design, with RMvdB and KCR providing statistical and trial expertise. LPTJ and G-JG wrote the first manuscript draft and subsequent revisions. All authors critically reviewed and revised the manuscript before granting approval.

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Competing interests G-JG and FHR report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer and Daiichi Sankyo. MEWH reports personal fees from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer and Daiichi Sankyo, and grants from The Netherlands Organisation for Health Research and Development (ZonMw), outside the submitted work. MVH reports grants from The Netherlands Organisation for Health Research and Development (ZonMw), Dutch Healthcare Fund and grants and personal fees from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer, Daiichi Sankyo and Aspen, outside the submitted work. All other authors (LPTJ, SvD, AWH, MCN, NMW, HLK, KCR, RMvdB and WFB) report no competing interests.

Patient consent for publication Not required.

Ethics approval The protocol was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht, the Netherlands (reviewing committee) on 7 September 2017, and by the Central Committee on Research Involving Human Subjects, the Netherlands (competent authority) on 3 July 2017.

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ORCID iDs

Linda P T Joosten <http://orcid.org/0000-0002-0926-9749>

Sander van Doorn <http://orcid.org/0000-0003-4319-3503>

REFERENCES

- 1 Heeringa J, van der Kuip DAM, Hofman A, *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–53.
- 2 McCormick Det *et al*. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. *Arch Intern Med* 2001;161:2458–63.
- 3 Hart RG, Pearce LA, Aguilar MI. Meta-analysis : antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–67.
- 4 Torn M, Bollen WLEM, van der Meer FJM, *et al*. Risks of oral anticoagulant therapy with increasing age. *Arch Intern Med* 2005;165:1527–32.
- 5 Laliberté F, Cloutier M, Nelson WW, *et al*. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin* 2014;30:1317–25.
- 6 Zalesak M, Siu K, Francis K, *et al*. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circulation* 2013;6:567–74.
- 7 Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med Overseas Ed* 2009;361:1139–51.

- 8 Patel MR, Mahaffey KW, Garg J, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
- 9 Granger CB, Alexander JH, McMurray JJV, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
- 10 Giugliano RP, Ruff CT, Braunwald E, *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
- 11 Sharma M, Cornelius VR, Patel JP, *et al.* Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism. *Circulation* 2015;132:194–204.
- 12 Romanelli RJ, Nolting L, Dolginsky M, *et al.* Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2016;9:126–34.
- 13 Kirchhof P, Benussi S, Kotecha D, *et al.* 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016;50:e1–88.
- 14 Hägg L, Johansson C, Jansson J-H, *et al.* External validity of the ARISTOTLE trial in real-life atrial fibrillation patients. *Cardiovasc Ther* 2014;32:214–8.
- 15 Pfeilschifter W, Luger S, Brunkhorst R, *et al.* The Gap between Trial Data and Clinical Practice - An Analysis of Case Reports on Bleeding Complications Occurring under Dabigatran and Rivaroxaban Anticoagulation. *Cerebrovasc Dis* 2013;36:115–9.
- 16 Hellfritzsch M, Adelborg K, Damkier P, *et al.* Effectiveness and safety of direct oral anticoagulants in atrial fibrillation patients switched from vitamin K antagonists: a systematic review and meta-analysis. *Basic Clin Pharmacol Toxicol* 2019;128.
- 17 Chan A-W, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- 18 Steverink N, Slaets J, Schuurmans H, *et al.* Measuring frailty: developing and testing the GFI (Groningen frailty indicator). *Gerontologist* 2001;41:236–7.
- 19 Baitar A, Van Fraeyenhove F, Vandebroek A, *et al.* Evaluation of the Groningen frailty indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. *J Geriatr Oncol* 2013;4:32–8.
- 20 Mant J, Hobbs FDR, Fletcher K, *et al.* Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493–503.
- 21 Kooistra HAM, Calf AH, Piersma-Wichers M, *et al.* Risk of bleeding and thrombosis in patients 70 years or older using vitamin K antagonists. *JAMA Intern Med* 2016;176:1176–83.
- 22 Boehringer Ingelheim Pharma GmbH & Co. KG. Samenvatting van de productkenmerken van dabigatran. Available: http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf [Accessed 1 Aug 2018].
- 23 Bayer Pharma AG and Bayer HealthCare Manufacturing S.r.l. Samenvatting van de productkenmerken van rivaroxaban. Available: http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf [Accessed 1 Aug 2018].
- 24 Bristol-Myers Squibb S.r.l. and Phizer Manufacturing Deutschland GmbH. Samenvatting van de productkenmerken van apixaban. Available: http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf [Accessed 1 Aug 2018].
- 25 Daiichi Sankyo Europa GmbH. Samenvatting van de productkenmerken van edoxaban. Available: http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf [Accessed 1 Aug 2018].
- 26 Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–4.
- 27 Kaatz S, Ahmad D, Spyropoulos AC, *et al.* 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. *J Thromb Haemost* 2015;13:2119–26.
- 28 Hakkaart-van Roijen L, van der Linden N, Bouwmans C, *et al.* *Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg*, 2015: 1–24.
- 29 World Medical Association. *WMA Declaration of Helsinki -Ethical principles for medical research involving human subjects*, 2013.
- 30 Wet medisch-wetenschappelijk onderzoek met mensen, 1998. Available: <https://wetten.overheid.nl/BWBR0009408/2018-08-01> [Accessed 1 Aug 2018].
- 31 van Miert JHA, Kooistra HAM, Veeger NJGM, *et al.* Choosing between continuing vitamin K antagonists (VKA) or switching to a direct oral anticoagulant in currently well-controlled patients on VKA for atrial fibrillation: a randomised controlled trial (GAINN). *Br J Haematol* 2019;186:e21–3.
- 32 Ogilvie IM, Newton N, Welner SA, *et al.* Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;123:638–45.
- 33 Attaya S, Bornstein T, Ronquillo N, *et al.* Study of warfarin patients investigating attitudes toward therapy change (SWITCH survey). *Am J Ther* 2012;19:432–5.
- 34 Boom MS, Berghuis EM, Nieuwkerk PT, *et al.* When do patients prefer a direct oral anticoagulant over a vitamin K antagonist? *Neth J Med* 2015;73:368–72.