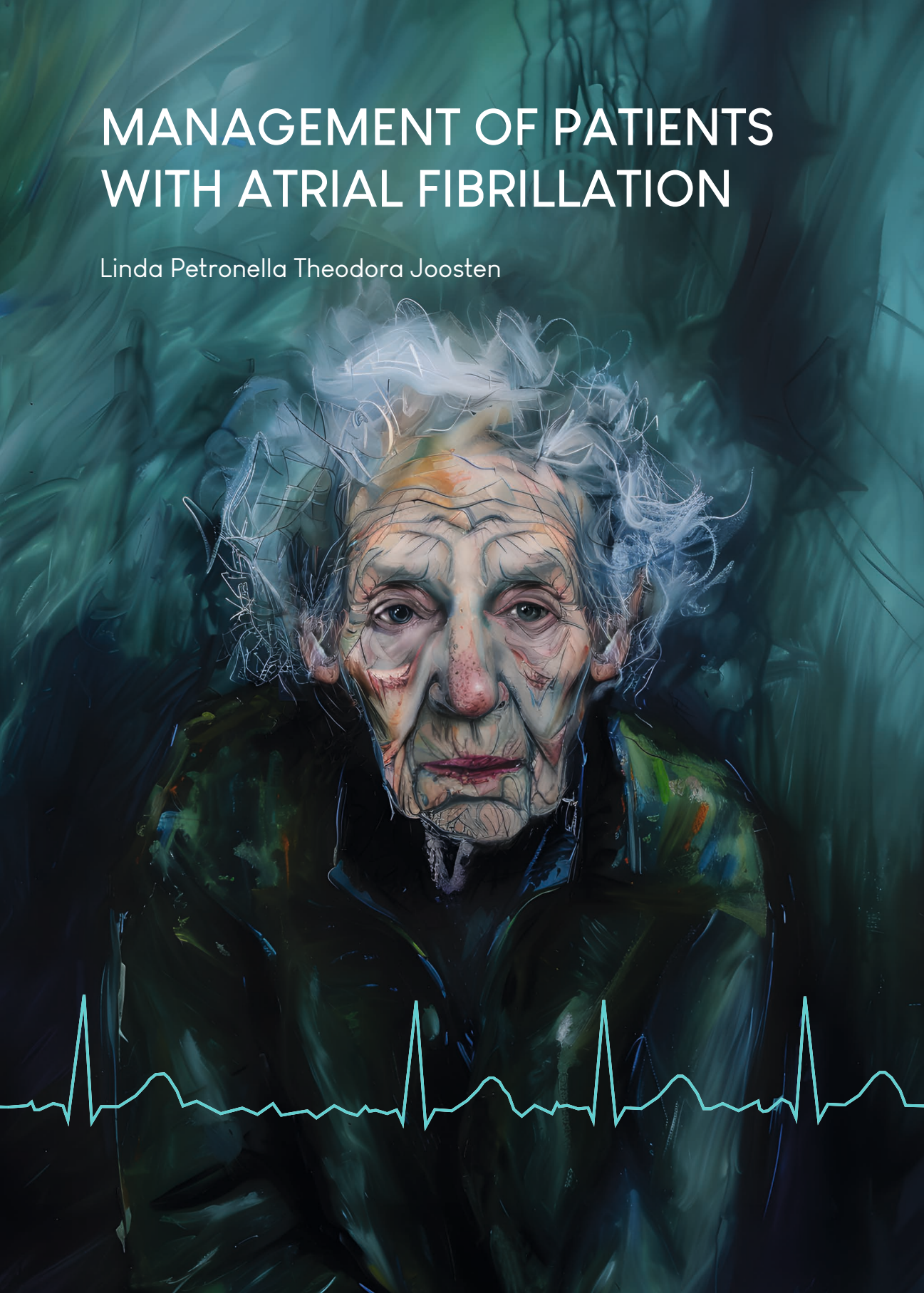
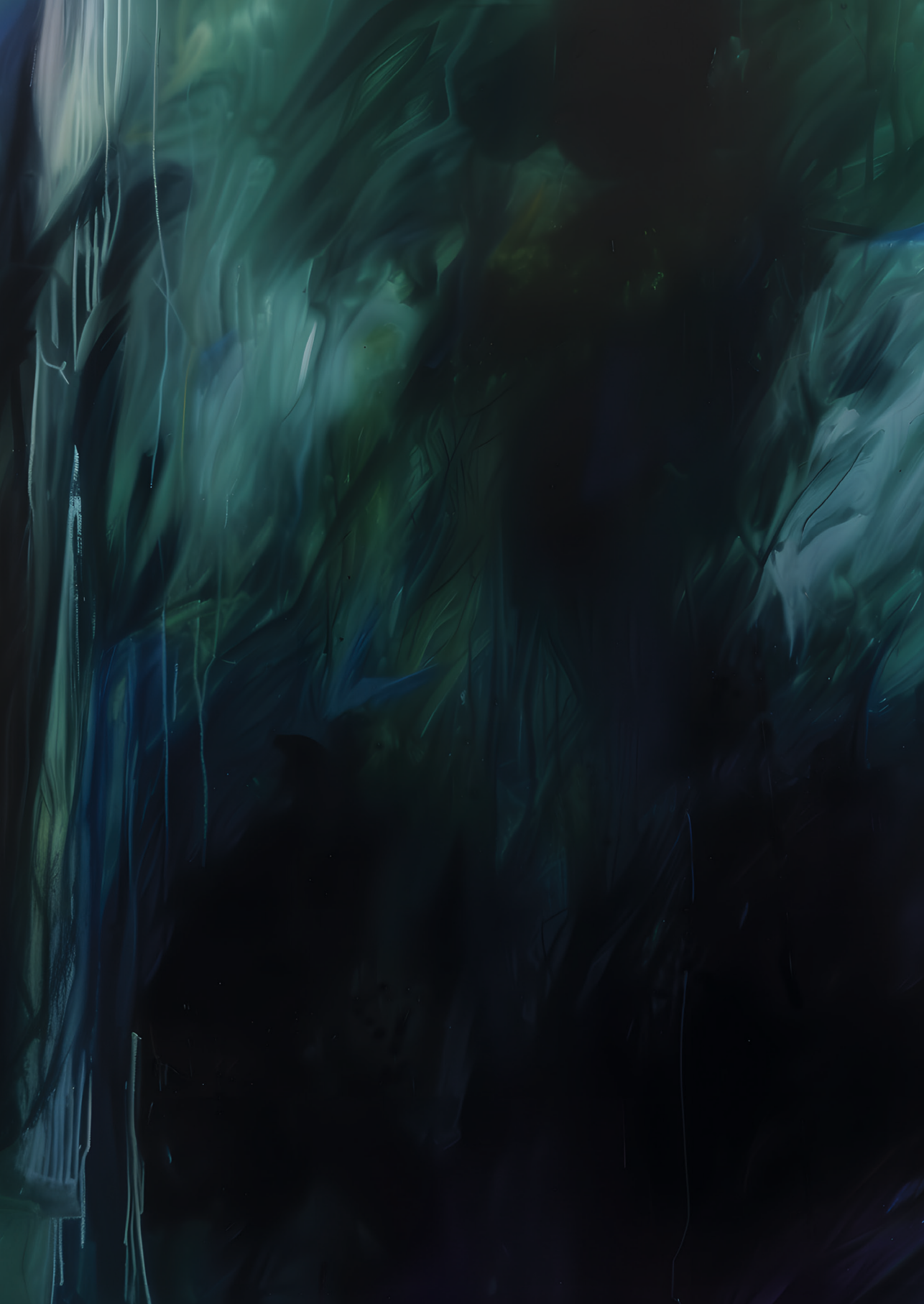
MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION

Linda Petronella Theodora Joosten





MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION

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Management of patients with atrial fibrillation
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MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION

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Voor mijn ouders

CONTENTS

GENERAL INTRODUCTION: MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION

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Linda P.T. Joosten

THE CASE OF MRS. DE JONG

Mrs. de Jong is 80-years old and has been living alone since her husband died two years ago in 2018. She is frequently visited by her general practitioner (GP), most often for complaints of pain caused by coxarthrosis and shortness of breath due to heart failure; both reasons why she no longer manages to go out for grocery shopping on her own. In addition, she is known with hypertension, mitral valve insufficiency, vascular disease, diabetes mellitus, presbycusis, and mild cognitive impairment. Her medication list includes six different types of drugs.

May 2020 – Her GP receives a phone call from her worried son. Mrs. de Jong has been admitted with coronavirus disease 2019 (COVID-19) and has also developed atrial fibrillation (AF) during admission. The GP had previously read an interesting paper in the journal 'Huisarts & Wetenschap', stating that during a respiratory tract infection patients are more prone to developing cardiovascular diseases, including AF, and that they are in an increased prothrombotic state. The GP wonders whether the pathophysiology of an increased ischaemic stroke risk in AF is actually fully understood and whether everything the GP learned about it at medical school is still valid. The son of Mrs. de Jong brings the GP back to reality; he fears that his mother will not survive the admission given these two diseases new to her and her advanced age. He asks whether her GP can tell him anything about her risk of dying. Unfortunately, the GP has to explain that it is not possible to predict mortality risk, because there is still very little known about the impact of COVID-19.

July 2020 – Mrs. de Jong survived the hospital admission and is back home where daily home care has been initiated by her GP. Her AF appeared to be permanent. This means, considering her CHA_2DS_2-VASc score of 5, that her ischaemic stroke risk would be 8.4% per year on average if left untreated.[1] A vitamin K antagonist oral anticoagulant (VKA) was started during hospitalisation. According to the available evidence, a VKA will reduce her ischaemic stroke risk by 67% (from 8.4% to 2.8% per year; i.e. an absolute risk reduction of 5.6% per year) .[2] Thus, although accompanied by an increase in major bleeding (from around 0.9% to 1.5% per year),[2] there is no doubt that Mrs. de Jong should receive oral anticoagulation. Importantly, her GP wonders how certain the optimal threshold of the CHA_2DS_2-VASc score above which oral anticoagulation should be initiated (i.e. 3 for women and 2 for men) actually is. Moreover, the GP wonders why the cardiologist chose a VKA instead of a non-VKA oral anticoagulant (NOAC) given that cardiologists are increasingly prescribing NOACs instead of VKAs when initiating oral anticoagulation in AF patients.

April 2023 – For several months, Mrs. de Jong complains that she suffers more frequently from nosebleeds and that she dislikes the bruises on her skin, especially on her arms. Her GP wonders whether it might be better for her to switch from her VKA to a NOAC as randomised controlled trials showed that NOACs compared to VKAs are at least as

effective in preventing ischaemic stroke but cause less (major) bleeding in patients with AF. However, the GP realises that frail old patients such as Mrs. de Jong were highly underrepresented in these pivotal trials. While thinking about how to minimise both the risk of stroke and the risk of bleeding as much as possible, the GP also considers switching to a NOAC with an off-label reduced NOAC dose. Eventually, the GP decides not to switch at all, because of the lack of evidence for either option.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is one of the most common cardiac conditions with a lifetime risk of one in three individuals of Western ancestry.[3] AF is particularly common in the ageing population with a prevalence of 0.7% in people aged 55 to 59 years, rising to 17.8% in those aged 85 years and older,[4] and rising even further to 38% in the most frail population in society (i.e. nursing home residents).[5] Importantly, the overall prevalence of AF is increasing due to the ageing of the population and is expected to double within half a century.[6] This has a major impact on public health as AF is associated with severe morbidity and mortality.

The most feared complication of AF is the occurrence of an ischaemic stroke which, without anticoagulation, occurs nearly five times more often in patients with AF compared to patients without AF.[7] However, it is important to note that this evidence dates back to 1991, which makes it very well possible that this risk is different in today's AF population that generally suffers from more comorbidities but benefits from improved healthcare. To estimate stroke risk in untreated AF patients, prediction models have been developed, of which the CHA_2DS_2-VASc model is the most widely used.[8] However, with a concordance-statistic for ischaemic stroke of 0.67 (95% confidence interval (95% CI) 0.66-0.68), the ability to predict stroke, in particular for intermediate and high risk patients, is not very accurate.[1] Nevertheless, the European Society of Cardiology recommends oral anticoagulation therapy, with the aim to prevent stroke, when the CHA_2DS_2-VASc score is ≥2 points in men or ≥3 points in women.[9,10]

ANTICOAGULANTS

Without anticoagulation, stroke risk can be as high as 14.4% per year in AF patients with multimorbidity, as summarised by the CHA_2DS_2-VASc risk model.[1] In 1989, the AFASAK study was the first randomised controlled trial (RCT) showing effectiveness of oral anticoagulation for stroke prevention in AF.[11] During the years that followed, it became apparent that treatment with oral anticoagulants reduced the risk of an ischaemic stroke by 67% (95% CI 54%-77%).[2] Until 2008, the only type of oral

anticoagulation effective in stroke prevention in patients with AF was a vitamin K antagonist (VKA), such as warfarin, acenocoumarol and phenprocoumon. From 2008 onwards, another oral anticoagulant became available, namely a non-VKA antagonist oral anticoagulant (NOAC), also known as a direct oral anticoagulant (DOAC). There are currently four different NOACs on the market: apixaban, dabigatran, edoxaban, and rivaroxaban. The four pivotal NOAC trials showed that, compared with VKAs, NOACs are at least as effective in preventing ischaemic stroke, but overall have a better safety profile, i.e. a lower risk of severe bleeding, notably intracranial bleeding (relative risk reduction ranging from 29% in patients receiving rivaroxaban to 74% in patients receiving a non-reduced dose of dabigatran).[12–15]. Therefore, since 2016, guidelines recommend a NOAC in newly diagnosed AF patients instead of VKA treatment, especially when there are no contraindications for a NOAC. Also according to these guidelines, in AF patients already treated with a VKA, switching to NOAC treatment may be considered if time in therapeutic range is not well controlled despite good adherence, or if patients prefer a NOAC and have no contra-indications a NOAC.[9] Which NOAC is best is not known, because NOACs have never been compared head-to-head to each other in an RCT.

FRAILTY AND THE CONSISTENT LACK OF EVIDENCE

Frailty involves a lot more than just ageing, multiple comorbidities and polypharmacy. It is a clinical syndrome defined by a high biological vulnerability and a reduced capacity to resist stressors, all leading to reduced homeostatic reserve and to dependency on others.[16] In the Netherlands, it is estimated that there are currently 730,000 frail older people (i.e. more than 1 in 25 individuals).[17,18] The population of frail elderly grows rapidly as, largely due to improved healthcare, there is a shift in the burden of morbidity from acute to chronic diseases (including AF) and life expectancy increases.[17–19] As described above, AF is common, especially in frail older people in whom the prevalence is around 40%.[5] The incidence of stroke in frail older patients with AF peaks at 12.3% per year compared to 3.9% per year in non-frail older patients with AF.[5] A considerable amount of research has been conducted on AF and its treatment with oral anticoagulation, but important questions remain, especially for the frail elderly population. For example, it is uncertain whether NOACs should be preferred over VKAs in frail older AF patients and it is even more questionable whether frail elderly patients with AF who are stable on VKA treatment should be switched to a NOAC. Observational studies do not provide a proper answer to these questions because they suffer from confounding. And, surprisingly, almost no RCTs have been conducted in frail older people (neither in the field of AF nor in most other clinical fields), which is unjustified given that in this large and increasing population there is the greatest need for evidence and personalised management. Currently, results from

RCTs performed in a selective population including few or no frail elderly are incorrectly generalised to frail older people.

The assumption that the results from RCTs in general cannot simply be generalised to the population of frail older people is entirely valid. Frail older people have a large volatility, for example in anticoagulation status. This large volatility is due to problems with treatment adherence which is often associated with polypharmacy and some degree of cognitive impairment. Furthermore, these fluctuations are due to different pharmacokinetics and pharmacodynamics, which respectively means that the human body of frail elderly, who often suffer from multimorbidity, processes medication differently compared to non-frail elderly (i.e. they have a different absorption, distribution, metabolism and excretion of medication), and that medication itself has different effects in frail elderly compared to non-frail elderly. Therefore, the balance, in this example between coagulation and bleeding, is more fragile in frail older people. Regarding AF management, this fragile balance may influence the effects of oral anticoagulation. Perhaps VKA treatment with monitoring through international normalised ratio testing instead of NOAC treatment is safer for frail older patients because it allows early intervention by titrating the VKA dose to the most optimal range. Given the differences between frail and non-frail elderly and current speculations rather than evidence, RCTs in frail elderly patients are urgently needed, especially towards comparing VKA treatment with NOAC treatment in frail older patients with AF.

THESIS OUTLINE

In the management of patients it may be useful to understand the underlying pathophysiological mechanisms of the disease involved or to have an explainable model of the particular disease. Therefore, in **Chapter 2** the role of a hypercoagulable or prothrombotic state as pathophysiological mechanism for increased ischaemic stroke risk in patients with AF was explored. A hypercoagulable or prothrombotic state may also at least partly explain why patients with an respiratory tract infection, such as coronavirus disease 2019 (COVID-19), are more prone to developing AF and other (cardiovascular) morbidities. In **Chapter 3**, the sex- and age specific association of new-onset AF with in-hospital mortality was assessed in hospitalised COVID-19 patients mainly during the first COVID-19 wave.

Chapters four to eight consist of studies on oral anticoagulant treatment of AF. **Chapter 4** is a response letter to a published article about stroke rate variation and anticoagulation benefit in patients with AF. Notably, the balance between the risk of ischaemic stroke and bleeding in those with a low CHA_2DS_2-VASc score was discussed. **Chapter 5** provides an overview of the trends in prevalence of AF and antithrombotic

prescriptions in the community from 2008 to 2017. In Chapter 6 and 7, in-depth exploration was conducted through an RCT: the FRAIL-AF trial which aimed to evaluate the safety of switching from a VKA to a NOAC compared to continuing with a VKA in frail older patients with AF. In **Chapter 6,** the rationale and design of the FRAIL-AF trial were described and in **Chapter 7** the results of this RCT were presented. Important in treatment with oral anticoagulation is determining the correct dose. Postmarketing observational studies show that some patients are treated with a reduced NOAC dose without a clear indication for dose reduction. In **Chapter 8** a systematic review and meta-analysis on the clinical consequences of this so-called off-label reduced dosing of NOACs was described in patients with AF.

In **Chapter 9,** the main findings of this thesis and their practical implications were described in relation to the case of Mrs. de Jong, unanswered questions in relation to the FRAIL-AF trial were provided and, most important, one of the main messages of this thesis was extensively discussed.

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ATRIAL FIBRILLATION: A SYSTEMIC CARDIOVASCULAR DISEASE IN NEED FOR INTEGRATED CARDIOVASCULAR RISK MANAGEMENT

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Submitted

INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac conditions with a prevalence of around 1-2% in the general population, and with higher rates among those with advancing age. The prevalence of AF is expected to double in the next few decades, mainly due to the ageing of the population.[1]

The latest ESC guidelines on AF recommend integrated care across all healthcare levels and among different specialties for all AF patients according to the 'Atrial Fibrillation Better Care (ABC) holistic pathway'. In this acronym, the A represents 'anticoagulation/avoid stroke', the B 'better symptom management', and the C 'cardiovascular and comorbidity optimisation'.[2] Currently, with the publications of the landmark EAST-AFNET randomised controlled trials reporting positive effects of (systematic) early ablation on improving patient outcomes, scientific focus is on 'better symptom management'.[3,4] Avoiding stroke and optimising the cardiovascular risk-factor burden and comorbidities are, however, at least equally important. By reaching back to the pathophysiology of increased stroke risk in patients with AF, we want to further explain the rationale behind the ABC strategy and provide suggestions on how to achieve optimal AF care.

THE CLASSIC PARADIGM IN PATHOPHYSIOLOGY

In the famous Framingham Heart cohort in which patients are followed for many years to study risk factors for cardiovascular disease, stroke risk in AF patients was found to be up to five times higher compared to patients without AF.[5] It is important to note, however, that this evidence originates from 1991. Therefore, it is very well possible that this risk is slightly different in today's AF population, which experiences more comorbidities but also benefits from advancements in healthcare. More importantly, why is it that stroke risk is so much higher in AF patients? Post mortem studies reported on cerebral emboli in a significant amount of AF patients,[6,7] which led to the theoretical concept that in fibrillating atria cardiac thrombi may develop because of blood stasis, most commonly in the left atrial appendage. When these thrombi migrate, they can cause ischaemic stroke further upstream. However, it is not likely that this is the only causal mechanism for ischaemic stroke in patients with AF for a variety of reasons. First, there is often a temporal dissociation between ischaemic stroke and AF, in which ischaemic stroke precedes a period of AF or in which ischaemic stroke occurs after having had AF for a long period of time.[8,9] Second, many studies have shown that there is a persistently increased stroke risk in AF patients, even after sinus rhythm is restored, thus after the period of fibrillating atria and blood stasis in the left atrial appendage.[10] Third, there is clear bidirectionality between AF and venous thromboembolism, where AF is associated with an increased risk not only of pulmonary embolism but also of

deep vein thrombosis, and vice versa, underpinning that ischaemic stroke risk in AF is also (at least partly) related to a hypercoagulable or prothrombotic state.[11]

ATRIAL FIBRILLATION: A SYSTEMIC CARDIOVASCULAR DISEASE

As is commonly known, haemostatic response starts with platelet adhesion, wherein damaged endothelial cells and collagen attract platelets to the site of injury according to Virchow's triad. Following adhesion, platelets undergo activation, transitioning to an active state and responding to various stimuli such as thrombin. This platelet activation leads to further adhesion and the formation of a platelet plug at the injured site. Ultimately platelet aggregation occurs, wherein activated platelets adhere to each other, forming a blood clot.

The view that AF is a complex systemic cardiovascular disease that, together with comorbidities, maintains a systemic hypercoagulable or prothrombotic state, thereby contributing to AF related complications such as ischaemic stroke, can be clarified using Virchow's triad for thrombogenesis. Below, we explain that, apart from abnormal decreased blood flow (i.e. stasis of the blood), also abnormal changes in the walls of blood vessels and atria and abnormal changes in blood constituents complete this triad for thrombogenesis in patients with AF.[12,13]

First of all, studies have shown abnormal changes in the walls of blood vessels and atria in patients with AF compared to patients without AF, a finding currently described as atrial cardiomyopathy. For example, a post mortem study in patients with ischaemic stroke described a 'rough' endocardium with a wrinkled appearance (due to oedema and fibrinous transformation), areas of denudation of the endothelium and aggregation of thrombi in those with AF compared to those without AF.[14] In addition, Weijs et al. showed that, over a period of five years, patients diagnosed with AF compared to those without AF, develop cardiovascular disease (such as ischaemic stroke, myocardial infarction and heart failure) more often (49% versus 20%, P=0.006), at a younger age (59 versus 64 years, P=0.027), and with a more severe disease profile.[15] Moreover, the presence of a complex plaque (i.e. a plaque with a thickness greater than 4 millimetre, or containing ulceration, pedunculation, or mobile elements) in the aorta of AF patients is a risk factor for ischaemic stroke.[16] These findings mean that AF patients, especially those with atherosclerosis or associated vascular risk factors (e.g. hypertension, hypercholesterolaemia, diabetes mellitus, obesity, long-lasting stress, smoking, family history for vascular disease), are more prone to developing ischaemic stroke. Monitoring the left atrial volume index as a biomarker of vascular remodelling may thus be useful to predict the risk of ischaemic stroke.[17]

In addition, it is known that main elements of the coagulation cascade (i.e. platelets and specific proteins) in patients with AF differ from those without AF. For example, specific coagulation proteins (e.g. von Willebrand factor and fibrinogen) and D-dimer are increased in AF.[18,19] Therefore, it is assumed that there is an increased activation of the coagulation cascade in patients with AF, leading to an increased risk of ischaemic stroke.[12,13] This increased activation is further amplified by pre-existing comorbidities. For example, a study showed that diabetes mellitus was strongly associated with increased platelet activation due to increased p-selectin (i.e. CD62p) expression in patients with AF compared to patients without AF.[20]

MANAGEMENT OF ATRIAL FIBRILLATION

Following the above, AF can be considered as a complex systemic cardiovascular disease that involves multiple pathophysiological mechanisms, and that is associated with increased stroke risk and other adverse outcomes, amplified by pre-existing comorbidities. Therefore, the latest ESC guidelines on the management of AF recommend a holistic approach with integrated management for all AF patients, including patient involvement, multidisciplinary teams consisting of physicians and other healthcare professionals working together across all healthcare levels, technology tools, and access to different treatment options.[2] Based on pathophysiology, it is important that within this integrated holistic AF care, stroke risk management in AF is determined by the specific stroke risk factors present in a given patient with AF, exemplified e.g. by the CHA_2DS_2-VASc risk tool.[21] Studies showed that regular controls and attention paid to these risk factors reduce cardiovascular hospitalisation and all-cause mortality in AF patients, both in hospital and in primary care.[22,23] For example, Hendriks et al. showed that integrated chronic care versus routine clinical care in AF patients led to a 35% reduction in cardiovascular hospitalisation and cardiovascular mortality. Furthermore, the ALL-IN trial showed that integrated AF care compared with AF care as usual let to a 45% reduction in all-cause mortality.[23] Therefore, an integrated strategy seems more effective than solely pharmacological or invasive attempts to control heart rhythm or heart rate, and underlines the importance of considering AF as a systemic cardiovascular disease in need for integrated holistic cardiovascular risk management and care. Since primary care currently plays a pivotal role in cardiovascular risk management, it seems efficient to integrate this holistic AF care into the already existing cardiovascular risk management programmes in the primary care setting.

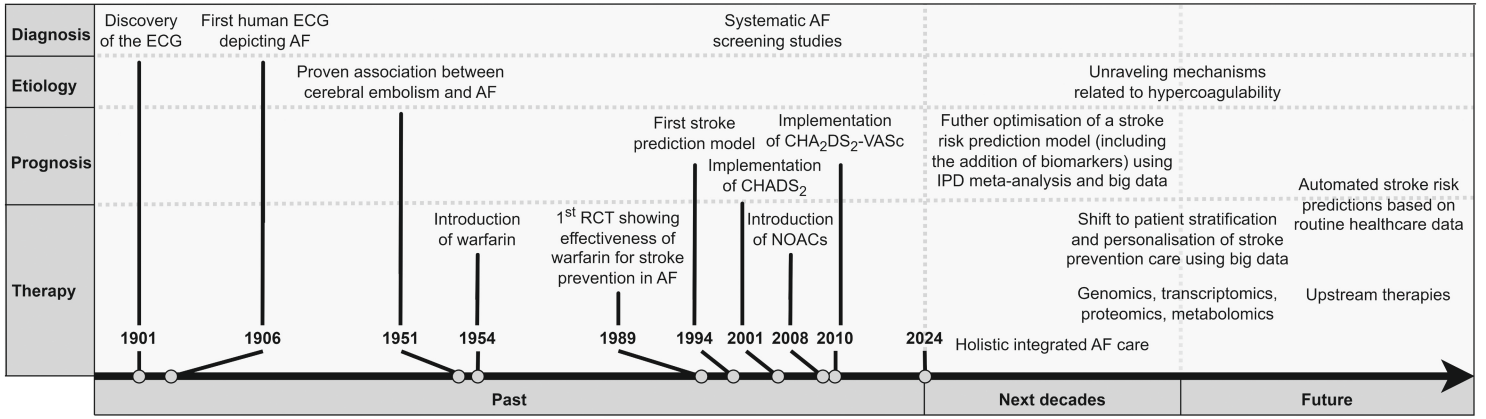
DIRECTIONS FOR FUTURE PRACTICE AND RESEARCH

As described above, it may be useful in the management of patients with AF to understand the underlying pathophysiological mechanisms or to have an explanatory model of the disease. Research on the pathophysiological mechanisms of AF with experimental in vitro studies, studies in clinical practice and the use of big data analytics can provide better insight in coagulation mechanisms that are related to the occurrence of AF itself and the subsequent association with ischaemic stroke. Such insight could serve as a starting point for future AF management. Figure 1 shows an overview of past achievements and predicted future developments in the management of patients with AF.

CONCLUSION

In patients with AF the pathophysiology of ischaemic stroke is multifactorial, which makes AF a complex systemic cardiovascular disease in need for integrated holistic cardiovascular risk management and care. A better understanding of the pathophysiology of AF could be valuable in the management of patients with AF.

FIGURE 1: PAST ACHIEVEMENTS AND PROPOSED FUTURE DEVELOPMENTS IN THE MANAGEMENT OF AF PATIENTS.



AF: atrial fibrillation; ECG: electrocardiogram; IPD: individual patient data; NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomised controlled trial.

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POTENTIAL CONFLICTS OF INTEREST

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CONTRIBUTORS

All authors conceived and initiated the study. LJ and SvD wrote the first version of the manuscript. All authors critically reviewed and revised the manuscript.

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SEX- AND AGE SPECIFIC ASSOCIATION OF NEW-ONSET ATRIAL FIBRILLATION WITH IN-HOSPITAL MORTALITY IN HOSPITALISED COVID-19 PATIENTS

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is a systemic disease with cardiovascular involvement, including cardiac arrhythmias. Notably, new-onset atrial fibrillation (AF) and atrial flutter (AFL) during hospitalisation in COVID-19 patients has been associated with increased mortality. However, how this risk is impacted by age and sex is still poorly understood.

Methods: For this multicentre cohort study, we extracted demographics, medical history, occurrence of electrical disorders and in-hospital mortality from the large international patient registry CAPACITY-COVID. For each electrical disorder, prevalence during hospitalisation was calculated. Subsequently, we analysed the incremental prognostic effect of developing AF/AFL on in-hospital mortality, using multivariable logistic regression analyses, stratified for sex and age.

Results: In total, 5,782 patients (64% male; median age 67) were included. Of all patients 11.0% (95% CI 10.2–11.8) experienced AF and 1.6% (95% CI 1.3–1.9) experienced AFL during hospitalisation. Ventricular arrhythmias were rare (<0.8% (95% CI 0.6-1.0)) and a conduction disorder was observed in 6.3% (95% CI 5.7-7.0). An event of AF/AFL appeared to occur more often in patients with pre-existing heart failure. After multivariable adjustment for age and sex, new-onset AF/AFL was significantly associated with a poorer prognosis, exemplified by a two- to three-fold increased risk of in-hospital mortality in males aged 60–72 years, whereas this effect was largely attenuated in older male patients and not observed in female patients.

Conclusion: In this large COVID-19 cohort, new-onset AF/AFL was associated with increased in-hospital mortality, yet this increased risk was restricted to males aged 60–72 years.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has infected more than 400 million people worldwide, including more than 160 million Europeans, with almost 5.8 million deaths attributed globally to the virus as of February 11th, 2022.[1] With multiple vaccines available as well as the recent increase in immunisation from the omicron variant, which is possibly associated with an overall lower risk of clinical deterioration, some are optimistic that the end of the coronavirus disease 2019 (COVID-19) pandemic is in sight and that SARS-CoV-2 will become a yearly recurring more endemic virus. However, subsequent waves of new infections with new variants are to be expected in the upcoming years, given the 1) low global vaccination rate of 36%,[2] and global shortage of vaccines, 2) high threshold needed for herd immunity,[3] 3) uncertainties regarding the duration of the immunological effect of the vaccines,[4] 4) high number of intermediate hosts for SARS-CoV-2,[5] and in part due to this, 5) the continuous threat of (more contagious) variants reducing vaccine efficacy.[6] Therefore, research into COVID-19 remains crucial.

Since the start of the pandemic, cardiovascular complications have been increasingly recognised in patients suffering from COVID-19, ranging from vascular damage and cardiac injury to arrhythmias.[7] Arrhythmias in COVID-19 patients may impact significantly on disease progression and outcome. As such, various population-based studies have reported a positive association between atrial fibrillation (AF)/atrial flutter (AFL) and mortality.[8–10] However, these studies did not look at sex-specific influences, nor at the incremental effect of age (on a continuous scale), despite the fact that these parameters are known to influence AF/AFL outcomes in the general population.[11,12]

Therefore, in the large international CAPACITY-COVID dataset (NCT04325412) of 5,782 hospitalised COVID-19 patients, using the latest methodology, we explored the relation of AF and AFL to in-hospital mortality, with specific attention for sex- and age-related differences.

METHODS

Study design and study population

For the current multicentre cohort study, pseudo-anonymous data generated during routine clinical care retrieved from the international patient registry CAPACITY-COVID (www.capacity-covid.eu) were used.[13] The data within CAPACITY-COVID have been collected by 72 hospitals in 8 European (Belgium, France, Italy, the Netherlands, Portugal, Spain, Switzerland, United Kingdom) and 5 non-European (Egypt, Iran, Israel, Russia, Saudi-Arabia) countries. For this study, patients aged 18 years or older, admitted to any of the participating hospital centres before October 25th, 2020,

with a laboratory confirmed SARS-CoV-2 infection during hospitalisation, were included. Readmission(s) from a single patient were evaluated as a single continuous presentation. Due to only few exclusion criteria, the database gives a reliable reflection of hospitalised COVID-19 patients during the first months of the pandemic, thus before availability of vaccine-induced immunity, and our analyses should therefore be interpreted as generalisable to patients with (largely) naïve immunity against SARS-CoV-2. Local ethics approval was obtained in all participating hospitals. Assessment of informed consent was site specific, depending on national regulations, and has been described previously.[13] Any researcher can request the data by submitting a proposal as outlined on https://capacity-covid.eu/for-professionals.

Data extraction

For this study the following variables were extracted: sex, age, medical history (including history of cardiac electrical disorders), body mass index (BMI), medication, physical examination findings, biomarkers, and follow-up data on the development of electrical disorders, cerebrovascular accident (CVA), pulmonary embolism, and mortality during hospitalisation. Electrical disorders were detected either through continuous rhythm monitoring or with (an) electrocardiogram(s) and were diagnosed according to the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2006 key data elements and definitions for electrophysiological studies and procedures.[14] Types of electrical disorders included AF, AFL, atrial tachycardia, atrioventricular (AV) nodal re-entry tachycardia, non-sustained ventricular tachycardia (nsVT), sustained ventricular tachycardia (sVT), ventricular fibrillation (VF), first degree AV block, second degree AV block, third degree AV block, complete left bundle branch block (LBBB), and complete right bundle branch block (RBBB).

Statistical analyses

Baseline characteristics of patients with COVID-19 disease are reported for the date of hospital admission. Categorical variables are presented as counts and percentages and numerical variables as means with standard deviations or medians with interquartile ranges (IQR), depending on the distribution.

The prevalence of the development of each arrhythmic and conduction disorder during hospitalisation was calculated for the entire follow-up time (i.e. the time from hospital admission to discharge, death or loss to follow-up) and divided into patients without and with a history of that specific arrhythmic or conduction disorder (i.e. new-onset and recurrent, respectively). Only for patients with AF and for patients with AFL, new-onset versus recurrent AF and new-onset versus recurrent AFL were defined as having no history of both AF and AFL versus a history of AF and/or AFL.

To explore the association between all predefined patient characteristics and the development of the most prevalent new-onset arrhythmic disorder (i.e. AF and/or AFL), univariable logistic regression analyses were performed to estimate crude odds ratios (OR) and corresponding 95% confidence intervals (95% CI).

Next, the association between development of new-onset AF and/or AFL during hospitalisation and in-hospital mortality in COVID-19 patients was first examined using univariable logistic regression analysis. Second, multivariable logistic regression analysis was performed with sex, a cubic spline function for age, the development of new-onset AF and/or AFL during hospitalisation, and the interaction between the latter two variables. The results of this analysis were depicted in plots for males and females separately. To explore whether other concomitant comorbidities and/or other known risk factors may have contributed to the observed results, we performed a sensitivity analysis where we additionally adjusted for CHA_2DS_2-VASc score.

For all analyses, the different AF subtypes (paroxysmal, persistent, and permanent) were merged. All statistical analyses were performed using R version 4.0.2 with the bias reduction in binomial-response generalised linear models (brglm) function in the package 'brglm' version 0.7.1, which implements Firth correction reducing finite sample bias in the regression coefficients compared to default maximum likelihood regression.[15] Non-linear relations are graphically displayed using the package 'rms' version 6.6.1 and the package 'ggplot2' version 3.3.2. In all univariable analyses with age and in all multivariable analyses, a cubic spline function for age (and in the univariable analyses for the association between BMI and new-onset AF and/or AFL also a cubic spline function for BMI) with four knots on recommended locations (on the percentiles 0.05, 0.35, 0.65, and 0.95) was used.[16] Missing data for each variable were reported as percentages in the text or as counts in the corresponding tables. Since missing data was overall limited (e.g. maximum n=24 in mortality analyses), we proceeded with analyses of complete cases. Associations with two-sided p-values <0.05 were considered statistically significant.

RESULTS

A total of 5,782 patients were included in this study. The majority of them were hospitalised in European countries (89.9%). The median duration of hospital admission was 8 (IQR 4–17) days, and 28.8% (n=1664) of all subjects were admitted to the intensive care unit (ICU). Of the total study population, 63.8% was male and the median age was 67 (IQR 56–76) years. 12.5% (n=725) had been diagnosed with an arrhythmic event in the past, of which 93.2% (n=676) consisted of at least one episode of supraventricular arrhythmia and 7.7% (n=56) at least one episode of ventricular arrhythmia. Of all patients, 1.7% (n=96) had been diagnosed with at least one conduction disorder

in the past. The most prevalent comorbidity registered was hypertension (47.6%), followed by diabetes mellitus (26.1%), chronic obstructive pulmonary disease (11.1%), renal impairment (10.7%), and prior myocardial infarction (9.2%). A complete list of all baseline characteristics, stratified by new-onset AF/AFL during hospitalisation and history of AF/AFL is presented in Table 1. Baseline characteristics stratified by other arrhythmias and conduction disorders are presented in Supplementary File S1. All variables had <3% missing, except for peripheral arterial disease (21.6%), BMI (24.7%), temperature (17.8%), C-reactive protein (12.2%), and white blood cell count (11.4%).

Prevalence of AF/AFL

The prevalence of AF and/or AFL in comparison to other arrhythmias and conduction disorders (recurrent and new-onset) during hospitalisation is summarised in Figure 1. Of all patients, 12.8% (95% CI 11.9–13.6) (n=737) experienced an arrhythmic event during hospitalisation, the vast majority being supraventricular (95.9%). AF and AFL were most common, occurring in 12.0% (95% CI 11.2–12.8) (n=692) of all patients, of which 86.7% (95% CI 84.0–89.1) (n=600) experienced only AF, 8.5% (95% CI 6.6–10.8) (n=59) experienced only AFL, and 4.8% (95% CI 3.4–6.6) (n=33) experienced both AF and AFL. In 60.7% (95% CI 57.0–64.3) (n=420) of patients the development of AF and/or AFL was new-onset, whereas in the remaining 39.3% (95% CI 35.7–43.0) (n=272) AF and/or AFL had been present before hospital admission. Ventricular arrhythmias were rare (0.8% (95% CI 0.6–1.0)) and 50% of them were sVT or VF (n=23). A conduction disorder during hospitalisation was observed in 6.3% (95% CI 5.7–7.0) (n=365) of all patients.

Association between patient characteristics and development of new-onset AF and/or AFL

In univariable logistic regression analyses, sex, age, heart failure, hypertension, peripheral arterial disease, prior myocardial infarction, renal impairment, certain drugs, white blood cell count, duration of hospitalisation, and development of pulmonary embolism, showed an increased statistically significant association with the development of AF and/or AFL. Of medical history, heart failure seemed to be most strongly associated with a higher likelihood of developing AF and/or AFL compared to patients without heart failure: OR 1.72 (95% CI 1.05–2.64) (Supplementary File S2).

Prognostic impact of new-onset AF and/or AFL on in-hospital mortality

In absolute terms, there were only few patients aged <50 years and >90 years in our dataset who developed new-onset AF and/or AFL (n=7 and n=10, respectively). Because these small numbers could affect the reliability and precision of the point estimates of the outcomes to a high extent, only patients aged ≥50 and ≤90 years for new-onset AF and/or AFL were included in the mortality analyses.

TABLE 1: BASELINE CHARACTERISTICS OF HOSPITALISED COVID-19 PATIENTS STRATIFIED BY THE AF/AFL EVENT DURING HOSPITALISATION AND HISTORY OF AF/AFL.

	Total (n=5,782)	No AF/AFL (n=4,712)	New-onset or recurrent AF/AFL (n=692)	New-onset AF/AFL (n=420)	Recurrent AF/AFL (n=271)
Demographics					
Male sex n (%)	3,686 (63.8)	2,955 (62.7)	482 (69.7)	294 (70.0)	188 (69.4)
Age in years median (IQR)	67 (56-76)	64 (54-74)	74 (69-81)	73 (66-79)	78 (73-83)
History of supraventricular tachycardia					
AF n (%)	616 (10.7)	0 (0.0)	257 (37.2)	0 (0.0)	257 (94.8)
AFL n (%)	52 (0.9)	0 (0.0)	23 (3.3)	0 (0.0)	23 (8.5)
Atrial tachycardia n (%)	21 (0.4)	12 (0.3)	3 (0.4)	3 (0.7)	0 (0.0)
AV nodal re-entry tachycardia n (%)	22 (0.4)	15 (0.3)	4 (0.6)	1 (0.2)	3 (1.1)
History of ventricular tachycardia					
Non-sustained ventricular tachycardia n (%)	21 (0.4)	12 (0.3)	7 (1.0)	4 (1.0)	3 (1.1)
Sustained ventricular tachycardia n (%)	15 (0.3)	14 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular fibrillation n (%)	24 (0.4)	17 (0.4)	6 (0.9)	6 (1.4)	0 (0.0)
History of conduction disorders					
1st AV block n (%)	19 (0.3)	13 (0.3)	2 (0.3)	1 (0.2)	1 (0.4)
2nd AV block n (%)	13 (0.2)	8 (0.2)	2 (0.3)	1 (0.2)	1 (0.4)
3rd AV block n (%)	26 (0.4)	16 (0.3)	2 (0.3)	1 (0.2)	1 (0.4)
Left bundle branch block n (%)	24 (0.4)	14 (0.3)	5 (0.7)	4 (1.0)	1 (0.4)
Right bundle branch block n (%)	18 (0.3)	12 (0.3)	4 (0.6)	2 (0.5)	2 (0.7)
Other medical history					
Heart failure n (%)	315 (5.5)	156 (3.3)	88 (12.7)	23 (5.5)	64 (23.6)
Hypertension n (%)	2,692 (47.6)	2,031 (44.0)	407 (60.2)	227 (55.4)	179 (67.5)
Diabetes mellitus (type I or II) n (%)	1,494 (26.1)	1,195 (25.6)	188 (27.6)	100 (24.2)	87 (32.6)
Peripheral arterial disease n (%)	271 (6.0)	181 (4.9)	54 (9.8)	26 (8.0)	28 (12.6)

Myocardial infarction[a] n (%)	523 (9.2)	374 (8.0)	81 (11.9)	47 (11.3)	34 (12.8)
Renal impairment n (%)	620 (10.7)	414 (8.8)	123 (17.9)	58 (13.9)	65 (24.4)
COPD n (%)	643 (11.1)	487 (10.3)	97 (14.1)	53 (12.7)	44 (16.3)
Risk factors					
BMI in kg/m² median (IQR)	27.5 (24.6-30.9)	27.5 (24.6-30.9)	27.2 (24.5-30.5)	27.2 (24.7-30.5)	26.9 (24.1-30.4)
Medication					
Digoxin n (%)	112 (1.9)	19 (0.4)	58 (8.4)	12 (2.9)	46 (17.0)
Anti-arrhythmic drugs - class I n (%)	28 (0.5)	6 (0.1)	12 (1.7)	0 (0.0)	12 (4.4)
Anti-arrhythmic drugs - class III n (%)	110 (1.9)	41 (0.9)	24 (3.5)	5 (1.2)	19 (7.0)
Anti-arrhythmic drugs - class IV n (%)	64 (1.1)	39 (0.8)	15 (2.2)	5 (1.2)	10 (3.7)
Beta blockers n (%)	1,562 (27.0)	1,028 (21.8)	308 (44.5)	136 (32.4)	172 (63.5)
Antihypertensive drugs[b] n (%)	2,575 (44.6)	1,913 (40.6)	397 (57.4)	204 (48.6)	192 (70.8)
Platelet inhibitors n (%)	1,270 (22.0)	1,100 (23.4)	139 (20.1)	111 (26.4)	28 (10.3)
Anticoagulants n (%)	779 (13.5)	219 (4.7)	284 (41.0)	59 (14.0)	224 (82.7)
Antidiabetic drugs n (%)	1,105 (19.1)	894 (19.0)	141 (20.4)	73 (17.4)	67 (24.7)
Physical examination, biomarkers (at the start of hospital admission)					
Temperature in °C median (IQR)	37.8 (37.0-38.5)	37.8 (37.0-38.6)	37.7 (37.0-38.5)	37.7 (37.0-38.5)	37.7 (36.9-38.4)
C-reactive protein in mg/L median (IQR)	76.0 (31.0-144.0)	74.0 (29.0-141.0)	95.0 (45.0-170.0)	110.0 (56.0-180.0)	76.0 (31.0-135.5)
White blood cell count x10⁹/L median (IQR)	6.8 (5.0-9.3)	6.8 (5.0-9.2)	6.8 (5.0-9.9)	7.1 (5.0-10.5)	6.3 (4.9-8.8)

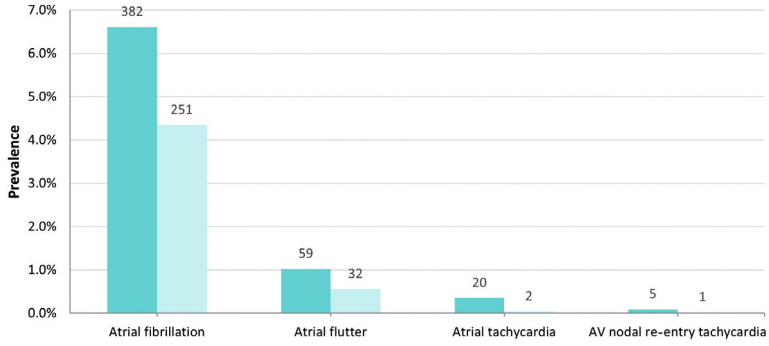
[a] *ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.*

[b] *Aldosterone antagonists, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics.*

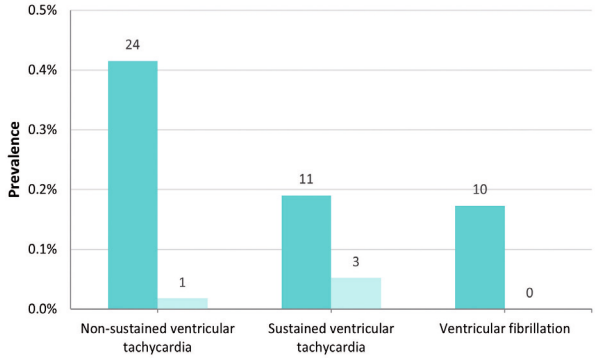
AF: atrial fibrillation; AFL: atrial flutter; AV: atrioventricular; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; n: number.

FIGURE 1: PREVALENCE OF ELECTRICAL DISORDERS IN HOSPITALISED COVID-19 PATIENTS.

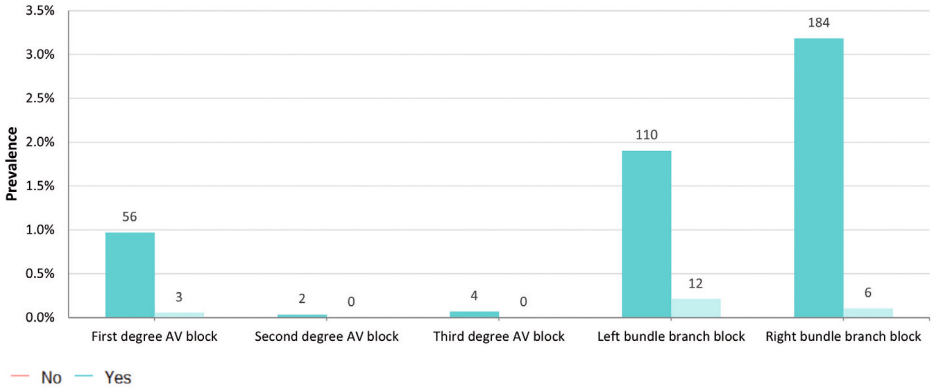
A. Supraventricular tachycardias



B. Ventricular tachycardias



C. Conduction disorders



Recurrent is defined as a history of that specific electrical disorder. Only for patients with atrial fibrillation (AF) and for patients with atrial flutter (AFL) new-onset versus recurrent AF and new-onset versus recurrent AFL were defined as having no history of both AF and AFL versus a history of AF and/or AFL. The number of patients per group is presented on top of the specific bar.

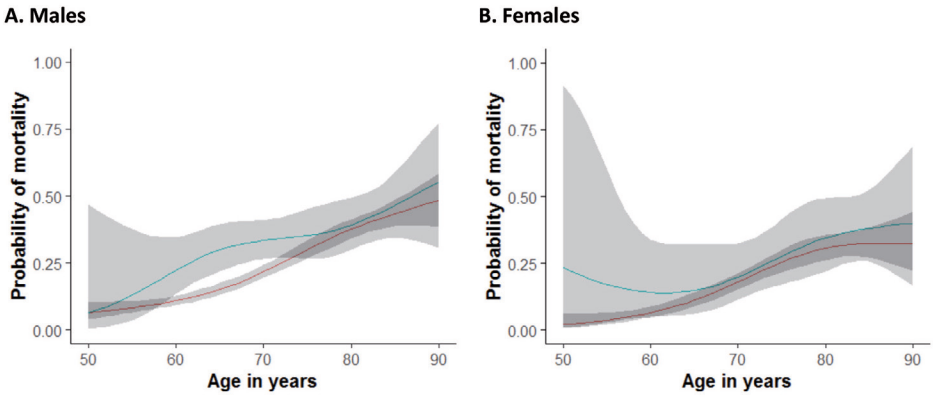
In univariable logistic regression analyses, we observed that the development of new-onset AF and/or AFL during hospitalisation was associated with increased in-hospital mortality with an unadjusted OR of 1.90 (95% CI 1.52–2.36) (Supplementary File S3). However, in a multivariable model with sex, age, and new-onset AF and/or AFL as covariates to predict in-hospital mortality, there was only an increased significant association between new-onset AF and/or AFL and in-hospital mortality in males aged between 60 and 72 years (see Figure 2). When extending this model with the CHA_2DS_2-VASc score in the 24.3% of patients in whom this score could be calculated (n=1033), the impact of the development of new-onset AF and/or AFL during hospitalisation appeared to be more strongly associated with increased in-hospital mortality: adjusted OR of 3.80 (95% CI 0.03–84.86) instead of 2.16 (95% CI 0.16–14.11) (Supplementary File S4).

In the new-onset AF and/or AFL group, 51.7% (n=217) was admitted to the ICU. In 24.0% (n=23) of the patients for which ICU admission date and AF and/or AFL onset date were available (n=96), AF and/or AFL occurred at least 1 day before ICU admission. In the total cohort, 1.0% (n=60) of patients developed a CVA, whereas in patients with new-onset AF and/or AFL this occurred in 1.7% (n=7).

DISCUSSION

In this multicentre cohort study, we extracted data of 5,782 hospitalised COVID-19 patients from the large international CAPACITY-COVID registry. Of all electrical disorders, AF and/or AFL was observed in 1 in every 8–9 in-hospital COVID-19 patients.

FIGURE 2: RISK OF IN-HOSPITAL MORTALITY BY SEX, AGE AND THE DEVELOPMENT OF NEW-ONSET ATRIAL FIBRILLATION AND/OR ATRIAL FLUTTER DURING HOSPITALISATION IN COVID-19 PATIENTS.



The plots in Figure 2 are developed with the interaction between a cubic spline function for age with four knots (on the percentiles 0.05, 0.035, 0.65, and 0.95) and the development of new-onset AF and/or AFL during hospitalisation.

Occurrence of AF and/or AFL during hospitalisation for COVID-19 was associated with a poorer prognosis exemplified by an increased in-hospital mortality in males aged 60–72 years, while this effect was not observed in female patients and largely attenuated in older male patients.

Arrhythmogenesis in COVID-19 and the effect of AF on mortality

Several mechanisms may contribute to arrhythmogenesis in the setting of COVID-19. Pre-existing cardiovascular pathologies, such as heart failure and coronary artery disease, may increase the likelihood of myocardial ischaemia in the setting of hypoxemia. Indeed, in our cohort, heart failure, hypertension, and prior myocardial infarction were frequently present and apparently associated with an increased likelihood of developing AF and/or AFL. In addition, SARS-CoV-2 has been linked to a pro-thrombotic and hypercoagulability state in patients, which by itself may promote the development and propagation of AF and/or AFL.[17] Furthermore, the virus may also directly affect the cardiomyocytes through expression of angiotensin-converting enzyme 2, inducing arrhythmogenic conditions such as intracellular ionic dysregulation, apoptosis, and possibly myocarditis.[18] Additionally, potentially pro-arrhythmic therapeutics (including vasopressors and (hydroxy)chloroquine) and electrolyte disturbances in COVID-19 patients can all contribute to arrhythmogenesis.[19] Irrespective of the underlying mechanism, our findings indicate that development of AF and/or AFL might be prognostically unfavourable in COVID-19 patients.

Sex- and age-dependent effect on AF on mortality

Our study confirms previous (smaller) studies which reported AF/AFL as the most prevalent arrhythmia in COVID-19 patients, in addition to its association with increased mortality. With respect to AF/AFL occurrence, Peltzer et al. and Mountantonakis et al. observed a slightly higher prevalence of AF/AFL compared to our study (16% and 18% compared to 12% respectively), whereas Musikantow et al. found a similar prevalence of 10%.[8,9,20] Conversely, Bhatla et al. reported a much lower prevalence of new-onset AF (3.5%), yet in a much smaller dataset of 700 patients.[10]

Similar to our study, Peltzer et al. and Mountantonakis et al. found AF and/or AFL, as well as new-onset AF and/or AFL, to be associated with increased in-hospital mortality.[8,9] Bhatla et al. did not find such an association between new-onset AF and/or AFL and in-hospital mortality, yet (again) this study included a relatively small dataset with only 25 incident AF cases reported.[10]

Importantly, using the latest prediction methodology (allowing age to remain continuous in all analyses using cubic spline functions), we were – for the first time – able to pinpoint the effect of AF/AFL occurrence on in-hospital mortality to male hospitalised COVID-19 patients aged 60–72 years. In fact, we ruled out an effect of AF/AFL occurrence on mortality in female patients with COVID-19, while in the general population females with AF/AFL have a worse outcome compared to males.[12] As an example, in a male hospitalised COVID-19 patient of 65 years, the occurrence of AF/AFL would increase his risk of mortality from ±15% to ±35%, whereas in a female patient of 65 years this risk remains well below ±15–20%, regardless of AF/AFL development. More importantly, the correlation between age and its interaction with AF and/or AFL follows a non-linear pattern, which is even different for males and females, thus underlining the importance of our statistical approach. As such, our analyses provide a much more granular assessment of the effect of new-onset AF and/or AFL during hospital admission for COVID-19 by better identifying subgroups of patients where the prognostic impact on mortality is most relevant.

Strengths and limitations

Major strengths of our work include the inclusion of a large international dataset of nearly 6,000 hospitalised COVID-19 patients, allowing to perform sophisticated analyses on the incremental impact of AF/AFL occurrence on in-hospital mortality beyond the effects of age and sex. However, our findings might not be restricted to or typical for COVID-19 patients. For example, a recent study by Musikantow et al. shows a similar increase in mortality in hospitalised influenza patients with AF/AFL.[20] This seems to indicate that the found association might be related to a general viral-induced systemic illness rather than specifically COVID-19, suggesting that the findings in this study might be generalised to other patients with viral induced respiratory

tract infections (e.g. influenza). Nevertheless, for full appreciation the following topics deserve attention.

First, while our findings show that AF and/or AFL appears prognostically unfavourable, particularly in males, this does not imply a causal relationship. In fact, it could be argued that the development of AF/AFL and its impact on mortality is merely a more general signal of progression of disease severity and accumulation of comorbidities (e.g. exemplified by higher CHA_2DS_2-VASc scores), and thus could be considered as an 'innocent bystander' in patients experiencing clinical deterioration. To explore the impact of the development of new-onset AF and/or AFL during hospitalisation on in-hospital mortality when adjusting for concomitant comorbidities and risk factors, we performed a sensitivity analysis with additional adjustment for CHA_2DS_2-VASc score. Although this analysis is inherently impacted by a lower degree of statistical robustness due to missing information on the CHA_2DS_2-VASc score in 75.7% of patients (n=2,779), it did yielded similar inferences (Supplementary File S3 and S4). Moreover, in our study the majority of AF and/or AFL cases (60.7%) were detected in patients either before ICU admission or in patients never admitted to the ICU (i.e. before widespread increase in disease severity occurred). Although it is possible that the threshold for ICU referral was higher due to limited capacity during the peak of the pandemic, this suggests that (new-onset) AF and/or AFL, would at least be an early marker for disease progression. Based on our findings this appears to be prognostically unfavourable, particularly in males aged between 60 and 72 years. Second, although diagnoses were centrally defined, with multicentre studies there is always a risk of heterogeneity due to differences in interpretation among centres. Given that the strategy for rhythm monitoring was defined by the attending physicians, and as a consequence was different per centre, it could well be that electrical disorders may have been underdiagnosed in patients on general wards where continuous rhythm monitoring is not performed. Moreover, grouping the different AF subtypes (paroxysmal, persistent, and permanent) may have resulted in missing subtle disease progression within the AF group. Finally, since only in-hospital death could be recorded, mortality outcome data are limited, and comparison with other studies is hampered by differential follow-up due to differences in length of hospital stay.

CONCLUSION

Using a large international database, this study confirms that AF and/or AFL is the most prevalent electrical disorder in hospitalised COVID-19 patients, and that new-onset AF and/or AFL is associated with a poorer prognosis exemplified by an increased in-hospital mortality. However, this increased mortality risk appears to be restricted to male patients aged between 60 and 72 years, and was not observed in female patients.

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POTENTIAL CONFLICTS OF INTEREST

FR and GJG report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance and Daiichi Sankyo. The other authors declare that they have no conflicts of interest.

CONTRIBUTORS

LJ, JO, GJG and CAR conceived and initiated the study. LJ and JO prepared the dataset. LJ, JO and MvS performed the statistical analyses. LJ, JO, MvS, ML, GJG and CAR interpreted the results. LJ, JO, GJG and CAR wrote the first version of the manuscript. All authors critically reviewed and revised the manuscript.

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SUPPLEMENTARY FILES

S1: BASELINE CHARACTERISTICS OF HOSPITALISED COVID-19 PATIENTS STRATIFIED BY THE OCCURRENCE OF DIFFERENT SUBTYPES OF CARDIAC ELECTRICAL EVENTS.

	Total (n=5,782)	No arrhythmic event (n=4,800)	AF/AFL (n=692)	Ventricular arrhythmia (n=46)	Conduction disorder (n=365)
Demographics					
Male sex n (%)	3,686 (63.8)	2,990 (62.3)	482 (69.7)	38 (82.6)	269 (73.7)
Age in years median (IQR)	67 (56-76)	65 (54-75)	74 (69-81)	71.5 (61.3-76.8)	76 (70-83)
History of supraventricular tachycardia					
AF n (%)	616 (10.7)	326 (6.8)	257 (37.2)	5 (10.9)	77 (21.2)
AFL n (%)	52 (0.9)	21 (0.4)	23 (3.3)	1 (2.2)	13 (3.6)
Atrial tachycardia n (%)	21 (0.4)	17 (0.4)	3 (0.4)	0 (0.0)	1 (0.3)
AV nodal re-entry tachycardia n (%)	22 (0.4)	18 (0.4)	4 (0.6)	0 (0.0)	1 (0.3)
History of ventricular tachycardia					
Non-sustained ventricular tachycardia n (%)	21 (0.4)	13 (0.3)	7 (1.0)	1 (2.2)	4 (1.1)
Sustained ventricular tachycardia n (%)	15 (0.3)	10 (0.2)	0 (0.0)	3 (6.5)	3 (0.8)
Ventricular fibrillation n (%)	24 (0.4)	16 (0.3)	6 (0.9)	1 (2.2)	2 (0.5)
History of conduction disorders					
1st AV block n (%)	19 (0.3)	12 (0.3)	2 (0.3)	0 (0.0)	7 (1.9)
2nd AV block n (%)	13 (0.2)	9 (0.2)	2 (0.3)	0 (0.0)	3 (0.8)
3rd AV block n (%)	26 (0.4)	20 (0.4)	2 (0.3)	0 (0.0)	5 (1.4)
Left bundle branch block n (%)	24 (0.4)	11 (0.2)	5 (0.7)	0 (0.0)	12 (3.3)
Right bundle branch block n (%)	18 (0.3)	10 (0.2)	4 (0.6)	0 (0.0)	7 (1.9)
Other medical history					
Heart failure n (%)	315 (5.5)	190 (4.0)	88 (12.7)	4 (8.7)	58 (15.9)
Hypertension n (%)	2,692 (47.6)	2,114 (45.0)	407 (60.2)	23 (53.5)	228 (63.9)

Diabetes mellitus (type I or II) n (%)	1,494 (26.1)	1,211 (25.5)	188 (27.6)	9 (20.0)	130 (36.3)
Peripheral arterial disease n (%)	271 (6.0)	199 (5.3)	54 (9.8)	6 (15.0)	22 (7.6)
Myocardial infarction[a] n (%)	523 (9.2)	397 (8.4)	81 (11.9)	6 (14.0)	57 (16.1)
Renal impairment n (%)	620 (10.7)	447 (9.3)	123 (17.9)	4 (8.7)	73 (20.1)
COPD n (%)	643 (11.1)	504 (10.5)	97 (14.1)	2 (4.3)	61 (16.8)
Risk factors					
BMI in kg/m² median (IQR)	27.5 (24.6-30.9)	27.5 (24.6-31.0)	27.2 (24.5-30.5)	25.2 (23.7-28.3)	27.6 (24.6-30.8)
Medication					
Digoxin n (%)	112 (1.9)	52 (1.1)	58 (8.4)	1 (2.2)	10 (2.7)
Anti-arrhythmic drugs - class I n (%)	28 (0.5)	14 (0.3)	12 (1.7)	0 (0.0)	2 (0.5)
Anti-arrhythmic drugs - class III n (%)	110 (1.9)	68 (1.4)	24 (3.5)	4 (8.7)	17 (4.7)
Anti-arrhythmic drugs - class IV n (%)	64 (1.1)	46 (1.0)	15 (2.2)	0 (0.0)	4 (1.1)
Beta blockers n (%)	1,562 (27.0)	1,143 (23.8)	308 (44.5)	21 (45.7)	159 (43.7)
Antihypertensive drugs[b] n (%)	2,575 (44.6)	1,994 (41.6)	397 (57.4)	30 (65.2)	244 (67.0)
Platelet inhibitors n (%)	1,270 (22.0)	1,024 (21.3)	139 (20.1)	14 (30.4)	122 (33.5)
Anticoagulants n (%)	779 (13.5)	444 (9.3)	284 (41.0)	10 (21.7)	101 (27.7)
Antidiabetic drugs n (%)	1,105 (19.1)	898 (18.7)	141 (20.4)	6 (13.0)	95 (26.1)
Physical examination, biomarkers (at the start of hospital admission)					
Temperature in °C median (IQR)	37.8 (37.0-38.5)	37.8 (37.0-38.5)	37.7 (37.0-38.5)	37.7 (37.1-37.9)	37.8 (36.9-38.6)
C-reactive protein in mg/L median (IQR)	76.0 (31.0-144.0)	72.0 (28.0-140.0)	95.0 (45.0-170.0)	130.5 (43.8-271.3)	83.0 (39.0-139.0)
White blood cell count x10⁹/L median (IQR)	6.8 (5.0-9.3)	6.7 (5.0-9.2)	6.8 (5.0-9.9)	7.9 (6.1-10.9)	6.6 (5.0-9.6)

[a] *ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.*

[b] *Aldosterone antagonists, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics.*

AF: atrial fibrillation; AFL: atrial flutter; AV: atrioventricular; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; n: number.

S2: CHARACTERISTICS OF COVID-19 PATIENTS AND THEIR RELATION TO THE DEVELOPMENT OF NEW-ONSET ATRIAL FIBRILLATION OR ATRIAL FLUTTER DURING HOSPITALISATION.

		No AF/AFL[a] (n=4,712)	AF/AFL[a] (n=420)	Unadjusted odds ratio (95% CI)
Demographics, risk factors, medical history, medication (before hospital admission)				
Male sex n (%)		2,955 (62.7)	294 (70.0)	1.38 (1.12-1.73)
Sex NA n (%)		1 (0.0)	0 (0.0)	
Age in years				1.15 (1.07-1.28)
Age in years'	median (IQR)[b]	64 (54-74)	73 (66-79)	0.92 (0.80-1.04)
Age in years''				1.05 (0.67-1.80)
Age in years NA n (%)		0 (0.0)	0 (0.0)	
BMI in kg/m²				1.06 (0.96-1.18)
BMI in kg/m²'	median (IQR)[b]	27.47	27.19	0.83 (0.53-1.26)
BMI in kg/m²''		(24.62-30.93)	(24.69-30.46)	1.47 (0.42-5.27)
BMI in kg/m² NA n (%)		1252 (26.6)	62 (14.8)	
Heart failure n (%)		156 (3.3)	23 (5.5)	1.72 (1.05-2.64)
Heart failure NA n (%)		10 (0.2)	1 (0.2)	
Hypertension n (%)		2,031 (44.0)	227 (55.4)	1.57 (1.29-1.93)
Hypertension NA n (%)		101 (2.1)	10 (2.4)	
Diabetes mellitus (type I or II) n (%)		1,195 (25.6)	100 (24.2)	0.93 (0.73-1.17)
Diabetes mellitus (type I or II) NA n (%)		51 (1.1)	7 (1.7)	
Peripheral arterial disease n (%)		181 (4.9)	26 (8.0)	1.70 (1.07-2.55)
Peripheral arterial disease NA n (%)		1,033 (21.9)	94 (22.4)	
Myocardial infarction[c] n (%)		374 (8.0)	47 (11.3)	1.47 (1.04-2.00)
Myocardial infarction[c] **NA** n (%)		56 (1.2)	3 (0.7)	
Renal impairment n (%)		414 (8.8)	58 (13.9)	1.69 (1.24-2.24)
Renal impairment NA n (%)		6 (0.1)	3 (0.7)	
Digoxin n (%)		19 (0.4)	12 (2.9)	7.36 (3.40-14.91)
Digoxin NA n (%)		4 (0.1)	0 (0.0)	

Anti-arrhythmic drugs (class I, III and/or IV) n (%)	85 (1.8)	9 (2.1)	1.25 (0.56-2.34)
Anti-arrhythmic drugs (class I, III and/or IV) NA n (%)	1 (0.0)	1 (0.2)	
Beta blockers n (%)	1,028 (21.8)	136 (32.4)	1.72 (1.38-2.13)
Beta blockers NA n (%)	4 (0.1)	0 (0.0)	
Antihypertensive drugs[d] n (%)	1,913 (40.6)	204 (48.6)	1.38 (1.13-1.69)
Antihypertensive drugs[d] **NA** n (%)	4 (0.1)	0 (0.0)	
Antithrombotics[e] n (%)	1,296 (27.5)	161 (38.3)	1.64 (1.33-2.01)
Antithrombotics[e] **NA** n (%)	4 (0.1)	0 (0.0)	
Physical examination, biomarkers (at the start of hospital admission)			
Temperature in °C median (IQR)	37.8 (37.0-38.6)	37.7 (37.0-38.5)	0.99 (0.89-1.10)
Temperature in °C NA median (IQR)	808 (17.1)	106 (25.2)	
C-reactive protein in mg/L median (IQR)	83.00 (40.75-150.00)	112.00 (61.75-182.10)	1.00 (1.00-1.00)
C-reactive protein in mg/L NA median (IQR)	566 (12.0)	64 (15.2)	
White blood cell count x10^9/L median (IQR)	6.80 (5.00-9.20)	7.10 (5.00-10.50)	1.03 (1.01-1.05)
White blood cell count x10^9/L NA median (IQR)	505 (10.7)	62 (14.8)	
Characteristics (during hospitalisation)			
Duration of hospitalisation in days median (IQR)	8 (4-16)	15 (6-30)	1.02 (1.02-1.03)
Duration of hospitalisation in days NA median (IQR)	135 (2.9)	13 (3.1)	
Development of pulmonary embolism n (%)	317 (6.7)	54 (12.9)	2.06 (1.49-2.78)
Development of pulmonary embolism NA n (%)	0 (0.0)	0 (0.0)	

[a] *There were no missing values for the outcome variable.*

[b] *Age and BMI were divided into three subgroups (depicted by [X], [X'], and [X''']) using cubic spline functions, because these variables follow a non-linear pattern with the outcome variable, as visualised in the two graphs below the table.*

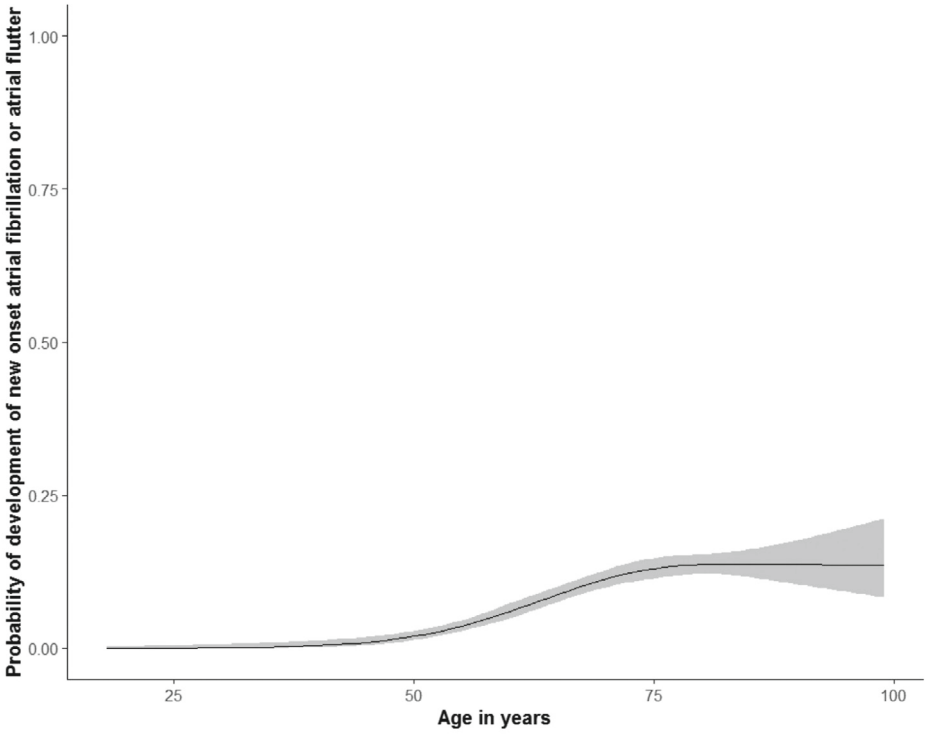
[c] *ST-elevation myocardial infarction or non-ST-elevation myocardial infarction.*

[d] *Aldosterone antagonists, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics.*

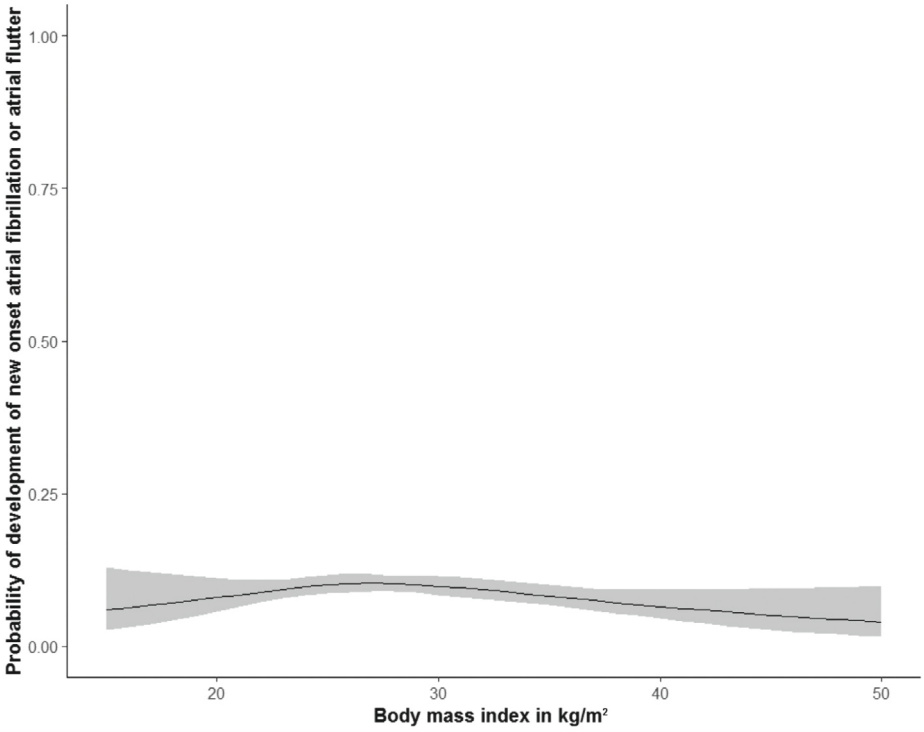
[e] *Platelet inhibitors, anticoagulants.*

AF: atrial fibrillation; AFL: atrial flutter; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; NA: not available.

RISK OF DEVELOPMENT OF NEW-ONSET ATRIAL FIBRILLATION OR ATRIAL FLUTTER BY AGE IN COVID-19 PATIENTS.



RISK OF DEVELOPMENT OF NEW-ONSET ATRIAL FIBRILLATION OR ATRIAL FLUTTER BY BODY MASS INDEX IN COVID-19 PATIENTS.



S3: CHARACTERISTICS OF COVID-19 PATIENTS AND THEIR RELATION TO IN-HOSPITAL MORTALITY IN PATIENTS WITHOUT A HISTORY OF ATRIAL FIBRILLATION OR ATRIAL FLUTTER.

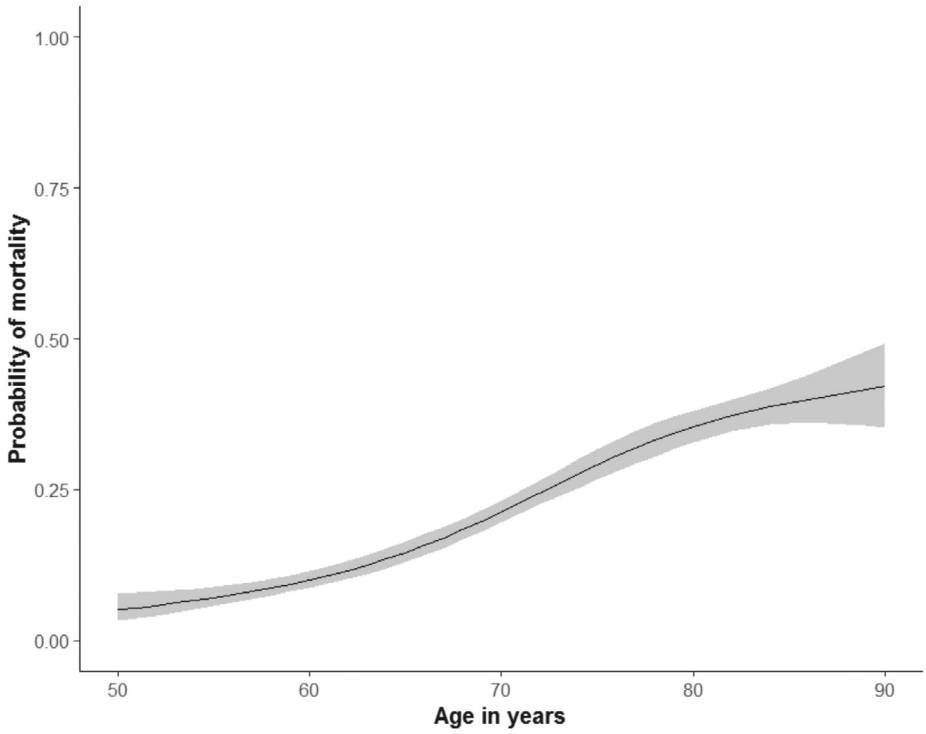
Univariable analyses[a]					
		Alive (n=3,317)	**Death (n=938)**	**Outcome NA (n=24)**	**Unadjusted odds ratio (95% CI)**
Male sex n (%)		2,081 (62.8)	656 (69.9)	15 (62.5)	1.38 (1.18-1.62)
Sex NA n (%)		1 (0.0)	0 (0.0)	0 (0.0)	
Age in years		66 (59-74)	75 (68-80)	67 (60.75-73)	7.85 (5.60-11.20)
Age in years'	median (IQR)[b]				26.22 (9.96-75.80)
Age in years''					7.96 (5.77-11.09)
Age in years NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
AF/AFL da n (%)		268 (8.1)	134 (14.3)	1 (4.2)	1.90 (1.52-2.36)
AF/AFL da NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
Multivariable analyses (with spline for age and the interaction between age and AF/AFL)[a]					
		Adjusted odds ratio (95% CI)			
Male sex		1.50 (1.28-1.78)			
Age in years [b]		8.29 (5.79-12.09)			
Age in years' [b]		23.36 (8.59-70.14)			
Age in years'' [b]		8.65 (6.12-12.36)			
AF/AFL da		2.16 (0.16-14.11)			
Interaction age and AF/AFL [b]		0.35 (0.10-1.58)			
Interaction age and AF/AFL' [b]		0.77 (0.01-169.24)			
Interaction age and AF/AFL'' [b]		0.52 (0.18-1.89)			

[a] *In all above analyses only patients with an age of 50-90 years were included, because the number of patients developing new-onset AF and/or AFL during admission was too low in patients <50 years and >90 years in order to obtain reliable results.*

[b] *Age was divided into three subgroups (depicted by [X], [X'], and [X'']) using a cubic spline function, because it follows a non-linear pattern with the outcome variable, as visualised in the graph below the table.*

AF: atrial fibrillation; AFL: atrial flutter; CI: confidence interval; da: during admission; IQR: interquartile range; n: number; NA: not available.

RISK OF IN-HOSPITAL MORTALITY BY AGE IN COVID-19 PATIENTS WITHOUT A HISTORY OF ATRIAL FIBRILLATION OR ATRIAL FLUTTER.



S4: CHARACTERISTICS OF COVID-19 PATIENTS, INCLUDING CHA_2DS_2-VASC SCORE, AND THEIR RELATION TO IN-HOSPITAL MORTALITY IN PATIENTS WITHOUT A HISTORY OF ATRIAL FIBRILLATION OR ATRIAL FLUTTER.

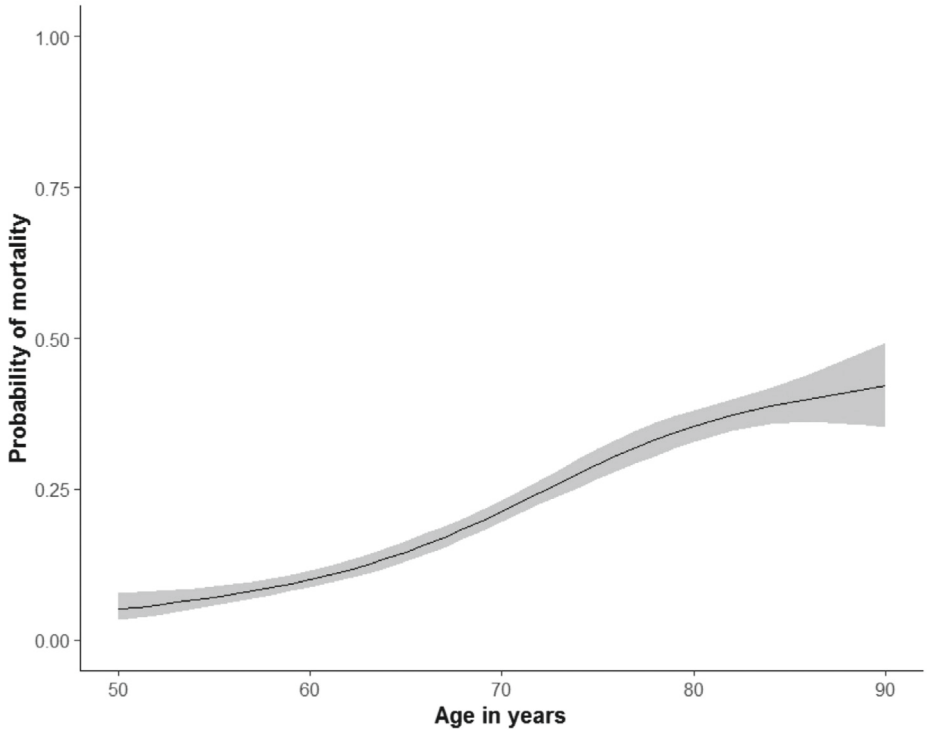
Univariable analyses[a]					
		Alive (n=3,317)	**Death (n=938)**	**Outcome NA (n=24)**	**Unadjusted odds ratio (95% CI)**
Male sex n (%)		2,081 (62.8)	656 (69.9)	15 (62.5)	1.38 (1.18-1.62)
Sex NA n (%)		1 (0.0)	0 (0.0)	0 (0.0)	
Age in years	median (IQR)[b]	66 (59-74)	75 (68-80)	67 (60.75-73)	7.85 (5.60-11.20)
Age in years'					26.22 (9.96-75.80)
Age in years''					7.96 (5.77-11.09)
Age in years NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
CHA_2DS_2-VASc score ≥2 n (%)		718 (21.6)	315 (33.6)	0 (0.0)	4.26 (3.05-6.17)
CHA_2DS_2-VASc score ≥2 NA n (%)		2,197 (66.2)	582 (62.0)	22 (91.7)	
AF/AFL da n (%)		268 (8.1)	134 (14.3)	1 (4.2)	1.90 (1.52-2.36)
AF/AFL da NA n (%)		0 (0.0)	0 (0.0)	0 (0.0)	
Multivariable analyses (with spline for age and the interaction between age and AF/AFL)[a]					
		Adjusted odds ratio (95% CI)			
Male sex		1.60 (1.22-2.13)			
Age in years [b]		8.66 (4.27-19.14)			
Age in years' [b]		17.45 (2.47-185.93)			
Age in years'' [b]		6.13 (3.23-12.21)			
CHA_2DS_2-VASc score ≥2		2.02 (1.32-3.17)			
AF/AFL da		3.80 (0.03-84.86)			
Interaction age and AF/AFL [b]		0.25 (0.04-4.16)			
Interaction age and AF/AFL' [b]		0.21 (0.00-5981.88)			
Interaction age and AF/AFL'' [b]		0.13 (0.02-1.33)			

[a] *In all above analyses only patients with an age of 50-90 years were included, because the number of patients developing new-onset AF and/or AFL during admission was too low in patients <50 years and >90 years in order to obtain reliable results.*

[b] *Age was divided into three subgroups (depicted by [X], [X'], and [X'']) using a cubic spline function, because it follows a non-linear pattern with the outcome variable, as visualised in the graph below the table.*

AF: atrial fibrillation; AFL: atrial flutter; CI: confidence interval; da: during admission; IQR: interquartile range; n: number; NA: not available.

RISK OF IN-HOSPITAL MORTALITY BY AGE IN COVID-19 PATIENTS WITH NEW-ONSET ATRIAL FIBRILLATION OR ATRIAL FLUTTER.



STROKE RATE VARIATION AND ANTICOAGULATION BENEFIT IN ATRIAL FIBRILLATION

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TO THE EDITOR

We read the recent publication by Shah and colleagues with great interest.[1] Using data from 4 population-based studies and a rigorous modelling approach, the authors demonstrated the uncertainty of defining the optimal threshold for the CHA_2DS_2-VASc score above which anticoagulant treatment for stroke prevention in atrial fibrillation (AF) should be initiated. The optimal CHA_2DS_2-VASc threshold varied considerably, ranging from 0 points (i.e. anticoagulation for all patients with AF) to 3 points, depending on the predicted stroke risk for each score.

In our recent meta-analysis of all 19 studies validating the CHA_2DS_2-VASc rule in patients with AF who were not receiving anticoagulation, we found, similar to Shah and colleagues, that it is not possible to adequately decide about anticoagulation in individual patients with AF on the basis of the CHA_2DS_2-VASc rule.[2] To illustrate this, we calculated 95% prediction intervals (PI) indicating the range of expected stroke rates for any patient who presents with AF similar to those included in the meta-analysis. For a CHA_2DS_2-VASc score of 2, the 95% PI for the annual risk for stroke ranged from 0.4% to 3.3% in community-dwelling patients with AF. Of interest, variation was more pronounced in studies recruiting patients with AF from the hospital setting: For a CHA_2DS_2-VASc score of 2, the 95% PI for the annual risk for stroke ranged from 0.03% to 7.8%.

Disease burden in AF is insufficiently captured by the CHA_2DS_2-VASc rule. In addition to comorbidity, its severity (such as the type of heart failure or the extent of hypertension or diabetes control) and other already known predictors of stroke in AF (such as renal insufficiency) should be considered. Therefore, we believe the difference between settings of care as observed in our study further strengthens the work by Shah and colleagues.

More accurate stroke prediction is needed for safe and effective anticoagulation in patients with AF. Therefore, future research should focus on model revision. Until then, we agree with Shah and colleagues that guidelines on anticoagulation in AF should include the uncertainty around the current thresholds for anticoagulation and the associated predicted stroke risks per CHA_2DS_2-VASc score.

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POTENTIAL CONFLICTS OF INTEREST

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CONTRIBUTORS

LJ wrote the first version of the letter. All authors critically reviewed and revised the letter.

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ATRIAL FIBRILLATION: TRENDS IN PREVALENCE AND ANTITHROMBOTIC PRESCRIPTIONS IN THE COMMUNITY

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ABSTRACT

Introduction: In the past decade, the atrial fibrillation (AF) landscape, including the treatment modalities, has drastically changed. This raises the question how AF prevalence and choices in antithrombotic therapy prescription have developed in the community over time.

Methods: Routine care data from the Julius General Practitioners' Network (JGPN) were used to calculate the yearly prevalence of AF and to quantify the percentage of all patients who were prescribed a platelet inhibitor, vitamin K antagonist (VKA), non-VKA oral anticoagulant (NOAC) or no antithrombotic medication. To explore whether certain patient characteristics are associated with selective prescription of oral anticoagulants (OAC), we applied logistic regression analyses.

Results: From 2008 through 2017, the JGPN database included 7,459 unique AF patients. During this period, the prevalence of AF increased from 0.4% to 1.4%. The percentage of patients prescribed a VKA declined from 47% to 41%, whereas the percentage of patients prescribed a NOAC rose from 0% to 20%. In patients with new-onset AF, older age, heart failure, diabetes mellitus, vascular disease and dementia were independently associated with a higher likelihood of VKA rather than NOAC prescription. In 2017, 25% of all patients with AF and a CHA_2DS_2-VASc score ≥2 were not prescribed OAC therapy (i.e. 8% with platelet inhibitor monotherapy and 17% without any antithrombotic therapy).

Conclusion: Between 2008 and 2017, AF prevalence in the community more than tripled. Prescription patterns showed possible 'channelling' of VKAs over NOACs in frailer, elderly patients, whereas still about one in every four AF patients with a CHA_2DS_2-VASc score ≥2 was not prescribed any prophylactic OAC therapy.

What is new?

- The prevalence of reported atrial fibrillation (AF) in the general population more than tripled, from 0.4% in 2008 to 1.4% in 2017.
- In patients with new-onset AF, older age and concurrent presence of heart failure, diabetes, vascular disease and dementia were independently associated with a higher likelihood of vitamin K antagonist (VKA) rather than non-VKA oral anticoagulant prescription.
- In 2017, approximately one in every four patients with a diagnosis of AF and a CHA_2DS_2-VASc score ≥2 did not receive prophylactic oral anticoagulant therapy.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia among adults. AF patients are at greater risk of stroke and thromboembolism than patients without AF. On average, the stroke and thromboembolic risk in patients with AF is 2–3% per year, but this can be as high as 14% per year in untreated AF patients with multimorbidity, as summarised by the CHA_2DS_2-VASc risk model.[1] If the CHA_2DS_2-VASc score is equal to or exceeds 2 points, the stroke risk is considered high enough to warrant chronic oral anticoagulant (OAC) therapy for stroke prevention.[1,2] Still, there is uncertainty about this threshold.[3,4]

Such prophylactic OAC therapy can be categorised into vitamin K antagonists (VKA) and non-VKA OACs (NOAC). Although both VKAs and NOACs are effective in preventing stroke, they inherently also increase the bleeding risk.[5–11] Patients prescribed NOACs have a lower risk of intracranial bleeding compared with those taking VKAs, but a higher risk of gastrointestinal haemorrhage (particularly in the elderly).[11] Platelet inhibitors are no longer indicated for stroke prevention in AF,[2] because they are far less effective in stroke risk reduction than OAC therapy (22% versus 64%), and they are (nearly) not effective at all in those over 75 years.[12,13] Nevertheless, platelet inhibitors are sometimes prescribed, notably in patients with (presumable) contraindications for VKAs or NOACs or in patients unwilling to receive OAC therapy.

In this changing AF landscape with changing treatment modalities, the question is how AF prevalence and the choices in prescription of OACs have developed over time. Therefore, the aim of this study was to describe trends in AF prevalence and patterns of antithrombotic therapy prescriptions in the community. Furthermore, we explored if certain patient characteristics are associated with selective OAC prescription (i.e. channelling).

METHODS

Data from the Julius General Practitioners' Network (JGPN) were used for this study. The JGPN database contains pseudo-anonymous routine healthcare data from structured fields in electronic medical records of a large, ongoing, dynamic cohort consisting of all patients of the approximately 160 affiliated general practitioners (GPs) in the city of Utrecht and its vicinity in the Netherlands. The JGPN population is representative of the Dutch community with regard to sex and age and consisted of approximately 385,000 patients in 2017.[14]

Data extraction

Patients with AF were identified in the JGPN database by using the International Classification of Primary Care (ICPC) code K78 (AF or atrial flutter), from 1 January 2008 to 31 December 2017.[15] The following variables were extracted: sex, age, medical history using ICPC codes (see Supplementary File S1) and cardiovascular medication prescriptions (see Supplementary File S2). Medication prescriptions were classified according to the Anatomical Therapeutic Chemical classification system. Antithrombotic therapy was divided into three categories: VKA, NOAC and platelet inhibitor therapy. Medication prescription was not necessarily initiated by the GP but may have been started by a hospital specialist and continued by the GP.

Statistical analyses

Baseline characteristics of AF patients are reported for 2008 (if AF was first recorded in or before 2008) or for the year AF was first recorded (if this was after 2008 and before 2018). They are presented as count and percentage for categorical variables and as median with interquartile range (IQR) for continuous variables.

The prevalence of reported AF was calculated for each year of the entire study period, whereby the whole JGPN population was placed in the denominator. In addition, the prevalence of AF was stratified by sex and by age (<55 years, 55–64 years, 65–74 years, 75–84 years and ≥85 years).

The percentages of all AF patients who were prescribed VKA monotherapy, NOAC monotherapy, platelet inhibitor monotherapy, a combination of these antithrombotic treatments or no antithrombotic medication were calculated for each year of the entire study period. In addition, for the group of patients with a diagnostic code for AF and with a CHA_2DS_2-VASc score ≥2, the percentage of patients who were not prescribed OAC therapy (i.e. platelet inhibitor monotherapy or no antithrombotic therapy at all) was calculated for each year of the study period, to investigate possible changes over time in the percentage of patients who did not receive OAC therapy while this was considered necessary.

To explore the association between all predefined patient characteristics and VKA versus NOAC prescriptions in patients with new-onset AF, univariable logistic regression analyses were performed on the data of the year in which a new diagnostic code for AF or atrial flutter (ICPC code K78) for a certain patient was reported. To create a final set of variables that may be independently associated with VKA or NOAC prescription in patients with new-onset AF, multivariable logistic regression analyses with stepwise backward elimination (eliminated if p-value ≥0.05) were applied. Only AF patients who were prescribed OACs (either VKAs or NOACs) were included in these analyses, since the indication for prophylactic antithrombotic therapy is overall the same for this patient group. The group of patients who were prescribed a combination of antithrombotic treatments consisted of patients who switched antithrombotic medication within the concerning year(s) and patients who truly received antithrombotic medications from different medication groups at the same time. Because it was not possible to distinguish between them in our dataset, patients within this group were excluded from the univariable and multivariable logistic regression analyses in the year(s) in which this combination therapy was recorded.

All statistical analyses were performed using IBM SPSS Statistics 25.0.0.2.[16]

RESULTS

From 1 January 2008 through 31 December 2017, the JGPN database included 7,459 unique patients with ICPC code K78 (AF or atrial flutter). The median follow-up time was 4 years (IQR 2–7) (see Table 1). The median age was 74 years (IQR 65–82), 51.4% were men, and the median CHA_2DS_2-VASc score was 3 (IQR 2–4). The most prevalent comorbidity registered was hypertension (49.8%). Of the cardiovascular medication, beta blockers (62.7%) were most often prescribed, alongside antithrombotic therapy (76.0%).

Prevalence of atrial fibrillation

Prevalence of reported AF increased over time, from 0.43% (95% confidence interval (CI) 0.41%–0.45%) in 2008 to 1.43% (95% CI 1.39%1.47%) in 2017 (see Figure 1). Men had a higher AF prevalence than women (1.6% versus 1.3%) in 2017. AF prevalence was highest in the oldest patients (0.1% in patients <55 years versus 15.9% in those aged ≥85 years in 2017) and, over time, the increase was more pronounced in the older age categories than in the younger age categories.

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS WITH ATRIAL FIBRILLATION.

Variable	Patients (n=7,459)
Follow-up time, years	4 (2–7)
Male sex	3,836 (51.4)
Age in years	74 (65–82)
<55	698 (9.4)
55–64	1,131 (15.2)
65–74	1,993 (26.7)
75–84	2,257 (30.3)
≥85	1,380 (18.5)
CHA_2DS_2-VASc score	3 (2–4)
CHA_2DS_2-VASc score ≥2	5,829 (78.1)
Heart failure	1,250 (16.8)
Hypertension	3,717 (49.8)
Diabetes mellitus	1,497 (20.1)
CVA or TIA	833 (11.2)
Vascular disease[a]	1,617 (21.7)
Renal impairment[b]	1,313 (17.6)
Dementia	256 (3.4)
Asthma or COPD	1,295 (17.4)
Malignancy[c]	623 (8.4)
History of bleeding[d]	1,407 (18.9)
Antithrombotic therapy	5,667 (76.0)
Beta blocker	4,680 (62.7)
Calcium channel blocker	1,543 (20.7)
Digoxin	1,451 (19.5)

Data are median (interquartile range) or n (%).

[a] *Coronary artery disease or peripheral vascular (arterial or venous) disease.*

[b] *International Classification of Primary Care (ICPC) code U99.01 (renal impairment) or estimated glomerular filtration rate <60 mL/min/1.73 m^2.*

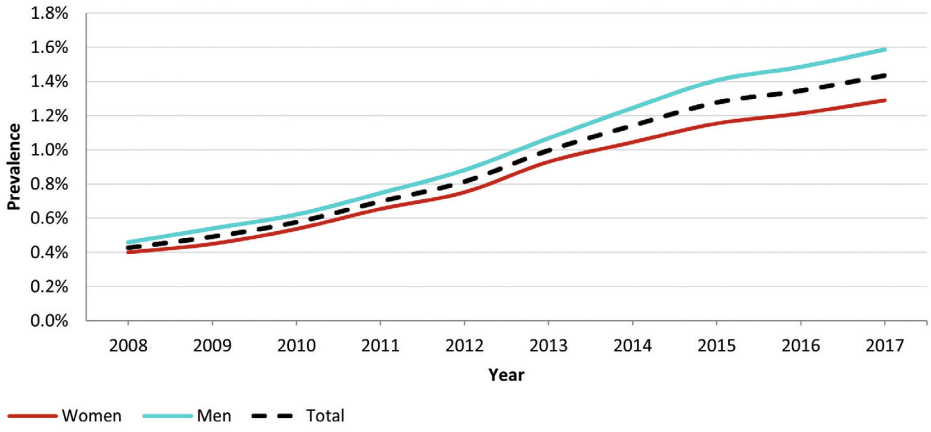
[c] *Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.*

[d] *Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melaena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.*

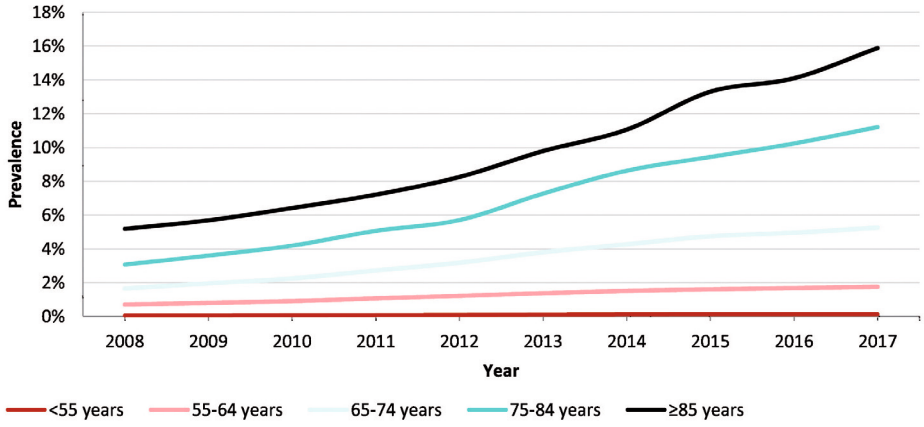
COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; n: number; TIA: transient ischaemic attack.

FIGURE 1: TRENDS IN PREVALENCE OF ATRIAL FIBRILLATION IN PRIMARY CARE.

A. Stratified by sex



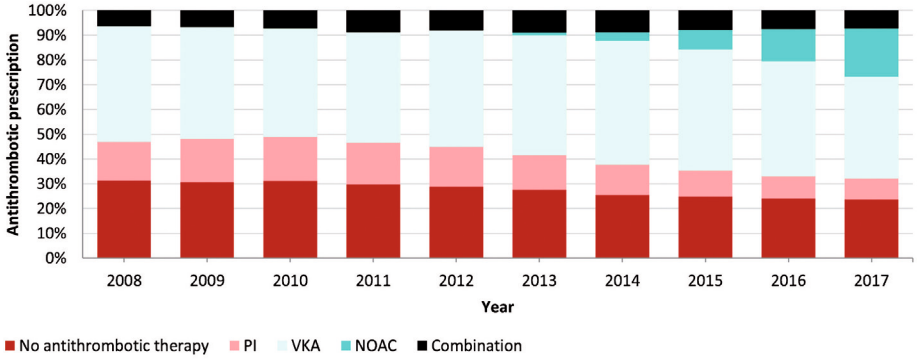
B. Stratified by age



Prescription of antithrombotic therapy

During the entire study period, most patients were prescribed VKA monotherapy, with a decline from 46.7% in 2008 to 41.3% in 2017 (see Figure 2). The percentage of patients who were prescribed NOAC monotherapy steadily increased, from 0.0% in 2011 to 19.5% in 2017. Most of the 1,608 AF patients who were prescribed NOAC monotherapy for the first time during the study period, were new-onset AF patients (57.4%). The percentage of patients with a diagnostic code for AF and with a CHA_2DS_2-VASc score ≥2 (justifying OAC therapy for stroke prevention) who were not prescribed OAC therapy decreased from 42.2% in 2008 (consisting of 15.3% who were prescribed platelet inhibitor monotherapy and 26.9% who were prescribed no antithrombotic therapy at all) to 25.4% in 2017 (8.5% were prescribed platelet inhibitor monotherapy and 16.9% were not prescribed any antithrombotic therapy).

FIGURE 2: TRENDS IN ANTITHROMBOTIC PRESCRIPTIONS IN ALL PATIENTS WITH ATRIAL FIBRILLATION IN PRIMARY CARE.



NOAC: non-vitamin K antagonist oral anticoagulant; PI: platelet inhibitor; VKA: vitamin K antagonist.

Selective anticoagulant prescription

In univariable logistic regression analyses, each predefined patient characteristic might be related to VKA prescription rather than NOAC prescription, except for sex, hypertension, asthma or COPD, history of cerebrovascular accident or transient ischaemic attack and history of bleeding (not statistically significant) and except for history of malignancy, which in itself might be related to NOAC prescription compared with VKA prescription (see Table 2). After multivariable logistic regression analyses with stepwise backward elimination, older age and concurrent heart failure, diabetes mellitus, vascular disease and dementia were independently associated with a higher likelihood of VKA rather than NOAC prescription, whereas hypertension and malignancy were independently associated with a higher likelihood of NOAC rather than VKA prescription (see Table 2). Dementia was most strongly associated with a higher likelihood of VKA rather than NOAC prescription (adjusted odds ratio 2.11, 95%

CI 1.04–4.28 for patients with dementia compared with patients without dementia). Regarding age, for every year increase in age, the relative proportion of prevalent VKA prescriptions versus prevalent NOAC prescriptions seemed to increase with a factor 1.03 (95% CI 1.02–1.04).

DISCUSSION

This study was conducted in the general population to investigate trends in AF prevalence and antithrombotic treatment prescriptions from 2008 through 2017.

Comparison with literature

The prevalence of reported AF more than tripled in our study (from 0.4% in 2008 to 1.4% in 2017). Krijthe et al. estimated that the prevalence will more than double from 2010 to 2060.[17] Interestingly, our study indicates that, at least in the Netherlands, the steep increase in AF prevalence occurs in a much shorter time period (i.e. tripling in a decade instead of doubling in half a century). Although the purpose of our study was not to explain the observed trends, this steeper than expected increase in reported AF prevalence deserves some consideration.

Firstly, several factors may have contributed to the steep increase in reported AF prevalence: 1) increased awareness of AF related to the introduction of NOACs and the updated Dutch and European AF guidelines, 2) recent developments in Dutch primary care, which include disease managing programmes for patients with increased cardiovascular risk, and 3) enhanced digitalisation, resulting in improved accurateness and completeness of (AF) registration in electronic healthcare records.

Secondly, in developed countries, a plausible reason for the steep increase in reported AF prevalence is a better survival after a first cardiovascular event, due to improved healthcare and an overall improvement in cardiovascular risk factor predisposition. This improved survival could expose patients to the spectrum of later-onset chronic cardiovascular disease, such as AF. This hypothesis is strengthened by studies in which a clear reduction in total cardiovascular morbidity and mortality over the last decades and a shift in the burden of cardiovascular morbidity from acute to chronic cardiovascular diseases, including the development of AF, were observed.[18,19]

In our study, 25.4% of all AF patients with a CHA_2DS_2-VASc score ≥2 were not prescribed OAC therapy (8.5% were prescribed platelet inhibitor monotherapy and 16.9% were not prescribed any antithrombotic therapy) in 2017. This is comparable to the results of the international GLORIA-AF registry (study period 2011–2014): 16.7% of new-onset AF patients with a CHA_2DS_2-VASc score ≥2 did not receive OAC therapy (10.0% were prescribed a platelet inhibitor and 6.7% were not prescribed any antithrombotic therapy).[20]

TABLE 2: PATIENT CHARACTERISTICS PROBABLY ASSOCIATED WITH VKA VERSUS NOAC PRESCRIPTION IN PATIENTS WITH NEW-ONSET ATRIAL FIBRILLATION DIAGNOSED FROM 2011 THROUGH 2017.

Univariable analyses			
Variable	**VKA (n=1,842)**	**NOAC (n=603)**	**Unadjusted odds ratio (95% CI)**
Male sex	939 (51.0)	305 (50.6)	1.02 (0.85–1.22)
Age in years	76 (69–83)	72 (65–79)	1.03 (1.03–1.04)
Age ≥75 years	1,039 (56.4)	235 (39.0)	2.03 (1.68–2.45)
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)	1.21 (1.14–1.28)
CHA_2DS_2-VASc score ≥2	1,570 (85.2)	467 (77.4)	1.68 (1.34–2.12)
Heart failure	365 (19.8)	60 (10.0)	2.24 (1.67–2.99)
Hypertension	934 (50.7)	316 (52.4)	0.93 (0.78–1.12)
Diabetes mellitus	439 (23.8)	102 (16.9)	1.54 (1.21–1.95)
CVA or TIA	160 (8.7)	48 (8.0)	1.10 (0.79–1.54)
Vascular disease[a]	349 (18.9)	76 (12.6)	1.62 (1.24–2.12)
Renal impairment[b]	444 (24.1)	99 (16.4)	1.62 (1.27–2.06)
Dementia	84 (4.6)	9 (1.5)	3.15 (1.58–6.31)
Asthma or COPD	313 (17.0)	110 (18.2)	0.92 (0.72–1.17)
Malignancy[c]	158 (8.6)	69 (11.4)	0.73 (0.54–0.98)
History of bleeding[d]	349 (18.9)	107 (17.7)	1.08 (0.85–1.38)
Multivariable analyses[e]			
Variable	**Adjusted odds ratio (95% CI)**		
Age in years	1.03 (1.02–1.04)		
Heart failure	1.72 (1.27–2.32)		
Hypertension	0.80 (0.66–0.97)		
Diabetes mellitus	1.45 (1.13–1.85)		
Vascular disease[a]	1.38 (1.05–1.82)		
Dementia	2.11 (1.04–4.28)		
Malignancy[c]	0.63 (0.46–0.85)		

Data are n (%) or median (interquartile range).

[a] Coronary artery disease or peripheral vascular (arterial or venous) disease.

[b] International Classification of Primary Care (ICPC) code U99.01 (renal impairment) or estimated glomerular filtration rate <60 mL/min/1.73 m^2.

[c] Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.

[d] Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melaena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.

[e] Multivariable analyses with stepwise backward elimination (eliminated if p-value ≥0.05) and with age and CHA_2DS_2-VASc score as continuous instead of dichotomous variables.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; n: number; NOAC: non–vitamin K antagonist oral anticoagulant; TIA: transient ischaemic attack; VKA: vitamin K antagonist.

In the international GARFIELD-AF registry (study period 2009–2016), 38.0% of new-onset AF patients with an indication for OAC therapy did not receive any anticoagulation.[21] Since the percentages of undertreatment cannot be fully explained by patients with a contraindication for anticoagulants (around 2.2%),[22] all three studies (GLORIA-AF registry,[20] GARFIELD-AF registry,[21] and our study) clearly emphasise that antithrombotic treatment in AF patients still leaves room for improvement and undertreatment remains a point of attention for both patients and physicians.[23,24]

Identifying subgroups at risk of stroke due to inappropriate treatment should be the focus of new research. However, as a first step, we performed additional descriptive analyses, stratified by CHA_2DS_2-VASc score, to explore the characteristics of all AF patients who were prescribed a platelet inhibitor or no antithrombotic therapy at all in 2017 (see Supplementary File S3). It seemed, among other things, that physicians regard platelet inhibitors as a reasonable alternative for OAC therapy or they do not consider initiating OAC therapy in AF patients with pre-existing vascular disease, such as coronary artery disease or peripheral vascular disease, perhaps because these patients are already prescribed a platelet inhibitor.

Strengths and limitations

A major strength of our study is that we used uniformly registered, routine clinical practice data on trends in AF in primary care spanning a decade.

Two limitations, which are inherent to using data derived from structured fields in electronic health records, are: 1) lack of specific granular information (e.g. no differentiation based on AF subtype (paroxysmal, persistent, permanent) and inability to differentiate between primary versus secondary AF and between AF versus atrial flutter); and 2) risks of misclassification in predictor values used in the CHA_2DS_2-VASc model, misclassification in diagnosis and - to a lesser extent when using data from the JGPN database - misclassification in treatment. However, the JGPN consists of a dedicated group of GPs who have been trained in accurately coding diseases using ICPC codes. Moreover, van Doorn et al. have demonstrated that the risk of substantial misclassification in individual predictors of the CHA_2DS_2-VASc model is relatively small in multivariable analyses, albeit present.[25]

Clinical implications

The clinical implications of this study are multiple. Firstly, the large increase in reported AF prevalence over time was far greater than previously expected.[17] This can lead to an increase in AF care, in particular care aimed at stroke prevention, which could, for example, be realised to a large extent through integrated management of AF in primary care.[26]

Secondly, there is still room for improvement in stroke prevention by further reducing OAC undertreatment (i.e. platelet inhibitor monotherapy or no antithrombotic therapy at all) in patients with a CHA_2DS_2-VASc score ≥2.

Finally, the number of NOAC prescriptions is expected to increase further. We observed that the diminishing group of patients who were (still) prescribed a VKA for new-onset AF, were older and had more comorbidity (e.g. heart failure, diabetes mellitus and vascular disease) than patients receiving a NOAC, as has also been shown by the GARFIELD-AF registry.[21] Moreover, based on performed additional explanatory analyses over time, we concluded that channelling of VKAs over NOACs in older patients and in patients with more comorbidity still took place in 2017, which was the first year in which more new-onset AF patients received a NOAC instead of a VKA (see Supplementary File S4). In the Netherlands, GP guidelines on AF recommend to be cautious when prescribing a NOAC to these frail (aged) patients.[27] Although observational data suggest that certain NOACs are as safe as (or safer than) VKAs in frail elderly,[28] more research is needed to confirm or refute the current caution in guidelines for this patient group. One such study is already on its way: the randomised controlled FRAIL-AF trial, in which frail AF patients on VKA therapy are switched to a NOAC.[29] Nonetheless, it is imaginable that the organisation of care for (frailer) VKA users—in the Netherlands, this is currently provided by the Dutch Thrombosis Services—may have to change in order to guarantee quality and continuity for AF patients who continue to take a VKA, for example by means of integrated management of AF in primary care.[26]

CONCLUSION

Between 2008 and 2017, the prevalence of reported AF in the community more than tripled. Prescription patterns of antithrombotic treatment showed possible channelling of VKAs over NOACs in frailer, elderly patients, whereas still about one in every four patients with a diagnostic code for AF and a CHA_2DS_2-VASc score ≥2 was not prescribed any prophylactic OAC therapy.

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POTENTIAL CONFLICTS OF INTEREST

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CONTRIBUTORS

LJ, AdB, EvE, MB and GJG conceived and initiated the study. EvE prepared the dataset. LJ and EvE performed the statistical analyses. LJ, Eve, AdB and GJG interpreted the results. LJ and AdB wrote the first version of the manuscript. All authors critically reviewed and revised the manuscript.

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SUPPLEMENTARY FILES

S1: INTERNATIONAL CLASSIFICATION OF PRIMARY CARE (ICPC) CODES USED IN THIS STUDY.

Medical history	ICPC code
Heart failure	K77
Hypertension	K85, K86, K87
Diabetes mellitus	T90
CVA or TIA	K89, K90
Vascular disease[a]	K74, K75, K76, K92.01, K94, W77.03
Renal impairment	U99.01 or eGFR <60 mL/min/1.73 m^2
Dementia	P70
Asthma or COPD	R95, R96
Malignancy[b]	B72, B73, B74, D75, R84, R85, X76, Y77
History of bleeding[c]	A10, D14, D15, D16, N80.01, N80.02, N80.03, R06, R24, U06, W17, X06

[a] *Coronary artery disease or peripheral vascular (arterial or venous) disease.*

[b] *Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.*

[c] *Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.*

COPD chronic obstructive pulmonary disease; CVA: cerebrovascular accident; eGFR: estimated glomerular filtration rate; ICPC: International Classification of Primary Care; TIA: transient ischemic attack.

S2: ANATOMICAL THERAPEUTIC CHEMICAL (ATC) CLASSIFICATION SYSTEM CODES USED IN THIS STUDY.

Antithrombotic therapy	ACT code
Platelet inhibitor (PI)	
Clopidogrel	B01AC04
Acetylsalicylic acid	B01AC06
Dipyridamole	B01AC07
Carbasalate calcium	B01AC08
Epoprostenol	B01AC09
Prasugrel	B01AC22
Ticagrelor	B01AC24
Selexipag	B01AC27
Combinations	B01AC30
Vitamin K antagonist (VKA)	
Warfarin	B01AA03
Phenprocoumon	B01AA04
Acenocoumarol	B01AA07
Non-vitamin K antagonist oral anticoagulant (NOAC)	
Dabigatran	B01AE07
Rivaroxaban	B01AF01
Apixaban	B01AF02
Edoxaban	B01AF03
Other medication	**ACT code**
Beta blocker	C07
Calcium channel blocker	C08
Digoxin	C01AA

S3: CHARACTERISTICS OF ALL PATIENTS WITH ATRIAL FIBRILLATION WHO WERE PRESCRIBED ANTICOAGULATION THERAPY, A PLATELET INHIBITOR OR NO ANTITHROMBOTIC THERAPY AT ALL IN 2017 (STRATIFIED BY CHA_2DS_2-VASC SCORE).

Variable	CHA_2DS_2-VASc <2			CHA_2DS_2-VASc ≥2		
	ACT (n=33)	PI (n=75)	No ATT (n=539)	ACT (n=3,014)	PI (n=385)	No ATT (n=766)
Male sex	299(89.8)	63(84.0)	422(78.3)	1,422 (47.2)	193 (50.1)	335 (43.7)
Age in years	62(56-68)	60(55-67)	55(46-62)	79(72-84)	78(70.5-85)	77(70-84)
Age ≥75 years	0(0.0)	0(0.0)	0(0.0)	1,975 (65.5)	238(61.8)	458(59.8)
CHA_2DS_2-VASc score	1 (0-1)	1 (0-1)	0 (0-1)	4 (3-5)	4 (3-5)	3 (2-5)
Heart failure	9 (2.7)	0 (0.0)	2 (0.4)	766 (25.4)	62 (16.1)	176 (23.0)
Hypertension	57(17.1)	12(16.0)	61(11.3)	2,022 (67.1)	270(70.1)	499(65.1)
Diabetes mellitus	11 (3.3)	1 (1.3)	12 (2.2)	855 (28.4)	99 (25.7)	184 (24.0)
CVA or TIA	0 (0.0)	0 (0.0)	0 (0.0)	523 (17.4)	84 (21.8)	96 (12.5)
Vascular disease[a]	9 (2.7)	6 (8.0)	5 (0.9)	883 (29.3)	173 (44.9)	183 (23.9)
Renal impairment[b]	21 (6.3)	3 (4.0)	3 (0.6)	902 (29.9)	110 (28.6)	185 (24.2)
Dementia	1 (0.3)	0 (0.0)	0 (0.0)	122 (4.0)	15 (3.9)	52 (6.8)
Asthma or COPD	47 (14.1)	9 (12.0)	66 (12.2)	659 (21.9)	76 (19.7)	169 (22.1)
Malignancy[c]	17 (5.1)	8 (10.7)	14 (2.6)	410 (13.6)	36 (9.4)	90 (11.7)
History of bleeding[d]	85(25.5)	17(22.7)	73(13.5)	1,028 (34.1)	114(29.6)	215(28.1)
Beta blocker	238(71.5)	37(49.3)	119(22.1)	2,127 (70.6)	220(57.1)	278(36.3)
Calcium channel blocker	50 (15.0)	5 (6.7)	18 (3.3)	790 (26.2)	89 (23.1)	107 (14.0)
Digoxin	38 (11.4)	2 (2.7)	6 (1.1)	581 (19.3)	25 (6.5)	43 (5.6)

Data are n (%) or median (interquartile range).

[a] Coronary artery disease or peripheral vascular (arterial or venous) disease.

[b] International Classification of Primary Care (ICPC) code U99.01 (renal impairment) or estimated glomerular filtration rate <60 mL/min/1.73 m².

[c] Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.

[d] Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melaena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.

ACT: anticoagulation therapy (i.e. a vitamin K antagonist or a non-vitamin K antagonist oral anticoagulant); ATT: antithrombotic therapy; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; n: number; PI: platelet inhibitor; TIA: transient ischemic attack.

S4A: PATIENT CHARACTERISTICS PROBABLY ASSOCIATED WITH A VKA VERSUS A NOAC PRESCRIPTION IN PATIENTS WITH NEW-ONSET ATRIAL FIBRILLATION DIAGNOSED IN 2015.

Univariable analyses			
Variable	**VKA (n=295)**	**NOAC (n=115)**	**Unadjusted odds ratio (95% CI)**
Male sex	150 (50.8)	64 (55.7)	0.82 (0.54-1.27)
Age in years	77 (69-84)	68 (59-76)	1.07 (1.04-1.09)
Age ≥75 years	171 (58.0)	32 (27.8)	3.58 (2.24-5.72)
CHA_2DS_2-VASc score	3 (2-5)	2 (1-3)	1.53 (1.32-1.77)
CHA_2DS_2-VASc score ≥2	259 (87.8)	76 (66.1)	3.69 (2.20-6.21)
Heart failure	71 (24.1)	9 (7.8)	3.73 (1.80-7.75)
Hypertension	171 (58.0)	47 (40.9)	2.00 (1.29-3.09)
Diabetes mellitus	72 (24.4)	18 (15.7)	1.74 (0.99-3.07)
CVA or TIA	29 (9.8)	8 (7.0)	1.46 (0.65-3.29)
Vascular disease[a]	58 (19.7)	14 (12.2)	1.77 (0.94-3.31)
Renal impairment[b]	94 (31.9)	11 (9.6)	4.42 (2.27-8.62)
Dementia	12 (4.1)	4 (3.5)	1.18 (0.37-3.73)
Asthma or COPD	58 (19.7)	17 (14.8)	1.41 (0.78-2.54)
Malignancy[c]	41 (13.9)	11 (9.6)	1.53 (0.76-3.08)
History of bleeding[d]	66 (22.4)	15 (13.0)	1.92 (1.05-3.53)
Multivariable analyses[e]			
Variable	**Adjusted odds ratio (95% CI)**		
Age in years	1.06 (1.04-1.08)		
Renal impairment[b]	2.92 (1.46-5.84)		

Data are n (%) or median (interquartile range).

[a] *Coronary artery disease or peripheral vascular (arterial or venous) disease.*

[b] *International Classification of Primary Care (ICPC) code U99.01 (renal impairment) or estimated glomerular filtration rate <60 mL/min/1.73 m^2.*

[c] *Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.*

[d] *Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melaena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.*

[e] *Multivariable analyses with stepwise backward elimination (eliminated if p-value ≥0.05) and with age and CHA_2DS_2-VASc score as continuous instead of dichotomous variables.*

CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; n: number; NOAC: non-vitamin K antagonist oral anticoagulant; TIA: transient ischemic attack; VKA: vitamin K antagonist.

S4B: PATIENT CHARACTERISTICS PROBABLY ASSOCIATED WITH A VKA VERSUS A NOAC PRESCRIPTION IN PATIENTS WITH NEW-ONSET ATRIAL FIBRILLATION DIAGNOSED IN 2016.

Univariable analyses			
Variable	**VKA (n=221)**	**NOAC (n=156)**	**Unadjusted odds ratio (95% CI)**
Male sex	119 (53.8)	76 (48.7)	1.23 (0.82-1.85)
Age in years	78 (72-84.5)	72 (66.25-79)	1.07 (1.04-1.09)
Age ≥75 years	144 (65.2)	62 (39.7)	2.84 (1.86-4.33)
CHA_2DS_2-VASc score	4 (2.5-4)	3 (2-4)	1.35 (1.18-1.56)
CHA_2DS_2-VASc score ≥2	201 (91.0)	121 (77.6)	2.91 (1.61-5.27)
Heart failure	50 (22.6)	14 (9.0)	2.97 (1.58-5.59)
Hypertension	122 (55.2)	82 (52.6)	1.11 (0.74-1.68)
Diabetes mellitus	56 (25.3)	23 (14.7)	1.96 (1.15-3.36)
CVA or TIA	24 (10.9)	13 (8.3)	1.34 (0.66-2.72)
Vascular disease[a]	43 (19.5)	16 (10.3)	2.11 (1.14-3.91)
Renal impairment[b]	63 (28.5)	36 (23.1)	1.33 (0.83-2.13)
Dementia	11 (5.0)	0 (0.0)	-
Asthma or COPD	37 (16.7)	29 (18.6)	0.88 (0.52-1.51)
Malignancy[c]	25 (11.3)	13 (8.3)	1.40 (0.69-2.84)
History of bleeding[d]	58 (26.2)	30 (19.2)	1.49 (0.91-2.46)
Multivariable analyses[e]			
Variable	**Adjusted odds ratio (95% CI)**		
Age in years	1.06 (1.04-1.09)		
Diabetes mellitus	1.85 (1.06-3.22)		

Data are n (%) or median (interquartile range).

[a] *Coronary artery disease or peripheral vascular (arterial or venous) disease.*

[b] *International Classification of Primary Care (ICPC) code U99.01 (renal impairment) or estimated glomerular filtration rate <60 mL/min/1.73 m^2.*

[c] *Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.*

[d] *Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melaena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.*

[e] *Multivariable analyses with stepwise backward elimination (eliminated if p-value ≥0.05) and with age and CHA_2DS_2-VASc score as continuous instead of dichotomous variables.*

CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; n: number; NOAC: non-vitamin K antagonist oral anticoagulant; TIA: transient ischemic attack; VKA: vitamin K antagonist.

S4C: PATIENT CHARACTERISTICS PROBABLY ASSOCIATED WITH A VKA VERSUS A NOAC PRESCRIPTION IN PATIENTS WITH NEW-ONSET ATRIAL FIBRILLATION DIAGNOSED IN 2017.

Univariable analyses			
Variable	**VKA (n=145)**	**NOAC (n=255)**	**Unadjusted odds ratio (95% CI)**
Male sex	81 (55.9)	119 (46.7)	1.45 (0.96-2.18)
Age in years	79 (69-85)	73 (66-79)	1.04 (1.02-1.06)
Age ≥75 years	87 (60.0)	108 (42.4)	2.04 (1.35-3.09)
CHA_2DS_2-VASc score	3 (2-5)	3 (2-4)	1.13 (1.00-1.29)
CHA_2DS_2-VASc score ≥2	126 (86.9)	211 (82.7)	1.38 (0.77-2.47)
Heart failure	36 (24.8)	32 (12.5)	2.30 (1.36-3.90)
Hypertension	72 (49.7)	145 (56.9)	0.75 (0.50-1.13)
Diabetes mellitus	36 (24.8)	50 (19.6)	1.35 (0.83-2.21)
CVA or TIA	12 (8.3)	23 (9.0)	0.91 (0.44-1.89)
Vascular disease[a]	36 (24.8)	37 (14.5)	1.95 (1.17-3.25)
Renal impairment[b]	38 (26.2)	47 (18.4)	1.57 (0.97-2.56)
Dementia	10 (6.9)	4 (1.6)	4.65 (1.43-15.10)
Asthma or COPD	26 (17.9)	54 (21.2)	0.81 (0.48-1.37)
Malignancy[c]	15 (10.3)	36 (14.1)	0.70 (0.37-1.33)
History of bleeding[d]	41 (28.3)	43 (16.9)	1.94 (1.19-3.17)
Multivariable analyses[e]			
Variable	**Adjusted odds ratio (95% CI)**		
Age in years	1.05 (1.02-1.08)		
CHA_2DS_2-VASc score	0.75 (0.61-.092)		
Heart failure	2.57 (1.38-4.79)		
Vascular disease[a]	2.36 (1.30-4.28)		
Dementia	3.80 (1.11-13.04)		
History of bleeding[d]	1.76 (1.05-2.95)		

Data are n (%) or median (interquartile range).

[a] *Coronary artery disease or peripheral vascular (arterial or venous) disease.*

[b] *International Classification of Primary Care (ICPC) code U99.01 (renal impairment) or estimated glomerular filtration rate <60 mL/min/1.73 m².*

[c] *Five most prevalent malignancies in the Netherlands (apart from skin cancer): breast cancer, prostate cancer, colon cancer, lung cancer, and haematological cancer.*

[d] *Posttraumatic extradural/subdural/intracerebral haemorrhage, haemoptysis, epistaxis, haematemesis, melaena, haematochezia, haematuria, menorrhagia, postpartum haemorrhage.*

[e] *Multivariable analyses with stepwise backward elimination (eliminated if p-value ≥0.05) and with age and CHA_2DS_2-VASc score as continuous instead of dichotomous variables.*

CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; n: number; NOAC: non-vitamin K antagonist oral anticoagulant; TIA: transient ischemic attack; VKA: vitamin K antagonist.

SAFETY OF SWITCHING FROM A VITAMIN K ANTAGONIST TO A NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANT IN FRAIL OLDER PATIENTS WITH ATRIAL FIBRILLATION: RATIONALE AND DESIGN OF THE FRAIL-AF RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Introduction: Clinical guidelines recommend non-vitamin K antagonist oral anticoagulants (NOAC) over vitamin K antagonists (VKA) for stroke prevention in most patients with atrial fibrillation (AF). Frail elderly were underrepresented 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 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: 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 <30mL/min/1.73 m^2) 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 twelve 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.

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 (VKA) 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 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

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 outcome 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, 3) diagnosed with AF, 4) receiving VKA treatment and monitoring by one of the participating thrombosis services, and 5) willing to consider switching from a VKA to a NOAC. Frailty will be assessed with the Groningen Frailty Indicator (GFI) questionnaire (see 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 (i.e. estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) 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 outcome major or CRNM bleeding complications in frail elderly patients with AF treated with a VKA as well as the effect size of reducing the occurrence of this composite outcome when switching to a NOAC.[7–10,20] Based on a Dutch study with an aged population we anticipate that the yearly incidence of major and CRNM bleeding complications is 10% to 15% in our frail elderly using a VKA.[21] A relative reduction of 20% to 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 1,250 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 1,250 patients per arm to be sufficient.

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

** The power is calculated assuming a two-sided alpha level of 0.05, a 1:1 allocation ratio, and n=1,250 per arm.*

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

Interim analysis plan

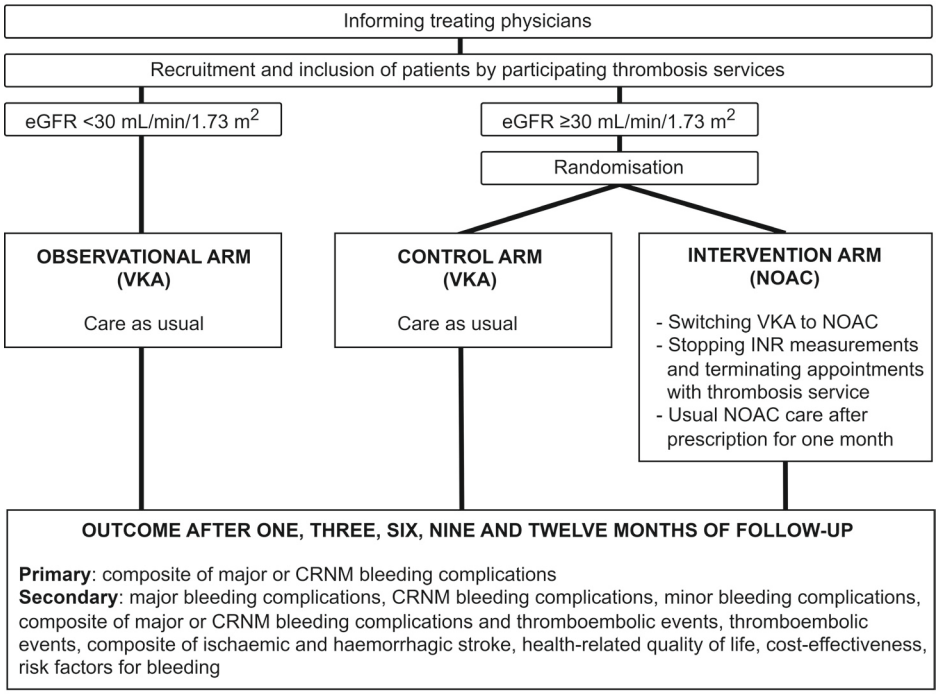
Given the uncertainty on the ability to demonstrate a reduction in bleeding events in this frail population, a pre-planned interim analysis will be performed to compare the hazard ratio (HR) on major or CRNM bleeding complications between both treatment arms, in order to anticipate futile or negative 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 twelve months, the proportion

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 2,500 subjects (each being followed for twelve 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 (i.e. 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 flowchart 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 (i.e. eGFR <30 mL/min/1.73 m^2) 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 m^2 either receive care as usual (i.e. 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 one month by the research team. After one month, the treating physician will take over the NOAC prescription. This strategy exemplifies the pragmatic real-life setting of this trial.

FIGURE 1: FLOWCHART OF THE FRAIL-AF STUDY.



CRNM: clinically relevant non-major; eGFR: estimated glomerular filtration rate; INR: international normalised ratio: NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist.

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 Supplementary file S1),[18] 3) all clinical items of the CHA_2DS_2-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 (e.g. peripheral artery disease or myocardial infarction), age 64–74 years, and female sex, 4) other relevant clinical information (e.g. 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 30-50 mL/min/1.73 m^2 and patients with an eGFR ≥50 mL/min/1.73 m^2. 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, 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 the treating physician and one of the senior researchers, and based on the summary of product characteristics (SPCs) and current guidelines.[22–25] 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 by 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 one month, the intervention itself (i.e. switching treatment from a VKA to a 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 (i.e. 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
Primary and secondary outcomes (see Supplementary file S2) are collected after one, three, six, nine, and twelve months of follow-up using a standardised questionnaire administered to the patient by telephone.[26,27] If necessary, additional information on outcomes is obtained from the patient's treating physician. Data are collected on medication use and on the primary composite outcome 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 two or more units of whole blood or red cells.[26] CRNM bleeding is defined as any sign or symptom of haemorrhage (e.g. 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 (i.e. not just a telephone or electronic communication) evaluation.[27] 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 (i.e. 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 six and twelve 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 (e.g. 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 outcomes 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 a VKA or a NOAC. For this, also data in the observational arm (i.e. subjects with an eGFR <30 mL/min/1.73 m^2) 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 Helsinki and in accordance with Dutch law (the Medical Research Involving Human Subjects Act (WMO)).[29,30] 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 a VKA (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 underrepresented 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] Older patients on a VKA showed that 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 a VKA to a 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 a VKA to a NOAC reduces the risk of bleeding complications compared with continuing VKA treatment. Thus, findings should be considered in that light and are not directly applicable to anticoagulant naive 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 (e.g. misclassification). Fourth, this study relies on patient reported outcome measures, collected at regular intervals at one, three, six, nine, and twelve 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.

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POTENTIAL CONFLICTS OF INTEREST

MEWH reports grants from The Netherlands Organisation for Health Research and Development (ZonMw) and personal fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance and Daiichi Sankyo. MVH reports grants from The Netherlands Organisation for Health Research and Development (ZonMw) and Dutch Healthcare Fund and grants and personal fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance, Daiichi Sankyo and Aspen. FR and GJG report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance and Daiichi Sankyo. The other authors declare that they have no conflicts of interest.

CONTRIBUTORS

GJG, FR and AH conceived and initiated the study. LJ, SvD, MN, NW, HK, MEWH, MVH and WB provided input on the study design, with RvdB and KR providing statistical and trial expertise. LJ and GJG wrote the first version of the manuscript. All authors critically reviewed and revised the manuscript.

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SUPPLEMENTARY FILES

S1: GRONINGEN FRAILTY INDICATOR QUESTIONNAIRE.

Physical components
Are you able to carry out these tasks single-handedly and without any help? (The use of help resources, such as a walking stick, walking frame, or wheelchair, is considered to be independent.)

1. Shopping
2. Walking around outside (around the house or to the neighbours)
3. Dressing and undressing
4. Going to the toilet

5. What mark do you give yourself for physical fitness? (Scale 0 to 10)
6. Do you experience problems in daily life because of poor vision?
7. Do you experience problems in daily life because of being hard of hearing?
8. During the past six months have you lost a lot of weight unwillingly?
9. Do you take four or more different types of medicine?

Cognitive component
10. Do you have any complaints about your memory?

Social component
11. Do you sometimes experience emptiness around yourself?
12. Do you sometimes miss people around yourself?
13. Do you sometimes feel abandoned?

Psychological component
14. Have you recently felt downhearted or sad?
15. Have you recently felt nervous or anxious?

Scoring: questions 1-4 (yes: 0, no: 1); question 5 (0-6: 1, 7-10: 0); questions 6-9 (yes: 1, no: 0); question 10 (yes: 1, sometimes/no: 0); questions 11-15 (yes/sometimes: 1, no: 0).

S2: PRIMARY AND SECONDARY OUTCOMES.

Primary outcome
Major or clinically relevant non-major bleeding complications[a,b]
Secondary outcomes
Major bleeding complications[a]
Clinically relevant non-major bleeding complications[b]
Minor bleeding complications[c]
Composite of major or clinically relevant non-major bleeding complications and thromboembolic events[a,b,d]
Thromboembolic events[d]
Ischaemic and haemorrhagic stroke
Health-related quality of life
Cost-effectiveness
Identification of risk factors for bleeding

[a] *Major bleeding complication according to the definition of the ISTH: fatal bleeding, and/or bleeding in a critical area or organ (such as 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 two or more units of whole blood or reds cells.*

[b] *Clinically relevant non-major bleeding complication according to the definition of the ISTH: 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 (i.e. not just a telephone or electronic communication) evaluation.*

[c] *Minor bleeding complications: all bleeding complications that are not classified as major or clinically relevant non-major bleeding complication according to the above definitions.*

[d] *Thromboembolic events: ischaemic stroke, or transient ischaemic attack, or peripheral arterial thromboembolism.*

ISTH: International Society on Thrombosis and Haemostasis.

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 RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Introduction: There is ambiguity whether frail patients with atrial fibrillation managed with vitamin K antagonists (VKA) should be switched to a non–VKA oral anticoagulant (NOAC).

Methods: We conducted a pragmatic, multicentre, open-label, randomised controlled superiority trial. Older patients with atrial fibrillation living with frailty (≥75 years of age plus a Groningen Frailty Indicator score ≥3) were randomly assigned to switch from international normalised ratio guided VKA treatment to a NOAC or to continue VKA treatment. Patients with a glomerular filtration rate <30 mL/min/1.73 m^2 or with valvular atrial fibrillation were excluded. Follow-up was twelve months. The cause-specific hazard ratio was calculated for the occurrence of the primary outcome, that 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 randomly assigned (mean age of 83 years, median Groningen Frailty Indicator score of 4). After randomisation, 6 patients in 'the switch to a NOAC arm' and 1 patient in 'the continue with a VKA arm' were excluded due to the presence of exclusion criteria, leaving 662 patients who switched from a VKA to a NOAC and 661 patients who continued with a VKA in the intention-to-treat population. After 163 primary outcome events (101 in the switch arm and 62 in the continue arm), the trial was stopped for futility according to a prespecified futility analysis. The hazard ratio for our primary outcome was 1.69 (95% CI 1.23–2.32). The hazard ratio for thromboembolic events was 1.26 (95% CI 0.60–2.61).

Conclusion: Switching international normalised ratio guided VKA treatment to a NOAC in frail older patients with atrial fibrillation was associated with more bleeding complications compared with continuing VKA treatment, without an associated reduction in thromboembolic complications.

What is new?

- In this pragmatic randomised trial in older patients with atrial fibrillation (AF), living with frailty, more major and 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 offset by a reduction in thromboembolic events, albeit the risk of thromboembolic events was low in both treatment arms.

What are the clinical implications?

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

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 cornerstone of AF management. Here, patients are prescribed anticoagulants, either a vitamin K antagonist (VKA) or a non–VKA oral anticoagulant (NOAC). In newly diagnosed non-frail patients with AF, 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 with VKAs.[2] However, there is a large population of older patients with AF who are (still) taking a VKA; ±30% to 40% of all patients with AF.[3,4] Many of these patients have the frailty syndrome, a clinical entity of accumulating comorbidities and polypharmacy, defined by a high biological vulnerability, dependency on others, and a reduced capacity to resist stressors.[5–7] These patients with AF living with frailty, currently receiving VKA treatment, are managed mainly in an outpatient setting, close to the communities where they live, by family medicine specialists, cardiologists, and/or internists.

The high proportion of older patients with AF that is prescribed a VKA instead of a NOAC is, at least in part, attributable to the lack of convincing trial evidence on the superiority of NOACs in older individuals with AF living with frailty. Previous studies on the effect of frailty on bleeding outcomes in AF were mainly observational, because frail patients were underrepresented in the landmark trials.[8–10] However, observational studies on the 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. This is very difficult to adjust for in observational studies.[5,11] Monitoring through international normalised ratio (INR) testing allows for intervening at an early stage by 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. As a result, it is uncertain whether the superiority of NOACs over VKAs observed in patients with AF also holds for frail patients with AF, and the question whether these patients with AF taking a VKA should be switched to a NOAC remains heavily debated. We therefore performed the FRAIL-AF study, a pragmatic randomised multicentre open-label clinical trial in older patients with AF living with frailty.

METHODS

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

Trial design and oversight

FRAIL-AF was a pragmatic, investigator-initiated, multicentre, open-label, randomised superiority trial. The protocol has been described previously.[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 at 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, Bayer Healthcare, BMS Pfizer, and Daiichi Sankyo. The University Medical Center Utrecht also supported this trial via institutional funding. 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.

An independent data safety monitoring board (DSMB), consisting of one cardiologist, one internal medicine specialist, and one biostatistician, had full access to accumulating study data and was deliberately left unblinded to randomisation status in order to fully assess patient safety in this frail population. The protocol allowed the DSMB to advice the trial steering committee on halting or modifying the trial if, in their view, the randomised comparison provided proof beyond reasonable doubt that one

particular treatment strategy (switch to a NOAC or continue with a VKA) was clearly indicated or clearly contraindicated in terms of a net difference in the primary outcome (i.e. a difference of at least 3 standard deviations; P value around 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 advise the trial steering committee to halt the trial for futility if, at that stage, the hazard ratio (HR) for the primary outcome of the intervention arm versus the control arm 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

To be eligible, patients needed to meet all 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 Supplementary file S1).[13] A potential subject who met any of the following criteria was excluded from randomisation: valvular AF (this is AF in the presence of a mechanical heart valve or severe mitral valve stenosis); an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2; taking part in another medical scientific research program; and unwilling or unable to provide written informed consent.

Randomisation, procedures, and follow-up

Patients were randomly assigned to either the intervention arm (i.e. switch to a NOAC based treatment strategy: stop the VKA and start a NOAC if the INR is <1.3), or to the control arm (i.e. continue with INR guided VKA management: either 1 mg acenocoumarol or 3 mg phenprocoumon with targeting INR levels between 2.0 and 3.0). Computerised block randomisation was used, stratified by thrombosis service and renal function at baseline (with two strata: an eGFR of 30–50 mL/min/1.73 m^2; an eGFR ≥50 mL/min/1.73 m^2).

Patients initially randomly assigned 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 bleeding during the switching period. As a result, 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 or the other. Yet, when asked to help making a NOAC choice, they 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, unless the treating physician deliberately opted for a different dose.

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

Secondary outcomes 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 events (ischaemic stroke; transient ischaemic attack; peripheral arterial thromboembolism); the composite of thromboembolic events and major or CRNM bleeding; and the composite of ischaemic and haemorrhagic stroke.

Statistical analysis

The yearly incidence of major and CRNM bleeding complications was assumed to be 10% to 15% in frail older patients with AF using a VKA.[16] A relative reduction of 20% to 30% was expected on the occurrence of these bleeding complications when switching to a NOAC. At a 2-sided α-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%).

All analyses were performed on an intention-to-treat (ITT) basis. In patients randomly assigned to the intervention arm, a variable amount of time occurred between the moment of randomisation and the actual start of the NOAC. In line with the ITT

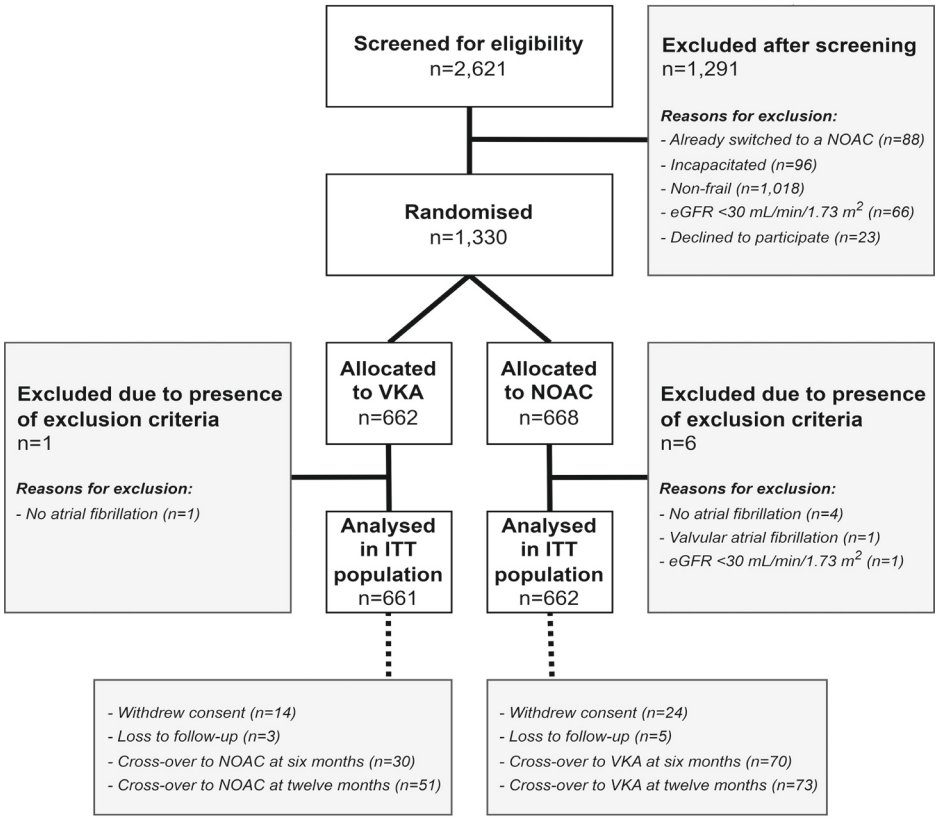
analysis, this time was assumed to be part of 'the switch to a NOAC treatment strategy' and therefore any outcome events observed during this period were included in the analyses. The primary outcome was compared between the trial arms (switching to a NOAC versus continuing with a VKA) using a cause-specific 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 an independent variable in the Cox model. Thrombosis services were included as stratification factor, allowing a 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. The 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 visualisation of the time to the 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 the strata of renal function. The primary analysis was followed for each subgroup. Analyses of secondary outcomes followed the primary analysis.

RESULTS

From 10 January 2018 through 25 April 2022, a total of 2,621 patients were screened for eligibility. Most of these patients were not included because they were considered non-frail. A total of 1,396 patients provided informed consent. In these patients renal function was assessed before randomisation, and an additional 66 patients were excluded from randomisation because of an eGFR <30 mL/min/1.73 m^2. Thus, a total of 1,330 underwent randomisation (see Figure 1). After randomisation, 7 patients (0.5% of the trial population) were excluded from analysis because they met a priori defined exclusion criteria for participating in our trial: 5 patients were in hindsight wrongly registered as having AF by the participating thrombosis services, 1 patient had an eGFR <30 mL/min/1.73 m^2, and 1 patient had valvular AF. 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). The mean age was 83±5.1 years and the median score of the GFI was 4. Other characteristics of the ITT population, such as comorbidities and renal function, are presented in Table 1. The median duration from randomisation to the start with a NOAC in the intervention arm was 52 days (interquartile range, 35–72 days). A total of 22 patients did not switch to a NOAC despite being allocated to switching (3.3%), 57 patients (8.6%) 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 randomly assigned to switch from a VKA to a NOAC, dosing followed the market-authorised 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 (6.6%) in the intervention arm and 46 (7.0%) in the control arm). Of the patients who died, a total number of 31 deaths were cardiovascular-related: 12 cardiovascular deaths (1.8%) in the intervention arm (8 terminal heart failure, 4 fatal myocardial infarction) and 19 cardiovascular deaths (2.9%) in the control arm (14 terminal heart failure, 5 fatal myocardial infarction). A total of 10 deaths were fatal bleedings: 5 (0.8%) in both the intervention and control arm. In total, 8 patients were lost to follow-up: 3 patients in the control arm and 5 patients in the intervention arm. In the remaining 1,269 patients who did not withdraw consent (99.4%) the occurrence of the primary outcomes was ascertained.

FIGURE 1: FLOWCHART WITH THE RESULTS OF INCLUSION.



eGFR: estimated glomerular filtration rate; ITT: intention to treat; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist.

TABLE 1: PATIENT CHARACTERISTICS.

	Continue with VKA (n=661)	Switch to NOAC (n=662)
Demographics		
Female sex n (%)	239 (36.2%)	274 (41.4%)
Age in years mean (SD)	82.8 (5.1)	83.0 (5.1)
Groningen Frailty Indicator		
Groningen Frailty Indicator score median (IQR)	4 (3-6)	4 (3-6)
Groningen Frailty Indicator 3 n (%)	171 (25.9%)	170 (25.7%)
Groningen Frailty Indicator ≥4 n (%)	490 (74.0%)	492 (74.3%)
Groningen Frailty Indicator (specific domains)		
Use of ≥4 different types of medication n (%)	581 (87.9)	589 (89%)
Complaints of memory n (%)	261 (39.5%)	237 (35.8%)
Unable to walk around the house n (%)	112 (16.9%)	112 (16.9%)
Problems due to impaired vision n (%)	279 (42.2%)	297 (44.9%)
Problems due to impaired hearing n (%)	353 (53.4%)	380 (57.4%)
Atrial fibrillation		
Duration of atrial fibrillation in years mean (SD)	13.0 (9.9)	12.0 (9.2)
Paroxysmal atrial fibrillation n (%)	201 (30.4%)	170 (25.7%)
Persistent atrial fibrillation n (%)	57 (8.6%)	63 (9.5%)
Permanent atrial fibrillation n (%)	335 (50.7%)	340 (52.7%)
Unknown n (%)	68 (10.3%)	89 (13.4%)
Medical history		
Heart failure n (%)	150 (22.7%)	129 (19.5%)
Hypertension n (%)	336 (50.8%)	365 (55.1%)
Diabetes mellitus n (%)	140 (21.2%)	140 (21.1%)
History of major bleeding n (%)	88 (13.3%)	105 (15.9%)
History of thromboembolic event n (%)	117 (17.7%)	139 (21.0%)
Active cancer n (%)	35 (5.3%)	44 (6.6%)
Liver cirrhosis n (%)	5 (0.8%)	3 (0.5%)
eGFR in mL/min/1.73 m² mean (SD)	62.7 (15.6)	62.5 (15.8)
Risc score		
CHA_2DS_2-VASc score median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)
Risk factor		
Body-mass index mean (SD)	27.4 (11.7)	27.4 (6.0)
Medication		
Off-label reduced NOAC dose n (%)	n.a.	44 (6.6%)
Concurrent platelet inhibitor use n (%)	13 (2.0)	16 (2.4)

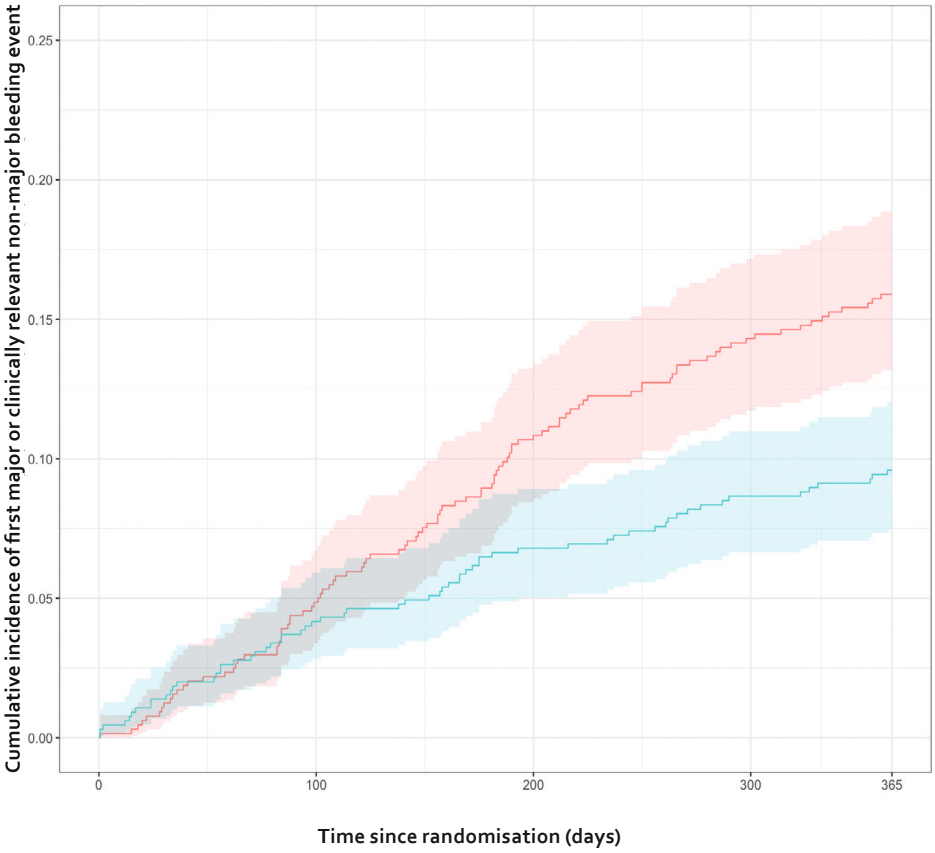
eGFR: estimated glomerular filtration rate; IQR: interquartile range; n.a.: not applicable; NOAC: non-vitamin K antagonist oral anticoagulant; SD: standard deviation; VKA: vitamin K antagonist.

Primary outcome

After having observed 163 primary outcome events (101 (15.3%) in the NOAC arm 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 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 HR for our primary outcome was 1.69 for switching to a NOAC relative to continuing INR guided VKA treatment (95% CI 1.23–2.32; P=0.00112; see Figure 2, see Table 2). The location of bleeding sites differed per treatment arm (see 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. Haemorrhagic stroke was seen in 7 patients (1.1%) who switched to a NOAC versus in 6 patients (0.9%) who continued with a VKA. 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, this is the time point when all patients were switched from a VKA to a NOAC in our intervention arm). Following the statistical analysis plan, in such circumstances, a step function using a time-period interaction term should be introduced in the Cox model. This sensitivity analysis showed a HR of 1.17 (95% CI 0.70–1.96) for the first 100 days and a HR of 2.10 (95% CI 1.40–3.16) for days 100 to 365 (see Supplementary file S2).

Subgroup analyses yielded no apparent differences in subgroups on the basis of age, sex, GFI score, or renal function (see Figure 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 (HR 1.95 (95% CI 1.36–2.79) and apixaban (HR 2.17 (95% CI 1.28–3.68)), yet appeared to be lower for edoxaban (HR 1.10 (95% CI 0.57–2.13)). Nevertheless, these analyses should be interpreted with caution because they were post-hoc and non-randomised.

FIGURE 2: CUMULATIVE INCIDENCE CURVE OF FIRST MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING EVENT.



	At risk (cumulative events)				
NOAC	662 (0)	602 (31)	558 (69)	524 (91)	503 (101)
VKA	661 (0)	613 (27)	584 (44)	562 (56)	545 (62)

Shaded areas represent the 95% confidence intervals.

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

TABLE 2: PRIMARY AND SECONDARY OUTCOMES.

	Continue with VKA		Switch to NOAC		Hazard Ratio (95% CI)
	n (%)	number of events/100 patient years (95% CI)	n (%)	number of events/100 patient years (95% CI)	
Primary outcome					
Major or CRNM bleeding	62 (9.4%)	10.5 (8.0-13.4)	101 (15.3%)	17.8 (14.5-21.6)	1.69 (1.23-2.32)
Secondary outcomes					
Major bleeding	16 (2.4%)	2.6 (1.5-4.2)	24 (3.6%)	3.9 (2.5-5.9)	1.52 (0.81-2.87)
CRNM bleeding	49 (7.4%)	8.2 (6.1-10.9)	84 (12.7%)	14.6 (11.7-18.1)	1.77 (1.24-2.52)
Thromboembolic events	13 (2.0%)	2.1 (1.1-3.6)	16 (2.4%)	2.6 (1.5-4.3)	1.26 (0.60-2.61)
Composite of thromboembolic events and major or CRNM bleeding	73 (11.0%)	12.4 (9.8-15.6)	115 (17.4%)	20.6 (17.0-24.7)	1.65 (1.23-2.21)
Composite of ischaemic and haemorrhagic stroke	11 (1.7%)	1.8 (0.9-3.2)	14 (2.1%)	2.3 (1.3-3.8)	1.30 (0.59-2.87)
All-cause mortality	46 (7.0%)	7.4 (5.4-9.8)	44 (6.7%)	7.1 (5.2-9.5)	0.96 (0.64-1.45)

CI: confidence interval; CRNM: clinically relevant non-major; NOAC: non vitamin-K antagonist oral anticoagulant; VKA: vitamin K antagonist.

TABLE 3: FIRST MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING LOCATION PER TREATMENT ARM.

	Major bleeding		CRNM bleeding	
	Continue with VKA	Switch to NOAC	Continue with VKA	Switch to NOAC
Skin n (%)			10 (1.5%)	23 (3.5%)
Oropharyngeal n (%)	1 (0.2%)		16 (2.3%)	19 (2.9%)
Gastrointestinal n (%)	1 (0.2%)	9 (1.4%)	3 (0.5%)	8 (1.2%)
Urogenital n (%)			11 (1.7%)	20 (3.0%)
Brain[a] n (%)	6 (0.9%)	7 (1.1%)		
Ophthalmic n (%)	1 (0.2%)		2 (0.3%)	3 (0.5%)
Musculoskeletal n (%)		1 (0.2%)	4 (0.6%)	1 (0.2%)
Lung n (%)	1 (0.2%)			
Other n (%)	3 (0.5%)	2 (0.3%)	3 (0.5%)	8 (1.2%)

[a] *Intracranial bleeding, subarachnoid haemorrhage, subdural bleeding, epidural bleeding.*

CRNM: clinically relevant non-major; NOAC: non vitamin-K antagonist oral anticoagulant; VKA: vitamin K antagonist.

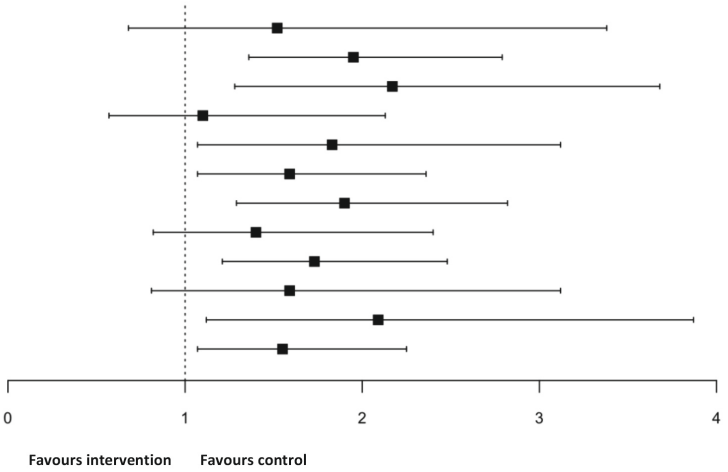
Secondary outcomes

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 (see Table 2): the HR for major bleeding was 1.52 (95% CI 0.81–2.87) and the HR for CRNM bleeding was 1.77 (95% CI 1.24–2.52).

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

FIGURE 3: FOREST PLOT OF SUBGROUP ANALYSES.

	NOAC n	IR (n of events)	VKA n	IR (n 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)



CI: confidence interval; eGFR: estimated glomerular filtration rate; GFI: Groningen Frailty Indicator; HR: hazard ratio; IR: incidence rate; n: number; NOAC: non vitamin-K antagonist oral anticoagulant; VKA: vitamin K antagonist.

DISCUSSION

In our pragmatic randomised controlled trial among frail older patients with AF, switching INR guided VKA management to a NOAC based treatment strategy compared to continue INR guided VKA management was associated with a 69% increase in major and CRNM bleeding complications. Event rates for thromboembolic events, major bleeding in isolation, haemorrhagic stroke, and the composite of haemorrhagic and ischaemic stroke were low in both treatment arms, preventing us from drawing firm conclusions on these clinically relevant outcomes. There was no clear signal for either a reduced or an improved efficacy for these outcomes in patients switching from a VKA to a NOAC compared to continuing with a VKA.

Our trial strengthens the evidence by studying the complete domain of frailty (surpassing individual domains) in a large pragmatic trial in older patients with AF, 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 has previously been largely excluded from clinical trials.

To elaborate on this, before our trial, trial evidence on the effect 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 in clinical trials. Moreover, in these subgroup analyses, apart from the effect of ageing, frailty was predominantly quantified as a cumulative deficit of an increasing number of comorbidities and increasing polypharmacy. Albeit ageing, multimorbidity, and polypharmacy are important drivers of the concept of frailty, frailty is a clinical syndrome which 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, NOAC treatment compared with warfarin was associated with a lower risk of major or CRNM bleeding in patients regardless of age: the overall HR was 0.87 (95% CI 0.75–1.02) for standard dose NOAC treatment and 0.70 (95% CI 0.59–0.82) for reduced dose NOAC treatment.[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 naive. Moreover, an interaction of ageing on safety outcomes was observed: every 10-year increase in age led to a 10.2% increase in the HR for major bleeding for standard dose NOAC treatment (P-interaction 0.02) and every 10-year increase in age led to a 17.6% increase in the HR for major bleeding for reduced dose NOAC treatment (P-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 effect 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] Last, 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; the HR for edoxaban 30 mg was 0.74 (95% CI 0.36–1.52) and the HR for edoxaban 60 mg was 0.60 (95% CI 0.29–1.26).[24] Hence, given that at the end of the trial tails from the pivotal NOAC trials a waning (and in some analyses a reversed) advantage of NOACs over VKAs in the oldest and most comorbid trial participants had already been observed, our findings of an increased risk of major or clinically relevant non-major bleeding associated with switching VKA treatment to a NOAC compared to continuing with a VKA 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 effect 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 trial evidence. For instance, a systematic review in 444,281 included older patients with AF found that the HR for haemorrhagic stroke was lower in older patients treated with a NOAC compared with a VKA: HR 0.61 (95% CI 0.48–0.79).[25] Similar to what we observed in our trial, the HR for gastrointestinal bleeding was higher in NOAC recipients compared with patients who received INR guided VKA treatment: HR 1.46 (95% CI 1.30–1.65). However, it is important to note that observational studies exploring the effect 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 arm that switched. Previous reports, using both aggregated or pooled individual patient data from the pivotal NOAC trials, also revealed that the efficacy and safety differences favoured NOACs over warfarin most strongly in patients with AF that were VKA naive.[2,21] However, including patients that currently use INR guided VKA treatment 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 the switching design, slightly more crossover in our trial was observed in 'the switch to a NOAC arm' (n=73) than in 'the continue with a VKA arm' (n=51). Nevertheless, adherence to the protocol in our trial was still relatively high, certainly for this frail older population: 89% adherence in the intervention arm versus 92% adherence in the control arm.

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) in the VKA arm of our trial. Levels of the TTR were not an inclusion criterion in our trial nor were the individual participants' TTR levels registered. Monitoring of the INR levels at the eight study sites of this pragmatic FRAIL-AF trial was done according to current Dutch clinical practice. The range of the 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 effect of the 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 the United States, the United Kingdom, Italy, Germany, and Canada.[27] At that TTR level, apixaban compared with warfarin was still associated with a lower rate of major bleeding in a non-frail population with a median age of 70 years. Hence, we believe that levels of TTR did not influence our findings significantly or hamper generalisability to the substantial population of older patients living with frailty in many countries, and we consider our findings to be generalisable 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 ±70%) to a NOAC, given our finding of a higher risk of major or CRNM bleeding. Our trial does not allow us 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 affected our results. In observational studies, rivaroxaban (the most prescribed NOAC in our trial) is associated with more bleeding complications than other NOAC types, notably gastrointestinal bleeding, with apixaban having the best safety profile in older individuals.[26,28–30] In our trial, a post-hoc analysis per NOAC type showed that rivaroxaban and apixaban had a similar HR for our primary outcome. Nevertheless, because the type of NOAC prescribed was

non-randomised, 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 haemorrhagic stroke. Due to the small number of events, we cannot draw any conclusions on possible differences between treatment arms.

Last, rather than comparing two types of anticoagulant molecules, it is important to acknowledge that our open-label pragmatic trial allows us 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 to continue with INR guided VKA therapy. This was done deliberately, because it answers the clinically relevant question on whether a 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, because 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 arm occurred while the patient was (still) taking a VKA, and vice versa. However, the proportion of the bleeding events occurring not on the anticoagulant strategy they were randomly allocated to, was small in both treatment arms: 7 of 101 bleeding events (6.9%) in the NOAC arm and 5 of 62 bleeding events (8.1%) in the VKA arm (see Supplementary file S3).

In conclusion, our FRAIL-AF pragmatic trial showed that switching from INR guided VKA treatment to a NOAC compared to continuing with INR guided VKA treatment is associated with more bleeding complications in frail older patients with non-valvular AF. Albeit our trial was not powered to demonstrate differences in thromboembolic events, major bleeding in isolation, haemorrhagic stroke, or the composite of haemorrhagic and ischaemic stroke, there was no clear signal that switching results in reduction of these outcomes in our trial population. Hence, we believe our trial indicates that careful consideration should be applied when choosing between continuing VKA treatment or switching from a VKA to a NOAC in older patients living with frailty.

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POTENTIAL CONFLICTS OF INTEREST

SvD reports an unrestricted research grant from Stoffels Hornstra. FR and GJG report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance and Daiichi Sankyo. MEWH reports grants from The Netherlands Organisation for Health Research and Development (ZonMw) and personal fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance and Daiichi Sankyo. MVH reports grants from The Netherlands Organisation for Health Research and Development (ZonMw), Dutch Healthcare Fund and Dutch Heart Foundation and grants and personal fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb/Pfizer Alliance, Daiichi Sankyo, Aspen and Leo Pharma. MK reports grants from The Netherlands Organisation for Health Research and Development (ZonMw), The Netherlands Thrombosis Foundation and Sobi and personal fees from Sobi and Roche. The other authors declare that they have no conflicts of interest.

CONTRIBUTORS

GJG, FR and AH conceived and initiated the study. LJ, SvD, MN, NW, HK, MEWH, MVH and WB provided input on the study design, with KR providing statistical and trial expertise. LJ, SvD, BK, MN, MK, LF, NW, RF, HA, FR and GJG conducted the study. LJ and SvD prepared the dataset. SvD and PvdV performed the statistical analyses. LJ SvD, BK, MEWH, MVH, FR and GJG interpreted the results. LJ, SvD, BK, MEWH, MVH, FR and GJG wrote the first version of the manuscript. All authors critically reviewed and revised the manuscript.

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SUPPLEMENTARY FILES

S1: GRONINGEN FRAILTY INDICATOR QUESTIONNAIRE.

Physical components
Are you able to carry out these tasks single-handedly and without any help? (The use of help resources, such as a walking stick, walking frame, or wheelchair, is considered to be independent.)

1. Shopping
2. Walking around outside (around the house or to the neighbours)
3. Dressing and undressing
4. Going to the toilet

5. What mark do you give yourself for physical fitness? (Scale 0 to 10)
6. Do you experience problems in daily life because of poor vision?
7. Do you experience problems in daily life because of being hard of hearing?
8. During the past six months have you lost a lot of weight unwillingly?
9. Do you take four or more different types of medicine?

Cognitive component
10. Do you have any complaints about your memory?

Social component
11. Do you sometimes experience emptiness around yourself?
12. Do you sometimes miss people around yourself?
13. Do you sometimes feel abandoned?

Psychological component
14. Have you recently felt downhearted or sad?
15. Have you recently felt nervous or anxious?

Scoring: questions 1-4 (yes: 0, no: 1); question 5 (0-6: 1, 7-10: 0); questions 6-9 (yes: 1, no: 0); question 10 (yes: 1, sometimes/no: 0); questions 11-15 (yes/sometimes: 1, no: 0).

S2: SENSITIVITY ANALYSIS.

Visual assessment of the cumulative incidence curves for the primary composite outcome of major bleeding and clinically relevant non-major bleeding revealed that the proportional hazard assumption for treatment arm was not met.
In line with the sensitivity analysis prespecified in the statistical analysis plan, a cause-specific Cox regression model was fitted that included a treatment by time period interaction. More specifically, a time-dependent coefficient for treatment arm was included in the model. Following the primary analysis, the renal function stratum was included as a fixed factor in the model and the thrombosis services stratum was included as stratification factor (allowing a separate baseline hazard function for each thrombosis service).

Based on visual inspection of the cumulative incidence curve, a step-function was used with time periods defined as period 1 (0-100 days of follow-up) and period 2 (101-365 days of follow-up).

In this sensitivity analysis, the hazard ratio (HR) for period 1 was 1.17 (95% confidence interval (CI) 0.70-1.96). For period 2 the HR was 2.10 (95% CI 1.40-3.16).

S3: DETAILS OF THE PRIMARY OUTCOME.

Treatment arm	Sex	Age in years	Frailty score	eGFR	Days since randomisation	Bleeding location	Anticoagulant at time of bleeding
Continue with VKA	Female	80.6	8	61	181	Brain	VKA
Continue with VKA	Female	83.6	4	46	98	Other	VKA
Continue with VKA	Male	79.8	4	67	363	Urogenital	VKA
Continue with VKA	Male	76.8	4	61	172	Oropharyngeal	VKA
Continue with VKA	Female	81.8	6	77	356	Skin	VKA
Continue with VKA	Male	81.9	7	59	331	Oropharyngeal	VKA
Continue with VKA	Female	80.9	5	55	70	Urogenital	VKA
Continue with VKA	Male	86.9	4	45	244	Ophthalmic	VKA
Continue with VKA	Female	92.1	7	48	261	Oropharyngeal	VKA
Continue with VKA	Male	81.1	5	82	287	Urogenital	VKA
Continue with VKA	Male	80.3	8	38	14	Oropharyngeal	VKA
Continue with VKA	Female	80.4	5	86	56	Other	VKA
Continue with VKA	Male	79.4	3	89	84	Skin	VKA
Continue with VKA	Female	91.5	4	34	53	Gastrointestinal	VKA
Continue with VKA	Male	86.9	4	78	24	Ophthalmic	VKA
Continue with VKA	Female	81.9	4	52	84	Skin	VKA
Continue with VKA	Male	86.9	3	41	54	Urogenital	VKA
Continue with VKA	Female	82.2	5	63	102	Brain	VKA
Continue with VKA	Male	88.4	4	61	56	Skin	VKA
Continue with VKA	Male	83.3	4	66	323	Brain	VKA
Continue with VKA	Male	82.3	3	69	161	Urogenital	VKA
Continue with VKA	Male	95.5	7	47	169	Lungs	NOAC
Continue with VKA	Male	81.7	7	51	24	Oropharyngeal	VKA
Continue with VKA	Male	78.8	4	68	290	Gastrointestinal	VKA
Continue with VKA	Male	79.9	3	76	113	Oropharyngeal	VKA
Continue with VKA	Male	79.1	3	52	166	Oropharyngeal	NOAC
Continue with VKA	Female	81.4	6	39	95	Musculoskeletal	VKA
Continue with VKA	Male	83.4	4	90	271	Other	VKA
Continue with VKA	Female	91.4	9	54	152	Skin	VKA
Continue with VKA	Female	83.5	6	83	138	Urogenital	VKA
Continue with VKA	Male	86.7	4	82	141	Skin	NOAC
Continue with VKA	Female	75.5	5	30	2	Oropharyngeal	VKA
Continue with VKA	Male	87.2	3	62	277	Brain	VKA
Continue with VKA	Male	86.3	5	59	1	Urogenital	VKA
Continue with VKA	Male	86.4	7	50	31	Brain	VKA
Continue with VKA	Male	91.8	3	49	256	Oropharyngeal	VKA
Continue with VKA	Male	85.9	3	74	157	Brain	VKA
Continue with VKA	Male	85.3	5	80	158	Ophthalmic	VKA
Continue with VKA	Female	76.4	7	85	262	Musculoskeletal	VKA
Continue with VKA	Male	79.5	4	76	355	Musculoskeletal	VKA
Continue with VKA	Male	76.6	3	38	175	Skin	VKA
Continue with VKA	Female	92.2	6	53	234	Oropharyngeal	VKA
Continue with VKA	Male	92.3	5	40	15	Urogenital	VKA

Continue with VKA	Male	76.8	4	64	175	Skin	VKA
Continue with VKA	Male	76.0	5	82	114	Skin	VKA
Continue with VKA	Male	76.0	5	56	93	Oropharyngeal	VKA
Continue with VKA	Male	77.1	6	87	36	Oropharyngeal	VKA
Continue with VKA	Male	75.4	3	92	77	Other	None
Continue with VKA	Female	75.5	4	76	327	Oropharyngeal	VKA
Continue with VKA	Female	78.8	7	86	17	Oropharyngeal	VKA
Continue with VKA	Female	92.0	3	58	1	Musculoskeletal	VKA
Continue with VKA	Male	76.1	3	74	79	Urogenital	VKA
Continue with VKA	Male	84.2	5	90	72	Gastrointestinal	NOAC
Continue with VKA	Male	83.3	7	74	237	Urogenital	VKA
Continue with VKA	Male	81.3	3	56	34	Oropharyngeal	NOAC
Continue with VKA	Female	80.5	8	58	193	Other	VKA
Continue with VKA	Female	85.6	6	49	266	Oropharyngeal	VKA
Continue with VKA	Male	78.6	3	87	33	Oropharyngeal	VKA
Continue with VKA	Male	89.1	8	73	216	Gastrointestinal	VKA
Continue with VKA	Male	84.6	3	44	62	Urogenital	VKA
Continue with VKA	Female	89.6	6	56	166	Other	VKA
Continue with VKA	Female	83.3	6	68	12	Skin	VKA
Switch to NOAC	Female	79.6	4	44	266	Oropharyngeal	NOAC
Switch to NOAC	Female	87.7	9	30	34	Urogenital	NOAC
Switch to NOAC	Female	85.7	8	34	108	Oropharyngeal	NOAC
Switch to NOAC	Male	90.7	7	48	302	Oropharyngeal	NOAC
Switch to NOAC	Female	90.8	7	71	33	Other	NOAC
Switch to NOAC	Female	84.8	7	73	250	Skin	VKA
Switch to NOAC	Male	89.8	5	86	189	Gastrointestinal	NOAC
Switch to NOAC	Male	81.9	5	43	88	Gastrointestinal	NOAC
Switch to NOAC	Male	85.9	8	53	15	Gastrointestinal	NOAC
Switch to NOAC	Female	81.9	4	39	263	Gastrointestinal	NOAC
Switch to NOAC	Male	81.9	4	52	22	Other	NOAC
Switch to NOAC	Female	87.0	8	54	212	Urogenital	NOAC
Switch to NOAC	Female	77.9	10	107	48	Skin	NOAC
Switch to NOAC	Female	87.3	5	63	284	Ophthalmic	NOAC
Switch to NOAC	Female	82.3	3	54	354	Gastrointestinal	NOAC
Switch to NOAC	Male	85.3	3	95	193	Urogenital	NOAC
Switch to NOAC	Male	84.3	3	36	182	Other	NOAC
Switch to NOAC	Male	85.3	5	97	29	Urogenital	NOAC
Switch to NOAC	Male	88.4	4	77	63	Urogenital	NOAC
Switch to NOAC	Female	81.5	3	62	264	Brain	NOAC
Switch to NOAC	Female	83.2	3	74	272	Skin	NOAC
Switch to NOAC	Male	87.3	4	53	149	Oropharyngeal	NOAC
Switch to NOAC	Female	79.4	3	37	138	Skin	NOAC
Switch to NOAC	Male	78.5	5	82	221	Urogenital	NOAC
Switch to NOAC	Female	86.0	6	63	323	Gastrointestinal	NOAC
Switch to NOAC	Male	78.1	5	89	99	Skin	NOAC
Switch to NOAC	Female	89.3	4	64	157	Urogenital	NOAC
Switch to NOAC	Female	94.2	8	40	82	Oropharyngeal	NOAC

Switch to NOAC	Male	82.2	6	65	1	Urogenital	NOAC
Switch to NOAC	Male	77.3	4	65	186	Oropharyngeal	NOAC
Switch to NOAC	Male	75.3	9	50	123	Skin	NOAC
Switch to NOAC	Female	81.3	9	81	18	Urogenital	VKA
Switch to NOAC	Male	81.3	4	72	36	Brain	VKA
Switch to NOAC	Male	77.4	5	72	102	Other	NOAC
Switch to NOAC	Male	93.5	5	55	336	Musculoskeletal	NOAC
Switch to NOAC	Male	88.4	3	52	342	Skin	NOAC
Switch to NOAC	Male	75.5	3	80	109	Urogenital	NOAC
Switch to NOAC	Male	82.5	3	69	141	Skin	NOAC
Switch to NOAC	Male	77.6	3	49	98	Gastrointestinal	NOAC
Switch to NOAC	Male	85.6	3	63	125	Urogenital	NOAC
Switch to NOAC	Male	79.7	3	50	30	Oropharyngeal	NOAC
Switch to NOAC	Female	86.7	3	54	158	Gastrointestinal	NOAC
Switch to NOAC	Male	91.7	6	69	28	Oropharyngeal	NOAC
Switch to NOAC	Male	84.0	4	40	266	Oropharyngeal	VKA
Switch to NOAC	Male	88.0	4	46	280	Urogenital	NOAC
Switch to NOAC	Male	92.3	4	77	84	Oropharyngeal	NOAC
Switch to NOAC	Female	75.4	4	74	121	Skin	NOAC
Switch to NOAC	Female	82.5	3	45	62	Oropharyngeal	NOAC
Switch to NOAC	Male	86.5	4	46	223	Skin	NOAC
Switch to NOAC	Male	75.6	4	90	142	Gastrointestinal	NOAC
Switch to NOAC	Male	87.7	6	72	212	Skin	NOAC
Switch to NOAC	Male	79.8	5	86	215	Oropharyngeal	NOAC
Switch to NOAC	Female	83.7	3	73	94	Other	NOAC
Switch to NOAC	Male	81.4	5	52	20	Brain	VKA
Switch to NOAC	Female	78.7	4	58	103	Urogenital	VKA
Switch to NOAC	Female	87.1	6	48	225	Oropharyngeal	NOAC
Switch to NOAC	Female	94.3	3	60	67	Gastrointestinal	NOAC
Switch to NOAC	Male	97.4	5	36	84	Skin	NOAC
Switch to NOAC	Male	94.4	10	73	181	Other	NOAC
Switch to NOAC	Female	77.4	3	42	328	Skin	NOAC
Switch to NOAC	Male	78.5	3	90	250	Skin	NOAC
Switch to NOAC	Female	81.6	7	86	176	Other	NOAC
Switch to NOAC	Male	77.6	6	90	356	Skin	VKA
Switch to NOAC	Male	93.6	8	74	151	Oropharyngeal	NOAC
Switch to NOAC	Male	80.7	3	52	190	Brain	NOAC
Switch to NOAC	Male	81.8	3	36	207	Skin	NOAC
Switch to NOAC	Female	90.9	3	59	64	Skin	NOAC
Switch to NOAC	Male	81.0	4	59	291	Gastrointestinal	NOAC
Switch to NOAC	Male	85.1	6	58	156	Urogenital	NOAC
Switch to NOAC	Male	91.1	6	60	87	Skin	NOAC
Switch to NOAC	Male	79.2	4	50	200	Other	NOAC
Switch to NOAC	Male	79.3	10	63	82	Gastrointestinal	NOAC
Switch to NOAC	Male	89.3	5	56	83	Urogenital	NOAC
Switch to NOAC	Female	79.3	4	62	146	Gastrointestinal	NOAC
Switch to NOAC	Male	78.4	3	83	156	Oropharyngeal	NOAC

Switch to NOAC	Male	81.4	4	75	88	Oropharyngeal	NOAC
Switch to NOAC	Male	78.4	3	88	147	Brain	NOAC
Switch to NOAC	Male	75.8	7	63	39	Urogenital	NOAC
Switch to NOAC	Male	84.6	4	57	182	Skin	NOAC
Switch to NOAC	Female	83.8	6	78	245	Brain	NOAC
Switch to NOAC	Male	79.9	3	49	164	Urogenital	NOAC
Switch to NOAC	Male	75.9	8	70	188	Gastrointestinal	NOAC
Switch to NOAC	Male	78.1	4	84	101	Oropharyngeal	NOAC
Switch to NOAC	Female	81.1	6	57	122	Skin	NOAC
Switch to NOAC	Male	79.1	3	88	176	Brain	NOAC
Switch to NOAC	Male	79.3	4	51	314	Urogenital	NOAC
Switch to NOAC	Male	75.5	4	55	114	Gastrointestinal	NOAC
Switch to NOAC	Male	75.4	3	78	106	Skin	NOAC
Switch to NOAC	Female	75.5	3	87	58	Oropharyngeal	NOAC
Switch to NOAC	Female	89.7	4	70	41	Oropharyngeal	NOAC
Switch to NOAC	Female	76.7	3	51	84	Musculoskeletal	NOAC
Switch to NOAC	Male	80.8	4	62	183	Skin	NOAC
Switch to NOAC	Male	86.9	3	64	204	Urogenital	NOAC
Switch to NOAC	Female	81.0	4	57	184	Skin	NOAC
Switch to NOAC	Male	85.1	5	71	169	Other	NOAC
Switch to NOAC	Male	83.2	3	48	190	Gastrointestinal	NOAC
Switch to NOAC	Male	82.3	4	46	333	Ophthalmic	NOAC
Switch to NOAC	Male	90.3	6	71	286	Urogenital	NOAC
Switch to NOAC	Male	79.5	3	72	360	Gastrointestinal	NOAC
Switch to NOAC	Male	86.6	4	70	217	Ophthalmic	NOAC
Switch to NOAC	Male	86.2	6	67	298	Other	NOAC

CLINICAL CONSEQUENCES OF OFF-LABEL REDUCED DOSING OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: Postmarketing observational studies report that a substantial percentage of patients with atrial fibrillation (AF) receive a reduced non-vitamin K antagonist oral anticoagulant (NOAC) dose without a clear indication. Recently, increasing evidence has become available to explore the clinical consequences of such off-label reduced dosing (OLRD). This study aims to systematically review and meta-analyse observational studies that report clinical outcomes associated with OLRD of NOACs compared with on-label non-reduced dosing (OLNRD) of NOACs in patients with AF.

Methods: We performed a systematic literature review and meta-analysis of observational studies reporting clinical outcomes in AF patients with OLRD of a NOAC compared with AF patients with OLNRD of a NOAC. Using random effects meta-analyses, we estimated the risk of stroke/thromboembolism, bleeding and all-cause mortality.

Results: We included 19 studies with a total of 170,394 NOAC users. In these studies, the percentage of OLRD of NOACs among patients with an indication for OLNRD ranged between 9% and 53%. 7 of these 19 studies met the predefined criteria for meta-analysis (n=80,725 patients). The pooled hazard ratio associated with OLRD of NOACs was 1.04 (95% confidence interval (CI) 0.83-1.29; 95% prediction interval (PI) 0.60-1.79) for stroke/ thromboembolism, 1.10 (95% CI 0.95-1.29; 95% PI 0.81-1.50) for bleeding, and 1.22 (95% CI 0.81-1.84; 95% PI 0.55-2.70) for all-cause mortality.

Conclusion: This meta-analysis shows no statistically significant increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD of NOACs. Future research may focus on differences between NOACs.

What is already known on this topic

- Postmarketing studies reported that many patients with atrial fibrillation receive a reduced dose of non-vitamin K antagonist oral anticoagulants (NOACs) without a clear indication.
- To what extent patients experience clinical consequences of such off-label reduced dosing (OLRD) is not yet known.

What this study adds

- While other studies have compared patients with OLRD to patients with on-label dosing (i.e. both on-label reduced and on-label non-reduced), we compared OLRD to on-label non-reduced dosing (OLNRD), which is clinically the most relevant comparison.
- Our systematic review and meta-analysis showed that there is no statistically significant increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD of NOACs compared with OLNRD of NOACs.

How this study might affect research, practice or policy

- This study summarises all observational studies on the clinical outcomes of OLRD of NOACs, thereby informing clinicians that they, in close discussion with their patients, should decide on the best treatment regimen in the specific situation of each patient.

INTRODUCTION

Oral anticoagulants are of critical value for stroke prevention in atrial fibrillation (AF). Despite the effectiveness of the oldest form of anticoagulation, vitamin K antagonists (VKA), studies have repeatedly shown that historically patients with AF often do not receive anticoagulants or antiplatelet therapy. Such 'underuse' of anticoagulants in patients with AF at high risk of stroke was in the order of 50%.[1] With the introduction of non-VKA oral anticoagulants (NOAC) in 2009, underuse of anticoagulants for AF decreased considerably given that randomised trials showed that NOACs are at least as effective as VKAs, have fewer drug and food interactions, and overall a lower risk of serious bleeding, notably intracranial bleeds.[2] Moreover, NOACs do not require INR monitoring: a fixed dose can be used.[3] Currently, four NOACs have been approved for patients with AF,[4–8] and these agents rapidly became recommended as first-line agents for most AF patients in clinical guidelines. While this initially alleviated the concerns about underuse of anticoagulants, a new pitfall has arisen. For each NOAC, besides a non-reduced dose, a reduced dose is available for specified subgroups of

patients. However, accrual of postmarketing evidence showed that many patients (in the order of 20%–30%) receive a reduced NOAC dose without any clear indication, likely to mitigate a presumed high risk of bleeding.[9–14] This so-called off-label reduced dosing (OLRD) may put patients in need of oral anticoagulants at unnecessary risk of thromboembolism, while the anticipated attenuation of bleeding risk may in fact be negligible, or at least does not justify this OLRD.[15]

Several systematic reviews have evaluated the clinical consequences of OLRD.[14,16–18] However, the included studies in these reviews are highly heterogeneous, suffer from confounding and/or compare patients with OLRD to all patients receiving an on-label dose (i.e. both on-label reduced and on-label non-reduced). A more clinically relevant comparison is the comparison of OLRD to on-label non-reduced dosing (OLNRD) only. After all, clinicians wonder what happens if they reduce the dose in patients who are presumed to be at high risk of bleeding (i.e. the most common incentive for clinicians to opt for OLRD of NOACs), but who do not formally meet the dose reduction criteria and should, therefore, receive an on-label non-reduced NOAC dose. We, therefore, systematically reviewed all observational studies that report clinical outcomes associated with OLRD of NOACs compared with OLNRD of NOACs in patients with AF and estimated the risk of stroke/thromboembolism, bleeding and all-cause mortality performing meta-analyses only in studies meeting predefined criteria (in order to reduce the impact of confounding).

METHODS

Search strategy

We performed a systematic search to identify all observational studies reporting on clinical outcomes associated with OLRD of NOACs for stroke prevention in AF patients from 1 January 2009 to 10 July 2022. We searched PubMed and Embase using search terms for 'dose reduction' and 'NOAC', including synonyms and MeSH headings where appropriate, and without language restrictions. For the full search syntax, see Supplementary File S1.

Definitions and study selection

We defined OLRD of NOACs as the use of a NOAC dose lower than the recommended on-label non-reduced NOAC dose in absence of a clear indication for dose reduction as formulated either by the Summary of Product Characteristics (SPC),[19–22] the Food and Drug administration (FDA),[23–26] the European Society of Cardiology (ESC),[27] the European Heart Rhythm Association (EHRA),[28] the landmark NOAC trials[5–8] (see Table 1), or other guidelines. Clinical outcomes under consideration were stroke/thromboembolism (defined as (ischaemic) stroke and/or transient ischaemic attack (TIA) and/or thromboembolism), bleeding (defined as (major) bleeding), all-cause

hospitalisation, all-cause mortality and major adverse clinical events (MACE) (defined as cardiovascular mortality, and/or myocardial infarction, and/or a composite of cardiovascular diseases, such as stroke/thromboembolism and bleeding).

We selected all original observational studies on stroke prevention in patients with AF without a mechanical heart valve and/or severe mitral valve stenosis, describing the use of any of the registered NOACs (i.e. dabigatran, rivaroxaban, apixaban, and/or edoxaban), and presenting data on clinical outcomes of treatment with an off-label reduced NOAC dose compared with treatment with the on-label (i.e. the recommended) non-reduced NOAC dose. We excluded studies including patients below the age of 18 years or including patients with venous thromboembolism (unless it was possible to analyse AF patients separately), and studies in highly selected patient populations (e.g. patients with a highly specific age, only patients with cancer, severe kidney disease, obesity or coronavirus disease 2019, or those on haemodialysis or after major surgery or arrhythmia surgery). Four reviewers (LJ, RvM, CvdD, and SvD) independently screened the total of selected articles based on title and abstract in duplicate and resolved any uncertainties by discussion. Of all potential studies, three reviewers (LJ, RvM, and SvD) independently evaluated the full text for eligibility in duplicate and resolved any disagreements by discussion. Reasons for exclusion were recorded. For each included study, the reference list was evaluated for any additional relevant studies.

Critical appraisal and risk of bias assessment

Three reviewers (LJ, RvM, and SvD) critically appraised all included studies and independently performed a risk of bias assessment in duplicate using the Newcastle-Ottawa quality Scale (NOS) for cohort studies[29] supplemented by an item for handling missing data (see Supplementary File S2), and resolved any disagreements by discussion.

Data extraction

From each included study, three reviewers (LJ, RvM, and SvD) extracted 1) study and patient characteristics (see Supplementary File S3), 2) the absolute number of patients receiving an off-label reduced NOAC dose and the absolute number of patients receiving the on-label non-reduced NOAC dose and 3) the exact definition of each clinical outcome (stroke/thromboembolism, bleeding, all-cause hospitalisation, all-cause mortality, and MACE), its associated relative risk for OLRD compared with OLNRD (if possible stratified by dabigatran, rivaroxaban, apixaban, and edoxaban) and the method used to adjust for confounding.

TABLE 1: INDICATIONS FOR DOSE REDUCTION OF NOACS USED FOR STROKE PREVENTION IN ATRIAL FIBRILLATION PATIENTS.

	NOAC trials[5–8]	SPC[19–22]	FDA[23–26]	ESC guidelines[27]	EHRA guidelines[28]
Dabigatran	**150 mg b.d.** No dose reduction in trial **110 mg b.d.** No dose reduction in trial	**150 mg b.d. → 110 mg b.d.** - Age ≥80 years - Verapamil use *Consider dose reduction in case of:* *- Age 75-80 years* *- CrCl 30-50 mL/min/1.73 m²* *- Gastritis/esophagitis/GERD* *- Other increased bleeding risk*	**150 mg b.d. → 75 mg b.d.** - CrCl 15-30 mL/min/1.73 m² - CrCl 30-50 mL/min/1.73 m² + dronedarone or systemic ketoconazole	**150 mg b.d. → 110 mg b.d.** Not reported	**150 mg b.d. → 110 mg b.d.** - Age ≥80 years - Verapamil use *Consider dose reduction in case of ≥2 of the following criteria:* *- Age ≥75 years* *- CrCl 30-49 mL/min/1.73 m²* *- Body weight ≤60 kg* *- Quinidine, amiodarone, clarithromycin, or erythromycin use* *- Other reasons for increased bleeding risk*
Rivaroxaban	**20 mg o.d. → 15 mg o.d.**[a] - CrCl 30-49 mL/min/1.73 m² **15 mg o.d. → 10 mg o.d.**[b] - CrCl 30-49 mL/min/1.73 m²	**20 mg o.d. → 15 mg o.d.** - CrCl 15-49 mL/min/1.73 m²	**20 mg o.d. → 15 mg o.d.** - CrCl 15-50 mL/min/1.73 m²	**20 mg o.d. → 15 mg o.d.** - CrCl 30-49 mL/min/1.73 m²	**20 mg o.d. → 15 mg o.d.** - CrCl 15-49 mL/min/1.73 m² *Consider dose reduction in case of ≥2 of the following criteria:* *- Age ≥75 years* *- Body weight ≤60 kg* *- Dronedarone, quinidine, clarithromycin, erythromycin, fluconazole, cyclosporin, tacrolimus* *- Amiodarone when CrCl <50 mL/min/1.73 m²* *- Other reasons for increased bleeding risk*

Apixaban	**5 mg b.d. → 2.5 mg b.d.** - ≥2 of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL (133 µmol/L) - Body weight ≤60 kg	**5 mg b.d. → 2.5 mg b.d.** - CrCl 15-29 mL/min/1.73 m² - ≥2 of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL (133 µmol/L) - Body weight ≤60 kg	**5 mg b.d. → 2.5 mg b.d.** - Concomitant dual inhibitors of P-gp and CYP3A4 - ≥2 of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL - Body weight ≤60 kg	**5 mg b.d. → 2.5 mg b.d.** - ≥2 of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL (133 µmol/L) - Body weight ≤60 kg	**5 mg b.d. → 2.5 mg b.d.** - CrCl 15-29 mL/min/1.73 m² - ≥2 of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL - Body weight ≤60 kg *Consider dose reduction in case of ≥2 of the following criteria:* *- Age ≥75 years* *- Body weight ≤60 kg* *- Amiodarone, diltiazem, dronedarone, or naproxen use* *- Other reasons for increased bleeding risk*
Edoxaban	**60 mg o.d. → 30 mg o.d.** - CrCl 30-50 mL/min/1.73 m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone **30 mg o.d. → 15 mg o.d.** - CrCl 30-50 mL/min/1.73 m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone	**60 mg o.d. → 30 mg o.d.** - CrCl 15-50 mL/min/1.73 m² - Body weight ≤60 kg - Ciclosporin, ketoconazole, dronedarone, erythromycin	**60 mg o.d. → 30 mg o.d.** - CrCl 15-50 mL/min/1.73 m²	**60 mg o.d. → 30 mg o.d.** - CrCl 30-50 mL/min/1.73 m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone **30 mg o.d. → 15 mg o.d.** - CrCl 30-50 mL/min/1.73 m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone	**60 mg o.d. → 30 mg o.d.** - CrCl 15-49 mL/min/1.73 m² - Body weight ≤60 kg - Dronedarone, clarithromycin, erythromycin, itraconazole, ketoconazole, posaconazole, voriconazole, cyclosporine, tacrolimus *Consider dose reduction in case of ≥2 of the following criteria:* *- Age ≥75 years* *- Amiodarone, quinidine, verapamil* *- Other increased bleeding risk*

[a] *ROCKET-AF*
[b] *J-ROCKET-AF*

CrCl: creatinine clearance; eGFR: estimated Glomerular Filtration Rate; EHRA: European Heart Rhythm Association; ESC: European Society of Cardiology; FDA: Food and Drugs Administration; GERD: gastroesophageal reflux disease; SPC: Summary of Product Characteristic.

Data analyses

First, we described the results of the systematic search, the main study and patient characteristics, and the results of risk of bias assessment. We calculated the percentage of patients with OLRD of NOACs as the number of patients with OLRD relative to the total number of patients with an indication for an on-label non-reduced NOAC dose (i.e. the sum of patients receiving OLRD and OLNRD).

Finally, where possible, we meta-analysed studies meeting predefined criteria. Foremost, observational studies often suffer from confounding (i.e. factors that influence both the use of OLRD and the risk of adverse clinical outcomes) that should always be taken into account in the analyses. Patients who receive a reduced dose without a clear indication do so for a reason. Therefore, only studies that aimed to reduce the impact of this confounding by indication by applying propensity scoring methods (for at least sex and age) in the analyses of all predefined clinical outcomes in relation to OLRD of NOACs and by reporting a hazard ratio (HR) were included in the meta-analysis, if in addition, the risk of bias was low in the representativeness of the exposed and non-exposed cohort (i.e. both awarded with a star according to the NOS) and appropriate guidelines (i.e. SPC, FDA, ESC, EHRA, or landmark NOAC trials) were used to determine whether a non-reduced or a reduced NOAC dose was indicated. Assuming heterogeneity among studies, we applied random effects meta-analysis of the log transformed HRs using restricted maximum likelihood estimation. We calculated 95% confidence intervals (CI) by using the Hartung-Knapp-Sidik-Jonkman method.[30] Between-study heterogeneity was expressed by the 95% prediction intervals (PI). The 95% PI indicates the range of occurrence of a specific clinical outcome within patients receiving an off-label reduced NOAC dose that can be expected in future observational studies with similar characteristics as those included in our review.

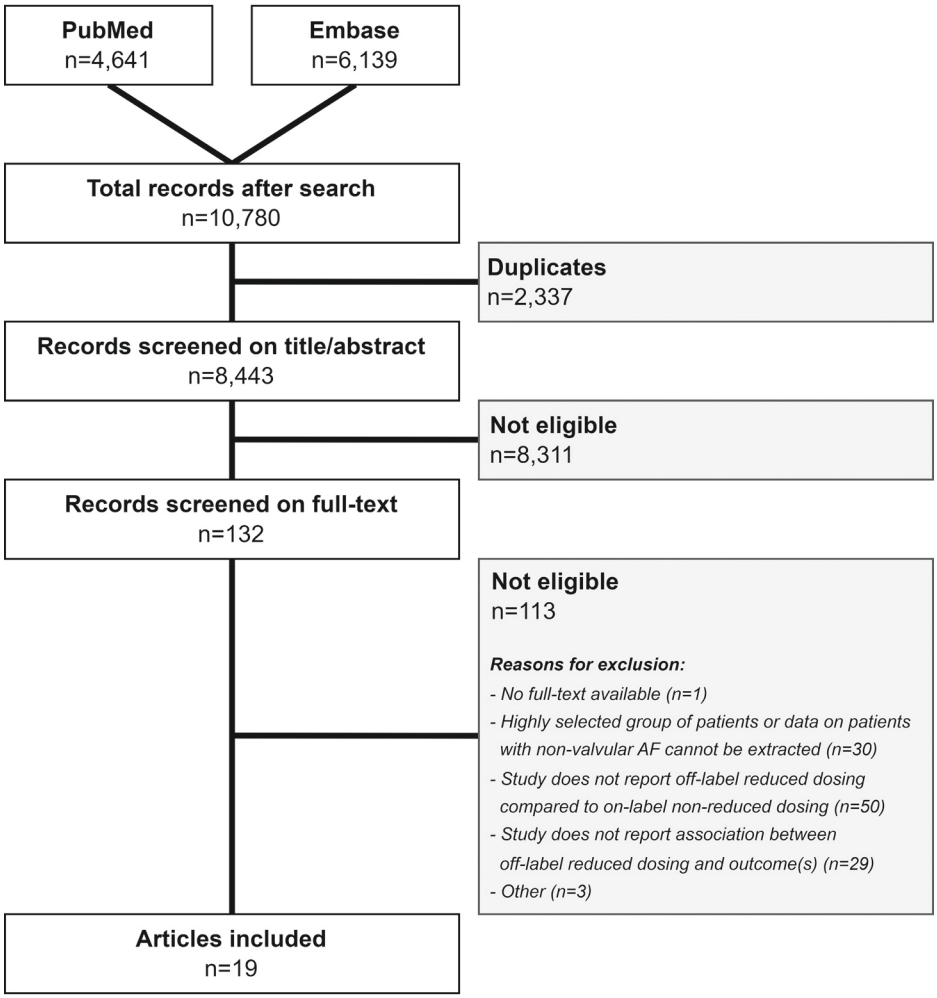
We performed analyses in R version 1.3.1093,[31] with the package 'metaphor' version 3.4–0.[32]

RESULTS

Systematic search

The results of the systematic search are shown in Figure 1. The initial search in PubMed and Embase yielded 10,780 records of which we removed 2,337 duplicates. Title and abstract screening of the remaining 8,443 records resulted in the selection of 132 records. After assessment of the full text, eligibility criteria were met in 19 articles. For an overview of the excluded studies based on full-text screening, including reason for exclusion, see Supplementary File S4. No additional relevant studies were found. Eventually, 19 studies were included in the current systematic review.[33–51]

FIGURE 1: FLOWCHART WITH THE RESULTS OF THE SYSTEMATIC SEARCH.



AF: atrial fibrillation.

Study and patient characteristics of all included studies

The 19 included original observational studies, involving 170,394 NOAC users, showed data from October 2010 to December 2017. The majority of the studies were carried out in Asian countries (most notable in Japan (n=8) and Korea (n=4)) and in the USA (n=4) and showed data on rivaroxaban (n=7), apixaban (n=7), dabigatran (n=4), and edoxaban (n=1). Duration of follow-up ranged from a median of 4.0 months to a median of 39.3 months.

The percentage of male sex ranged from 47.4% to 78.0%; the mean age of study populations ranged from 67.2 to 78.7 years. Overall, hypertension was the most common reported comorbidity, ranging from 54.0% to 95.4%. The percentage of patients with a history of (ischaemic) stroke (and TIA and/or thromboembolism) ranged from 5.9% to 49.8%. The percentage of OLRD ranged from 8.9% to 53.0%. A detailed overview of all extracted study and patient characteristics can be found in Supplementary File S5.

Risk of bias assessment

An overview of the risk of bias assessment can be found in Supplementary File S6. In general, all studies scored well on the selection, comparability and outcome category of the NOS, except for demonstrating that the outcome of interest was not present at the start of the study and adequacy of the follow-up of the cohorts. Three out of 19 studies reported on the handling of missing data, all using multiple imputation.

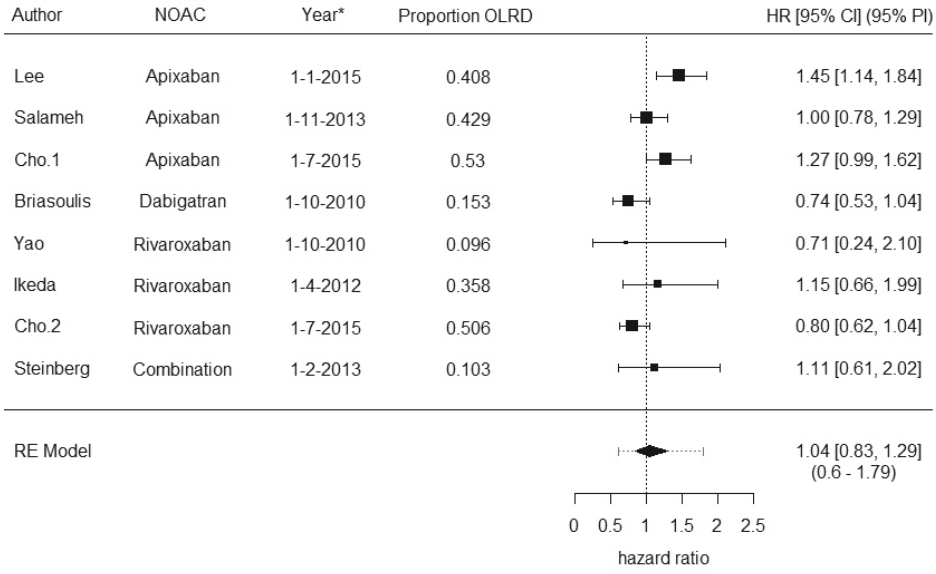
Meta-analysis of clinical outcomes associated with OLRD of NOACs

Seven studies met the predefined criteria for meta-analysis (n=80,725) (see Supplementary File S7).[35,36,38,44,47,48,51] The percentage of OLRD in these studies ranged from 9.6% to 53.0%. The pooled HR associated with OLRD of NOACs in AF patients was 1.04 (95% CI 0.83-1.29; 95% PI 0.60-1.79) for stroke/thromboembolism, 1.10 (95% CI 0.95-1.29; 95% PI 0.81-1.50) for bleeding, and 1.22 (95% CI 0.81-1.84; 95% PI 0.55-2.70) for all-cause mortality (see Figure 2). Of studies meeting our criteria for meta-analysis no study reported on all-cause hospitalisation, and only two studies reported on MACE, (HR of 1.2 (95% CI 1.05-1.37) and HR of 1.4 (95% CI 0.94-2.1)).[44,48]

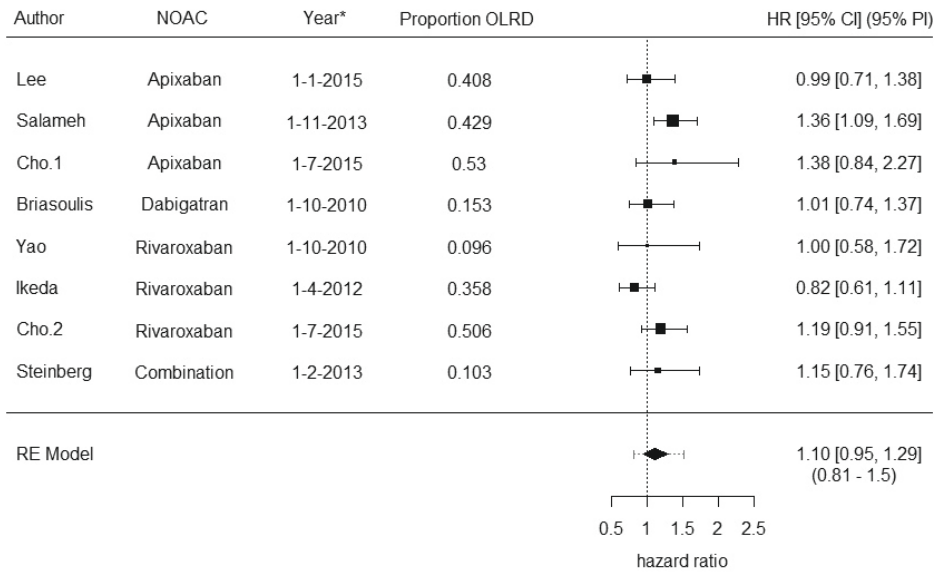
When also including studies that used multivariate regression to adjust for confounding, we could meta-analyse one additional study that did not change our results (data not shown).[33]

FIGURE 2: META-ANALYSES IN ATRIAL FIBRILLATION PATIENTS WITH OFF-LABEL REDUCED DOSING OF A NOAC VERSUS ON-LABEL NON-REDUCED DOSING OF A NOAC.

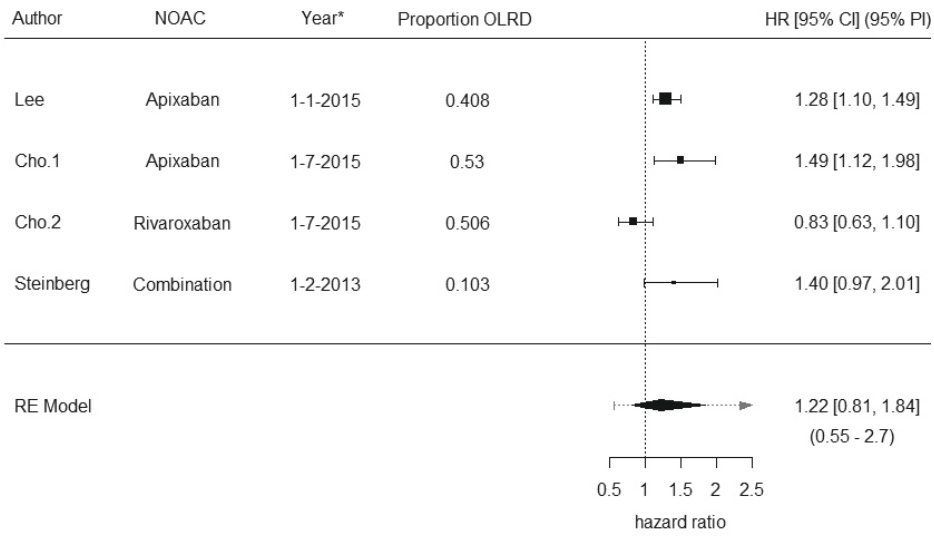
A. With outcome (ischaemic) stroke (and TIA and/or thromboembolism)



B. With outcome bleeding



C. With outcome mortality



** Year: starting date of inclusion of patients.*

NOAC: non-vitamin K antagonist oral anticoagulant; OLRD: off-label reduced dosing; PI: prediction interval; TIA: transient ischaemic attack.

DISCUSSION

In this systematic review and meta-analysis of observational studies, we found no statistically significant increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD compared with OLNRD of NOACs.

The effect of OLRD of NOACs

Although all point estimates in our meta-analysis lie above 1, indicating a possible harmful effect, it cannot be concluded from our meta-analysis that OLRD of NOACs overall is in fact harmful, not to mention beneficial. However, it should be realised that NOACs differ. First, plasma levels may be more stable for some NOACs than for others due to once daily (rivaroxaban and edoxaban) versus two times daily (dabigatran and apixaban) dosing. Second, NOACs vary in the percentage by which the dose should be reduced (25%–33% for dabigatran and rivaroxaban; 50% for apixaban and edoxaban). Finally, some NOACs have more extensive dose reduction criteria than others, which might suggest that OLNRD of NOACs with more extensive dose reduction criteria is more tailored to the individual patient and that OLRD of these NOACs might cause more harm. This may explain why data in our study suggest a harmful effect of OLRD specifically for apixaban (of the apixaban studies, almost all HRs for stroke/

thromboembolism, bleeding, and all-cause mortality are above 1). However, we cannot confirm this, because there were not sufficient studies meeting our inclusion criteria for meta-analysis stratified by the four different NOACs.

Comparison with existing literature

In a recent meta-analysis, Caso et al. compared OLRD to on-label dosing (i.e. both on-label reduced and on-label non-reduced dosing). This showed that OLRD increased the risk of all-cause mortality (HR 1.28 (95% CI 1.10-1.49)) with a null effect on major bleeding (HR 1.04 (95% CI 0.90-1.19)).[18]

In another previous meta-analysis, the authors also compared OLRD to, again, on-label dosing and used less stringent inclusion criteria, which allowed them to include more studies and examine each NOAC separately. This showed that OLRD of rivaroxaban may increase the risk of stroke/thromboembolism (HR 1.31 (95% CI 1.05-1.63)) compared with on-label dosing of rivaroxaban, whereas OLRD of apixaban may increase the incidence of all-cause mortality (HR 1.21 (95% CI 1.05-1.40)) compared with on-label dosing of apixaban. They reported no differences in outcomes when comparing OLRD versus on-label dosing of dabigatran and edoxaban.[16]

A third meta-analysis combined the four NOACs in their analyses and showed higher risk of stroke/systemic embolism (risk ratio (RR) 1.24 (95% CI 1.14-1.35)) without a reduction in bleeding risk (RR 1.18 (95% CI 0.91-1.53)) and a higher risk of all-cause mortality (RR 1.58 (95% CI 1.25-1.99)) in patients with OLRD compared with on-label dosing. However, this meta-analysis largely lacked measures to prevent confounding. Moreover, it also compared OLRD to on-label dosing (i.e. both on-label reduced and on-label non-reduced) instead of comparing OLRD to OLNRD as we did.[17]

In contrast to these previous studies, we did not find an increased risk for all-cause mortality in patients with OLDR. The most obvious explanation could be the comparison we choose. Unlike previous meta-analyses, we restricted our included studies to those comparing OLRD to OLNRD. This is the most clinically relevant comparison, as it represents the patient groups in whom clinicians face a dosing dilemma most often (i.e. those without an indication for dose reduction).

Strengths and limitations

The selection of studies comparing OLDR only with OLNRD is the major strength of our study. Second, we tried to minimise the influence of confounding by indication as best as possible by including only studies meeting predefined criteria, including applying of propensity scoring methods. Finally, we conducted a very comprehensive and thorough systematic search which resulted in a large sample size.

Limitations of our study are: 1) the inclusion of a predominantly Asian population who has shown to have different pharmacokinetics, meaning that our results cannot be generalised on a one-to-one basis to, for example, the Western population, 2) the fact that we could not include enough studies to stratify by NOAC in the meta-analysis, 3) risks of misclassification within studies (e.g. when a NOAC dose has been changed by a cardiologist but is not yet recorded in the general practitioner's file, while the latter has been requested by the study) and significant heterogeneity between studies (e.g. in the duration of follow-up (with a median ranging from 4 to 24 months in our meta-analyses)) which is both inherent to using data from observational studies, and 4) conducting our research at study level rather than at patient level (as we did not have data on individual patient level).

Clinical implications and areas for future research

Choosing a NOAC dose is all about balancing stroke risk against bleeding risk. Our results indicate that the risk of stroke may not be increased while the risk of bleeding may not be decreased in patients that are prescribed OLRD of NOACs compared with patients with OLNRD of NOACs. This may be considered as an argument to adhere to prescription guidelines in most, if not all, patients. However, our results may also indicate that OLRD of NOACs may not be harmful in specific cases. Physicians, in close discussion with their patients, may use our findings to decide on the treatment regimen in the specific situation of each patient. Future research may focus on these situations and, perhaps more importantly, on differences between NOACs.

In conclusion, this systematic review and meta-analysis shows that there is no statistically increased risk of stroke/thromboembolism, nor a decreased bleeding risk, nor a difference in risk of all-cause mortality in patients with OLRD of NOACs compared with patients with OLNRD of NOACs. Future research may focus on differences between NOACs.

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POTENTIAL CONFLICTS OF INTEREST

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CONTRIBUTORS

LJ, RvM, CvdD, GJG and SvD conceived and initiated the study. LJ, RvM, CvdD and SvD screened and selected the articles for inclusion. LJ, RvM and SvD performed the data extraction and risk of bias assessment. LJ, RvM and SvD prepared the dataset. SvD performed the statistical analyses. All authors interpreted the results. LJ, RvM and SvD wrote the first version of the manuscript. All authors critically reviewed and revised the manuscript.

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SUPPLEMENTARY FILES

S1: SEARCH SYNTAX.

Search from 1 January 2009 until 10 July 2022, PubMed:
(dose*[Title/Abstract] OR dosa*[Title/Abstract] OR dosi*[Title/Abstract]) AND

(low[Title/Abstract] OR lower*[Title/Abstract] OR adjust*[Title/Abstract] OR adapt*[Title/Abstract] OR alter*[Title/Abstract] OR modif*[Title/Abstract] OR regulat*[Title/Abstract] OR tailor*[Title/Abstract] OR reduc*[Title/Abstract] OR underdos*[Title/Abstract] OR *recommend*[Title/Abstract] OR inappropria*[Title/Abstract] OR appropria*[Title/Abstract] OR incorrect*[Title/Abstract] OR correct*[Title/Abstract] OR incongrue*[Title/Abstract] OR congrue*[Title/Abstract] OR discord*[Title/Abstract] OR concord*[Title/Abstract] OR offlabel[Title/Abstract] OR off-label[Title/Abstract] OR (off[Title/Abstract] AND label[Title/Abstract]) OR "Off-Label Use"[Mesh]) AND

(dabigatran[Title/Abstract] OR "dabigatran"[Mesh] OR pradaxa[Title/Abstract] OR rivaroxaban[Title/Abstract] OR "rivaroxaban"[Mesh] OR xarelto[Title/Abstract] OR apixaban[Title/Abstract] OR eliquis[Title/Abstract] OR edoxaban[Title/Abstract] OR lixiana[Title/Abstract] OR NOAC*[Title/Abstract] OR DOAC*[Title/Abstract] OR ((anticoagul*[Title/Abstract] OR anti-coagul*[Title/Abstract] OR "Anticoagulants"[Mesh]) AND (novel[Title/Abstract] OR new[Title/Abstract] OR direct[Title/Abstract])) OR (non[Title/Abstract] AND ((*vitamin*[Title/Abstract] AND *antagonist*[Title/Abstract]) OR VKA[Title/Abstract])))

Search from 1 January 2009 until 10 July 2022, EMBASE:
(dose*:ti,ab OR dosa*:ti,ab OR dosi*:ti,ab) AND

(low:ti,ab OR lower*:ti,ab OR adjust*:ti,ab OR adapt*:ti,ab OR alter*:ti,ab OR modif*:ti,ab OR regulat*:ti,ab OR tailor*:ti,ab OR reduc*:ti,ab OR underdos*:ti,ab OR recommend*:ti,ab OR non-recommend*ti,ab OR nonrecommend*ti:ab OR inappropria*:ti,ab OR appropria*:ti,ab OR incorrect*:ti,ab OR correct*:ti,ab OR incongrue*:ti,ab OR congrue*:ti,ab OR discord*:ti,ab OR concord*:ti,ab OR offlabel:ti,ab OR 'off-label':ti,ab OR 'off label':ti,ab OR 'off label drug use'/exp) AND

(dabigatran:ti,ab OR 'dabigatran'/exp OR 'dabigatran etexilate'/exp OR pradaxa:ti,ab OR rivaroxaban:ti,ab OR 'rivaroxaban'/exp OR xarelto:ti,ab OR apixaban:ti,ab OR 'apixaban'/exp OR eliquis:ti,ab OR edoxaban:ti,ab OR 'edoxaban'/exp OR lixiana:ti,ab OR noac*:ti,ab OR DOAC*:ti,ab OR

((anticoagul*:ti,ab OR 'anti-coagul*':ti,ab OR 'anticoagulant agent'/exp) AND (novel:ti,ab OR new:ti,ab OR direct:ti,ab) OR (non*:ti,ab AND ((vitamin*:ti,ab AND antagonist*:ti,ab) OR (VKA*:ti,ab))))) AND

'article'/it AND [embase]/lim AND [1-1-2009]/sd NOT [10-07-2022]/sd

S2: RISK OF BIAS ASSESSMENT ITEMS BASED ON THE NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES (NOS).

Selection

1. Representativeness of the exposed cohort
   A. truly representative of the average AF patient without a mechanical heart valve and/or severe mitral valve stenosis who is treated with a NOAC for stroke prevention in the community *
   B. Bsomewhat representative of the average AF patient without a mechanical heart valve and/or severe mitral valve stenosis who is treated with a NOAC for stroke prevention in the community *
   C. selected group of users e.g. nurses, volunteers
   D. no description of the derivation of the cohort
2. Selection of the non-exposed cohort
   A. drawn from the same community as the exposed cohort *
   B. drawn form a different source
   C. no description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
   A. secure record (e.g. surgical records) *
   B. structured interview *
   C. written self-report
   D. no description
4. Demonstration that outcome of interest was not present at start of study
   A. yes *
   B. no

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   A. study controls for sex and age *
   B. study controls for any additional factor *

Outcome

1. Assessment of outcome
   A. independent blind assessment *
   B. record linkage *
   C. self-report
   D. no description
2. Was follow-up long enough for outcomes to occur
   A. yes (i.e. >90 days) *
   B. no
   C. no follow-up period was reported
3. Adequacy of follow-up of cohorts
   A. complete follow-up – all subjects accounted for *
   B. subjects lost to follow-up unlikely to introduce bias – small number lost - >90% follow-up, or description provided of those lost *
   C. follow-up rate <90% and no description of those lost
   D. no statement

Missing data

1. Handling missing data
   A. multiple imputation *
   B. no multiple imputation
   C. not reported

*A study can be awarded a maximum of one star (i.e. *) for each numbered item within the Selection, Outcome and Missing data categories. A maximum of two stars can be given for Comparability.*

S3: EXTRACTED STUDY AND PATIENT CHARACTERISTICS.

Study characteristics	Data source (i.e. electronic health record, prospective registry)
	Country
	Setting (i.e. general care, specialist care, both)
	Time frame (i.e. inclusion period)
	NOAC (i.e. dabigatran, rivaroxaban, apixaban, edoxaban)
	Guideline used to determine whether a non-reduced or a reduced NOAC dose was indicated (i.e. SPC, FDA, ESC, EHRA, landmark NOAC trials, other guideline, not reported)
	Number of included patients with AF who use a NOAC
	Duration of follow-up in months
Patient characteristics	Male sex in percentage
	Age in years in mean (or median)
	Weight in kilograms in mean (or median)
	Body mass index in mean (or median)
	eGFR (or CrCl) in mean (or median)
	Patients with an eGFR <50 in percentage
	Patients with hypertension in percentage
	Patients with a history of (ischemic) stroke (and TIA and/or thromboembolism) in percentage (including definition)
	Patients with a history of hemorrhagic stroke in percentage
	Patients with (a history of) coronary heart disease in percentage (including definition)
	Patients with (a history of) (peripheral) vascular disease in percentage
	Patients with heart failure in percentage
	Patients with (a history of) other cardiovascular disease in percentage (including definition)
	Patients with diabetes mellitus in percentage
	Patients with chronic kidney disease in percentage (including definition)
	Patients using concomitant drugs that interact with NOACs in percentage (including the type of drug)

AF: atrial fibrillation; CrCl: creatinine clearance; eGFR: estimated Glomerular Filtration Rate; EHRA: European Heart Rhythm Association; ESC: European Society of Cardiology; FDA: Food and Drugs Administration; NOAC: non-vitamin K antagonist oral anticoagulant; SPC: Summary of Product Characteristics; VKA: vitamin K antagonist.

S4: OVERVIEW OF THE EXCLUDED STUDIES BASED ON FULL-TEXT SCREENING, INCLUDING REASON FOR EXCLUSION.

Author	Year	Reference	Reason for exclusion
Lafon	2018	[1]	No full-text available
Aguilar	2021	[2]	Highly selected group of patients or data on patients with non-valvular atrial fibrillation cannot be extracted
Alcusky	2018	[3]	
Alghadeer	2017	[4]	
Alnsasra	2018	[5]	
Altay	2017	[6]	
Asahina	2020	[7]	
Chaudhry	2021	[8]	
de Almeida	2020	[9]	
Eschler	2021	[10]	
Frol	2020	[11]	
George	2019	[12]	
Gurevitz	2021	[13]	
Haque	2021	[14]	
Inohara	2020	[15]	
Jackevicius	2021	[16]	
Khan	2016	[17]	
Kim	2019	[18]	
Kwon	2016	[19]	
Lafon	2017	[20]	
Mitrovic	2017	[21]	
Nahornyj	2020	[22]	
Paciaroni	2019	[23]	
Rutherford	2021	[24]	
Shinoda	2018	[25]	
Shinohara	2019	[26]	
Shinohara	2019	[27]	
Szeto	2021	[28]	
Ting	2020	[29]	
Tran	2017	[30]	
Whitworth	2017	[31]	
Akagi	2019	[32]	Study does not report off-label reduced dosing compared to on-label non-reduced dosing.
Akao	2014	[33]	
Amarenco	2018	[34]	
Anouassi	2021	[35]	
Armbruster	2014	[36]	
Ashraf	2021	[37]	
Blin	2019	[38]	
Bouget	2020	[39]	
Camm	2020	[40]	

Chan	2020	[41]	
Chen	2021	[42]	
Cheng	2019	[43]	
Cho	2019	[44]	
De Caterina	2021	[45]	
Ebrahimi	2017	[46]	
Feng	2021	[47]	
Fernandez	2021	[48]	
Forslund	2018	[49]	
Gabitova	2019	[50]	
Godino	2020	[51]	
Hecker	2016	[52]	
Helmert	2017	[53]	
Hussain	2012	[54]	
Inoue	2019	[55]	
Isaacs	2013	[56]	
Isaacs	2016	[57]	
Jang	2019	[58]	
Jansson	2019	[59]	
Kohsaka	2020	[60]	
Kotalczyk	2021	[61]	
Larsen	2013	[62]	
Lee	2015	[63]	
Li	2017	[64]	
Marzona	2021	[65]	
Muniz Lobato	2018	[66]	
Navarro-Almenzar	2019	[67]	
Nielsen	2017	[68]	
Ogawa	2014	[69]	
Perreault	2020	[70]	
Qian	2021	[71]	
Raccah	2021	[72]	
Rahme	2021	[73]	
Ruiz-Ortiz	2020	[74]	
Russo	2015	[75]	
Sato	2018	[76]	
Shrestha	2018	[77]	
Staerk	2018	[78]	
Sugrue	2021	[79]	
Wattanaruengchai	2020	[80]	
Yu	2020	[81]	

Bando	2018	[82]	Study does not report association between off-label reduced dosing and outcome(s).
Bang	2020	[83]	
Barra	2016	[84]	
Bastida	2017	[85]	
Brook	2020	[86]	
Chao	2021	[87]	
Eschler	2020	[88]	
Gustafson	2019	[89]	
Ionin	2021	[90]	
Kartas	2019	[91]	
Kilickiran Avci	2016	[92]	
Kimmons	2014	[93]	
Larock	2014	[94]	
Lee	2020	[95]	
Lodzinksi	2020	[96]	
Masunaga	2018	[97]	
Miyazaki	2022	[98]	
Pisters	2017	[99]	
Sato	2018	[100]	
Sato	2020	[101]	
Suwa	2019	[102]	
Tedders	2013	[103]	
Tellor	2015	[104]	
Tran	2014	[105]	
Umei	2017	[106]	
Vinding	2019	[107]	
Xing	2019	[108]	
Yiginer	2017	[109]	
Zeymer	2020	[110]	
Abe	2021	[111]	Other
Steinberg	2016	[112]	
Ueda	2020	[113]	

In case there were several reasons to exclude a study, the reason mentioned first in the table above is reported.

S5: DETAILED OVERVIEW OF ALL EXTRACTED STUDY AND PATIENT CHARACTERISTICS.

Author*		Year	Data source	Country	Setting (i.e. general care, specialist care, both)	First date of inclusion	Last date of inclusion	NOAC
Arbel [114]	Study characteristics	2019	EHR	Israel	Both	01-01-2011	31-12-2017	D/R/A
Atarashi [115]		2021	PR	Japan	Both	01-11-2012	30-06-2016	R
Briasoulis – D/R [116]		2020	EHR	USA	Both	01-10-2010	31-12-2016	D/R
Briasoulis – D [116]		2020	EHR	USA	Both	01-10-2010	31-12-2016	D
Briasoulis – R [116]		2020	EHR	USA	Both	01-10-2010	31-12-2016	R
Cho – R/A [117]		2020	EHR	Kora	SC	01-07-2015	31-12-2016	R/A
Cho – R [117]		2020	EHR	Korea	SC	01-07-2015	31-12-2016	R
Cho – A [117]		2020	EHR	Korea	SC	01-07-2015	31-12-2016	A
de Groot [118]		2020	PR	Multinational [1]	Both	01-08-2015	n.r.	E
Ikeda [119]		2019	PR	Japan	Both	01-04-2012	30-06-2014	R
Inoue – 2019 [120]		2019	PR	Japan	Both	12-12-2011	30-11-2013	D
Inoue – 2020 [121]		2020	PR	Japan	Both	01-09-2013	31-08-2014	A
Kobayashi [122]		2020	PR	Japan	SC	01-06-2011	30-11-2017	D/R/A/E
Lee – 2017 [123]		2017	EHR	Korea	SC	01-01-2012	31-12-2013	D
Lee – 2019 [124]		2019	EHR	Korea	Both	01-01-2014	31-12-2016	R
Lee – 2021 [125]		2021	EHR	Korea	Both	01-01-2015	31-12-2017	A
Murata [126]		2019	PR	Japan	Both	01-09-2013	31-12-2015	D/R/A/E
Ohno [127]		2020	PR	Japan	Both	01-06-2011	30-11-2017	D/R/A/E
Salameh [128]		2020	EHR	Israel	Both	01-11-2013	31-12-2017	A
Steinberg [129]		2018	PR	USA	Both	01-02-2013	31-07-2016	D/R/A/E
Tellor [130]		2017	EHR	USA	SC	01-01-2013	30-06-2016	A
Yagi [131]		2019	PR	Japan	SC	01-05-2012	31-07-2017	R
Yao – D [132]		2017	EHR	USA	Both	01-10-2010	30-09-2015	D
Yao – R [132]		2017	EHR	USA	Both	01-10-2010	30-09-2015	R
Yao – A [132]		2017	EHR	USA	Both	01-10-2010	30-09-2015	A

Guideline used	NOAC users (n)	Duration of follow-up (months)		Male sex (%)	Age in years (mean)	Weight in kg (mean)	Body mass index (mean)
SPC	8,425	23		48.0	75.5	n.r.	30.2
J-ROCKET-AF	6,806	n.r.		67.7	71.6	62.7	n.r.
D: FDA; R: other [2]	27,747	12.5		50.3	n.r.	n.r.	n.r.
FDA	8,035	14.8		50.6	n.r.	n.r.	n.r.
Other [2]	19,712	11.6		50.2	n.r.	n.r.	n.r.
R: ROCKET-AF; A: ARISTOTLE	16,568	15.0 ‡		54.4	70.3	n.r.	25.3
ROCKET-AF	9,639	15.0 ‡		59.4	69.8	n.r.	25.5
ARISTOTLE	6,929	15.0 ‡		47.4	71.0	n.r.	25.0
SPC	13,092	11.6 ‡		56.8	73.6	81.0	28.1
J-ROCKET-AF	6,521 [10]	±12		68.3	70.4	64.9	24.7
Other [3]	6,443	15.1 ‡		66.9	70.9	62.7	24.0
ARISTOTLE	6,294	17.4		58.9	74.5	59.5	n.r.
ARISTOTLE + other [4]	1,245	13.4		73.6	67.2	65.8	n.r.
Other [5]	844	±12		62.2	74.0	n.r.	n.r.
ROCKET-AF	13,594	16.8 ‡		57.4	69.8 ‡	64.9	24.8
ESC	8,512	24 ‡		56	72.6	63.6	24.6
ARISTOTLE + other [6]	1,658	39.3 ‡		71.5	71.7	63.8	24.1
ARISTOTLE + SPC + other [7]	2,195	13.4		63.6	71.6	60.9	23.7
SPC	27,765	15.3		48.3	78.7	78.1	n.r.
FDA	7,925	12.0 ‡		58.7	71 ‡	n.r.	n.r.
FDA	707	16.3		48.7	75.1	86.9	n.r.
J-ROCKET-AF	661	10.8 ‡	Patient characteristics	78	69.1	67.1	n.r.
Other [8]	4,653	4.0 ‡		61.7	68.3	n.r.	n.r.
FDA	5,399	4.0 ‡		59.9	69.6	n.r.	n.r.
Other [9]	3,340	4.0 ‡		50.6	72.4	n.r.	n.r.

eGFR (mean)	eGFR <50 (%)	Hyper-tension (%)	History of (ischemic) stroke (and TIA and/or thromboembolism) (%) – definition	History of haemor-rhagic stroke (%)	(History of) coronary heart disease (%) – definition	(History of) (peripheral) vascular disease (%)	Heart failure (%)
71.5	n.r.	95.4	31.4 – [12]	n.r.	n.r. – n.a.	16.6	26.9
n.r.	n.r.	71.2	20.2 – [13]	1.9	4.2 – MI	n.r.	26.5
n.r.	48.8 [11]	93.2	24.5 – [12]	0.9	6.5 –MI	n.r.	29.9
n.r.	53.0 [11]	93.9	24.8 – [12]	0.7	5.7 – MI	n.r.	34.4
n.r.	47.0 [11]	92.9	24.3 – [12]	1.0	6.8 – MI	n.r.	28.0
69.6 ◦	n.r.	87.6	19.9 – [14]	1.1	n.r. – n.a.	11.4	19.1
72.7 ◦	n.r.	88.4	18.6 – [14]	0.9	n.r. – n.a.	11.0	18.7
65.4 ◦	n.r.	86.4	21.8 – [14]	1.5	n.r. – n.a.	11.8	19.6
74.3 ◦	n.r.	77.1	5.9 – [13]	0.5	4.3 – MI	3.3 [18]	5.9
77.7 ◦	0	74.5	20.5 – [15]	n.r.	n.r. – n.a.	n.r.	21.0
72.9 ◦	18	66.7	20.2 – [12]	n.r.	n.r. – n.a.	n.r.	18.2
62.2 ◦	31.4	61.2	17.5 – [15]	n.r.	n.r. – n.a.	n.r.	30.4
80.3 ◦	n.r.	71.2	16.9 – [12]	n.r.	18.5 – CAD	n.r.	17.4
66.1 ◦‡	n.r.	65.2	49.8 – [16]	n.r.	5.8 – MI	n.r.	9.1
82.5 ◦	n.r.	72.2	n.r. – n.a.	n.r.	2.8 – MI	17.7 [18]	30.4
77.1	7.6	85.5	29.2 – [12]	n.r.	6.1 – MI	26.8 [18]	46.1
70.5 ◦	n.r.	69.4	10.1 – [16]	n.r.	n.r. – n.a.	11.7	19.1
65.4	n.r.	73.3	20.3 – [12]	n.r.	19.9 – CAD	7.2	32.5
63.8	n.r.	90.1	24.9 – [12]	n.r.	31.9 – MI	12.5	32.6
81.7 ◦‡	n.r.	n.r.	11.1 – [16]	n.r.	n.r. – n.a.	n.r.	n.r.
42 ◦	n.r.	n.r.	n.r. – n.a.	n.r.	n.r. – n.a.	n.r.	n.r.
64.1	15.7	54	6.0 – [15]	n.r.	n.r. – n.a.	n.r.	17.0
71.6	13.6	88.7	14.0 – [17]	1.0	n.r. – n.a.	25.2	27.9
76.4	0	88.1	13.1 – [17]	0.8	n.r. – n.a.	26.7	26.5
71.1	12.6	90.8	14.7 – [17]	1.6	n.r. – n.a.	29.1	31.8

(History of) other cardio-vascular disease (%) – definition	Diabetes mellitus (%)	Chronic kidney disease (%) – definition	Conco-mitant PI (%)	Conco-mitant NSAID (%)	Conco-mitant P-gp inhibi-tor (%)	Other concomitant drug that interacts with NOACs (%) – type of drug
n.r.	59.8	18.0 – [21]	42.3	43.3	n.r.	n.r. – n.a.
n.r.	24.7	n.r. – n.a.	9.4	n.r.	n.r.	n.r. – n.a.
n.r.	48.9	24.9 – [22]	26.6	51.0	19.6	18.2 – warfarin
n.r.	49.2	23.3 – [22]	27.5	50.9	22.5	24.4 – warfarin
n.r.	48.8	25.6 – [22]	26.2	51.0	18.4	15.7 – warfarin
n.r.	46.6	2.7 – [23]	9.1 [29]	n.r.	n.r.	4.9 – ADP-2 inhibitor
n.r.	47.0	1.8 – [23]	8.9 [29]	n.r.	n.r.	4.5 – ADP-2 inhibitor
n.r.	46.1	3.9 – [23]	9.5 [29]	n.r.	n.r.	5.6 – ADP-2 inhibitor
n.r.	22.0	n.r. – n.a.	n.r.	n.r.	n.r.	n.r. – n.a.
3.2 – [19]	23.3	0 – [24]	13.7	n.r.	n.r.	n.r. – n.a.
n.r.	20.4	n.r. – n.a.	13.8	n.r.	3.3	n.r. – n.a.
n.r.	55	41.5 – [25]	18.8	n.r.	n.r.	n.r. – n.a.
n.r.	28.4	n.r. – n.a.	21.9 [30]	n.r.	n.r.	n.r. – n.a.
n.r.	22.2	n.r. – n.a.	n.r.	n.r.	n.r.	n.r. – n.a.
n.r.	22.4	n.r. – n.a.	n.r.	n.r.	n.r.	n.r. – n.a.
n.r.	27.8	n.r. – n.a.	34.3	n.r.	n.r.	n.r. – n.a.
n.r.	21.6	n.r. – n.a.	12.7	2.0	n.r.	n.r. – n.a.
n.r.	26.1	39.2 – [26]	21.5	n.r.	n.r.	n.r. – n.a.
n.r.	46.4	2.8 – [27]	48.9	n.r.	n.r.	n.r. – n.a.
n.r.	n.r.	n.r. – n.a.	25.7 [30]	n.r.	n.r.	n.r. – n.a.
n.r.	n.r.	5- [28]	53.3	n.r.	n.r.	n.r. – n.a.
5.0 – [20]	16	n.r. – n.a.	11.0	n.r.	n.r.	n.r. – n.a.
n.r.	41.8	n.r. – n.a.	6.4	4.8	n.r.	n.r. – n.a.
n.r.	39.3	n.r. – n.a.	7.4	4.8	n.r.	n.r. – n.a.
n.r.	39.7	n.r. – n.a.	7.5	5.0	n.r.	n.r. – n.a.

	Off-label reduced dose (n)	On-label non-reduced dose (n)	OLRD of patients with an indication for an on-label non-reduced NOAC dose (%)
Off-label reduced and on-label non-reduced NOAC dose	3,285	5,140	39.0
	1,609	3,717	30.2
	3,564	14,962	19.2
	1,013	5,621	15.3
	2,551	9,341	21.5
	8,549	8,019	51.6
	4,879	4,760	50.6
	3,670	3,259	53.0
	1,114	8,872	11.2
	2,336	4,185	35.8
	1,181	1,196	49.7
	941	3,241	22.5
	338	907	27.1
	183	294	38.4
	5,796	7,798	42.6
	2,890	4,194	40.8
	369	746	33.1
	338	907	27.1
	9,885	13,141	42.9
	734	6,376	10.3
	98	477	17.0
	123	409	23.1
	412	4,241	8.9
	518	4,881	9.6
	550	2,790	16.5

** In case articles concern the same author, a note is added after the author to indicate what makes the articles distinct. Substudies are indented and greyed out. Studies included in the meta-analysis are underlined and presented against a white background; ǂ median instead of mean; ◦ CrCl instead of eGFR.*

[1] Austria, Belgium, Germany, Ireland, Italy, Portugal, Spain, Switzerland, The Netherlands, United Kingdom; [2] FDA or concomitant use of a dual P-gp-Cyp3A4 inhibitor (including ketoconazole, fluconazole, itraconazole, cobicistat, conivaptan, indinavir, voriconazole, posaconazole, nefzadone HCL, ritonavir, saquinavir, telithromycin); [3] age ≥70 years, CrCl of 30-50 mL/min, prior GI-bleeding, or concomitant use of oral P-gp inhibitors; [4] D: elderly >70 years, CrCl 30-50 mL/min, concomitant use of P-gp inhibitors, history of GI-bleeding, R: CrCl 15-49 mL/min, A: ARISTOTLE, E: body weight ≤60 kg, CrCl 15-50 mL/min, concomitant use of P-gp inhibitors; [5] old age (≥75 years old), renal dysfunction (glomerular filtration rate <50 mL/min), or low body weight (<50 kg); [6] D: 110 mg b.i.d.: CrCl 30-50 mL/min, age ≥70 years and a prior history of bleeding, R: 10 mg o.d.: CrCl 15-50 mL/min, A: 2.5 mg b.i.d.: ARISTOTLE, E: 30 mg o.d.: CrCl 15-50 mL/min or body weight <60 kg; [7] D: age ≥70 years, CrCl 30-50 mL/min, concomitant P-gp inhibitors, or history of GI-bleeding, R: SPC, A: ARISTOTLE, E: SPC; [8] eGFR<30 mL/min/1.73 m2; [9] serum creatinine level ≥1.5 mg/dL; [10] only patients with CrCl ≥50 mL/min; [11] eGFR <60 instead of eGFR <50; [12] stroke; [13] ischemic stroke; [14] stroke, TIA or thromboembolism; [15] ischemic stroke or TIA; [16] stroke or TIA; [17] thromboembolism (arterial); [18] peripheral artery disease; [19] MI and/or peripheral artery disease and/or aortic plaque; [20] MI or arteriosclerosis obliterans; [21] chronic renal failure; [22] renal disease (ICD-9 and ICD-10 codes): moderate (stage III) or severe (stage IV, V); [23] chronic kidney disease (i.e. presence of ICD-10 codes for chronic kidney disease); [24] CrCl <50 mL/min; [25] renal disorder; [26] insufficient kidney function; [27] chronic dialysis, renal transplantation or serum creatinine >200 mmol/L; [28] haemodialysis; [29] i.e. aspirin; [30] i.e. aspirin, cilostazol, clopidogrel, ticlopidine.

A: apixaban; ADP: adenosine diphosphate; AF: atrial fibrillation; b.i.d.: bis in die (i.e. twice a day); CAD: coronary artery disease; CrCl: creatinine clearance; D: dabigatran; E: edoxaban; eGFR: estimated glomerular filtration rate; EHR: electronic health record; ESC: European Society of Cardiology; FDA: Food and Drugs Administration; GI: gastrointestinal; ICD: International Classification of Diseases and Related Health Problems; kg: kilogram; MI: myocardial infarction; n.a.: not applicable; NOAC: non-vitamin K antagonist oral anticoagulant; n.r.: not reported; NSAID: non-steroidal anti-inflammatory drug; o.d.: omnie die (i.e. once a day); OLRD: off-label reduced dosing; P-gp: P-glycoprotein; PI: platelet inhibitor; PR: prospective registry; R: rivaroxaban; SC: specialist care; SPC: Summary of Product Characteristic; TIA: transient ischemic attack; USA: United States of America; VKA: vitamin K antagonist.

S6: RESULTS OF RISK OF BIAS ASSESSMENT.

			Selection				Comparability	Outcome			Missing data
Author	Year	Reference	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Handling missing data
Arbel	2019	[114]	*	*	*		**	*	*		
Atarashi	2021	[115]	*	*	*		**	*	*		
Briasoulis	2020	[116]	*		*		**	*	*		
Cho	2020	[117]	*		*		**	*	*		
de Groot	2020	[118]	*	*	*			*	*		
Ikeda	2019	[119]	*	*	*		**	*	*		
Inoue	2019	[120]	*	*	*		*	*	*	*	
Inoue	2020	[121]	*	*	*		*	*	*		
Kobayashi	2020	[122]	*	*	*		**	*	*		*
Lee	2017	[123]	*	*	*		**	*	*		
Lee	2019	[124]		*	*	*	**	*	*		
Lee	2021	[125]	*	*	*		**	*	*		
Murata	2019	[126]	*	*	*		**	*	*	*	
Ohno	2020	[127]	*	*	*		**	*	*		*
Salameh	2020	[128]	*	*	*		**	*	*		
Steinberg	2018	[129]	*	*	*		**	*	*	*	*
Tellor	2017	[130]	*		*			*	*		
Yagi	2019	[131]	*	*	*			*	*		
Yao	2017	[132]	*	*	*		**	*	*		

S7: RESULTS OF DEFINING THE MOST HOMOGENEOUS AND BEST QUALITY STUDIES FOR META-ANALYSES.

Author	Year	Reference	Low risk of bias in the representativeness of the exposed and non-exposed cohort (i.e. both awarded with a star according to the NOS)	Uses appropriate guidelines (i.e. SPC, FDA, ESC, EHRA, landmark NOAC trial(s))	Uses a form of propensity adjustment in the analysis of clinical outcomes associated with OLRD and reports a hazard ratio	Belongs to the most homogeneous and best quality studies
Arbel	2019	[114]	Yes	Yes	No	No
Atarashi	2021	[115]	Yes	Yes	No	No
Briasoulis - D/R	2020	[116]	Yes	No	Yes	No
Briasoulis - D	2020	[116]	Yes	Yes	Yes	Yes
Briasoulis- R	2020	[116]	Yes	No	Yes	No
Cho - R/A	2020	[117]	Yes	Yes	No	No
Cho - R	2020	[117]	Yes	Yes	Yes	Yes
Cho- A	2020	[117]	Yes	Yes	Yes	Yes
de Groot	2020	[118]	Yes	Yes	No	No
Ikeda	2019	[119]	Yes	Yes	Yes	Yes
Inoue	2019	[120]	Yes	No	No	No
Inoue	2020	[121]	Yes	Yes	No	No
Kobayashi	2020	[122]	Yes	No	Yes	No
Lee	2017	[123]	Yes	No	Yes	No
Lee	2019	[124]	No	Yes	Yes	No
Lee	2021	[125]	Yes	Yes	Yes	Yes
Murata	2019	[126]	Yes	No	Yes	No
Ohno	2020	[127]	Yes	No	No	No
Salameh	2020	[128]	Yes	Yes	Yes	Yes
Steinberg	2018	[129]	Yes	Yes	Yes	Yes
Tellor	2017	[130]	Yes	Yes	No	No
Yagi	2019	[131]	Yes	Yes	No	No
Yao - D	2017	[132]	Yes	No	Yes	No
Yao - R	2017	[132]	Yes	Yes	Yes	Yes
Yao - A	2017	[132]	Yes	No	Yes	No

In case articles concern the same author and year, a note is added after the author to indicate what makes the articles distinct.

A: apixaban; D: dabigatran; EHRA: European Heart Rhythm Association; ESC: European Society of Cardiology; FDA: Food and Drugs Administration; NOAC: non-vitamin K antagonist oral anticoagulant; NOS: Newcastle-Ottawa quality assessment Scale for cohort studies; OLRD: off-label reduced dosing; SPC: Summary of Product Characteristic; R: rivaroxaban.

S8: SUPPLEMENTAL REFERENCES.

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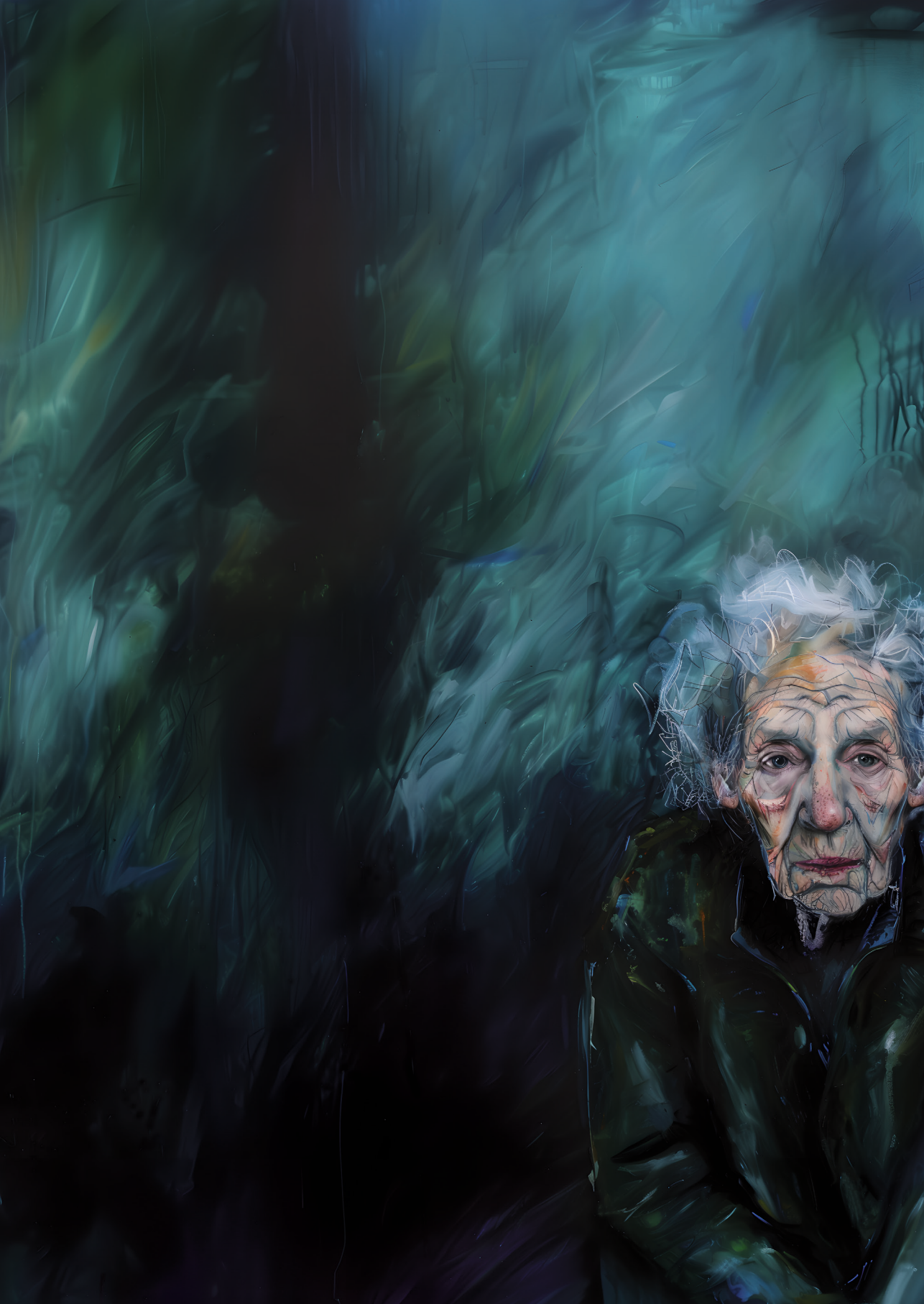


GENERAL DISCUSSION: FROM MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION TO THE 'INVERSE RESEARCH LAW'

9

Linda P.T. Joosten

INTRODUCTION

In this last chapter, the most important findings of this thesis and their practical implications are described and put into perspective by returning to the case of Mrs. de Jong. Furthermore, suggestions for future research on non-vitamin K antagonist oral anticoagulant (NOAC) therapy in the underserved population of frail older patients with atrial fibrillation (AF) are provided.

The FRAIL-AF randomised controlled trial (RCT), which is extensively described in this thesis, is one of the very few RCTs in frail older patients. This clearly highlights the paucity of evidence in frail older patients, while in real life these patients are often the most difficult to manage due to their often mutually reinforcing comorbidities and associated polypharmacy. In other words, we often know the least, scientifically, about patients we encounter the most as health professionals. Therefore, in the second part of this general discussion, the concept of the 'inverse research law' will be introduced; i.e. the availability of evidence and hence research efforts and fundings appear to be inversely related to the clinical problems where research is most needed to provide answers, a phenomenon also illustrated by the unexpected and remarkable findings of the FRAIL-AF RCT, the centrepiece publication of this thesis. Finally, a major message of this thesis (i.e. reverse the 'inverse research law') and some suggestions on how to achieve this are provided.

MOST IMPORTANT FINDINGS OF THIS THESIS AND THEIR PRACTICAL IMPLICATIONS IN RELATION TO THE CASE OF MRS. DE JONG

This thesis is about the management of AF, one of the most common cardiac conditions that has a major impact on healthcare, partly because the lifetime risk of AF is around 30% among people of Western ancestry.[1] AF is mainly affecting older people with a prevalence rising to 17.8% in those aged 85 years and older.[2] Since AF can at least be partly considered as accelerated ageing of the heart and since patients with AF who are not anticoagulated have an increased risk of an ischaemic stroke compared to patients without AF, it can be concluded that AF is much more than solely an arrhythmia.[3] The latest ESC guidelines on AF therefore recommend a holistic approach for the management of AF called 'Atrial Fibrillation Better Care (ABC) pathway' where the A stands for 'anticoagulation/avoid stroke', the B for 'better symptom management', and the C for 'cardiovascular and comorbidity optimisation'.[4] Better symptom management has recently received a lot of attention following the findings of the EAST-AFNET 4 trial. This landmark RCT demonstrated that early rhythm control therapy aimed at restoring sinus rhythm, regardless of symptom severity, reduced the composite outcome of cardiovascular death, stroke, or hospitalisation with worsening of heart failure or acute coronary syndrome, compared to a more lenient strategy in which

symptom-based rhythm control was applied.[5] This thesis focuses on the A and C of the ABC pathway for the management of AF. The most important findings of this thesis and their practical implications are as follows:

- The FRAIL-AF randomised trial showed that switching from a vitamin K antagonist (VKA) to a NOAC compared to continuing with a VKA in frail older patients with AF should not be considered without a clear indication, as switching leads to 69% more major or clinically relevant non-major bleeding.[6,7] Therefore, the decision of the general practitioner (GP) of Mrs. de Jong not to change the oral anticoagulation from a VKA to a NOAC, seems reasonable. As already mentioned, the FRAIL-AF randomised trial is unique as it is the first randomised NOAC trial that exclusively included frail older AF patients. Thereby, this RCT provides important information beyond available evidence; evidence that cannot be obtained from underpowered subgroup analyses of the pivotal NOAC trials that incorporated no or very low numbers of frail older patients, nor from observational data because of the inherent problem of bias due to residual confounding.[8–11] The fact that the results of the FRAIL-AF trial showed an effect that turned out to be completely different from what was expected, underlines the importance of proper research using RCTs in frail older patients prior to uncritically generalising the findings of studies conducted in non-frail populations.

- The prevalence of AF is increasing as a result of ageing of the population and increased awareness, detection and registration.[12] Routine care data from the Julius General Practitioners' Network in The Netherlands showed that the prevalence of AF already more than tripled from 0.4% in 2008 to 1.4% in 2017. In that period frail older patients with new-onset AF, such as Mrs. de Jong, were more likely to be prescribed a VKA instead of a NOAC.[12] Given the important increase in AF prevalence, AF care needs to be reorganised. A holistic approach following the aforementioned ABC pathway and coordinated by GPs seems to be an adequate answer in healthcare settings with a strong primary care system.[4] A good example is the ALL-IN trial where integrated AF care, orchestrated by primary care, compared with care as usual led to a 45% reduction in all-cause mortality.[13]

- Postmarketing observational studies reported that 20-30% of AF patients receive a reduced NOAC dose without a clear medical indication, maybe to minimise an assumed high bleeding risk.[14–19] After a comprehensive systematic review and meta-analysis of AF patients using a NOAC, it can be concluded that this so-called off-label reduced dosing (OLRD) of NOACs compared to on-label non-reduced dosing of NOACs did not reduce bleeding risk with a hazard ratio (HR) of 1.10 (95% confidence interval (CI) 0.95-1.29), nor all-cause mortality with a HR of 1.22 (95% CI 0.81-1.84) and had no clear effect on thromboembolism with a HR of 1.04 (95% CI 0.83-1.29)).[20]

Because this meta-analysis shows no compelling evidence that OLRD can be helpful,[20] physicians should adhere to prescription guidelines that are based on drug dosing studies.

- A recent meta-analysis showed that respiratory tract infections, such as coronavirus disease 2019 (COVID-19), increase the risk of cardiovascular diseases, including AF, about 1.5-5 fold within one month after the infection.[21] Moreover, the development of AF in COVID-19 patients has been associated with increased mortality.[22–24] However, these studies did not assess sex-specific influences, nor the effect of age (on a continuous scale). After conducting a multicentre cohort study of patients hospitalised with COVID-19, mainly during the first COVID-19 wave in spring 2020, it can be concluded that 7.3% of them developed new-onset AF or atrial flutter (AFL) during hospitalisation.[25] In a multivariable model with sex, age, and new-onset AF and/or AFL, new-onset AF and/or AFL in hospitalised COVID-19 patients was associated with a two- to three-fold increased risk of in-hospital mortality in men aged 60-72 years, but not in women (like Mrs. de Jong) or younger men.[25] This is an interesting finding knowing that women with AF and/or AFL generally have a worse prognosis than men with AF and/or AFL.[26] The results of this study were an important building block in creating more knowledge about COVID-19 during the pandemic, and might also be generalised to patients with other viral respiratory tract infections (e.g. influenza) as a recent study shows a similar increase in mortality in hospitalised influenza patients with AF and/or AFL.[27]

UNANSWERED QUESTIONS IN RELATION TO THE FRAIL-AF TRIAL

Like any study, the FRAIL-AF RCT also leads to new, unanswered questions. For example, it may be that the results of the FRAIL-AF trial are disadvantageous to NOACs because the current on-label NOAC dose (also used in the FRAIL-AF trial) was in fact too high for frail older AF patients. Frail older people have different pharmacokinetics and pharmacodynamics. For example, the distribution of medication is different because of an altered body composition (i.e. less muscle tissue and more fatty tissue) and lower elimination capacity of both liver and kidneys. This generally results in a longer availability of medication and thus in higher serum NOAC levels in (frail) older people. For example, a study in older AF patients receiving apixaban showed that apixaban concentrations were higher than expected based on clinical trial data,[28] and another study in frail older patients receiving a NOAC showed that higher levels of frailty were associated with higher apixaban exposure.[29] Therefore, an RCT on the optimal (perhaps lower) dosing of NOACs in frail older AF patients would be recommendable.

Another unanswered question following the results of the FRAIL-AF trial is whether frail older AF patients who are currently prescribed a NOAC or non-frail AF patients who are prescribed a NOAC and become frail later in life should switch to a VKA or not. After all, it is plausible that the switching of medication itself in these frail older patients increases the risk of adverse events (i.e. bleeding in the case of oral anticoagulation), particularly if they were more or less stable under the previous medication (regardless of which way the medication is switched). Perhaps the statement 'never change a winning team' applies in the frail older population in general, because the balance in frail older patients (in this case between coagulation and bleeding) is more fragile. Until an RCT is performed, physicians will have to decide on an individual basis and in shared decision with their patient whether or not to switch from their NOAC to a VKA.

Regarding the results of the FRAIL-AF trial, it is interesting that the rate of major and clinically relevant non-major bleeding complications in the arm that switched to a NOAC continued to increase more over time compared to the arm that continued with a VKA (see Chapter 7, Figure 2).[7] This may indicate that the increased bleeding risk of a NOAC compared to a VKA extends beyond just the switching moment and that frail older patients in general, including those with new-onset AF, are better off with a VKA than with a NOAC. Note that this is a precautionary statement: thorough research is needed in frail older patients with new-onset AF to avoid drawing preliminary and wrong conclusions.

A fourth question is which NOAC has the best profile in terms of effectivity and safety. This question should be answered in a head-to-head comparison of individual NOACs in an RCT. This question becomes more important as age and frailty increase, because the balance between coagulation and bleeding then becomes increasingly fragile and the slightest variation in medication could just make the difference.

THE CASE OF MRS. DE JONG, NINE MONTHS LATER

January 2024 – Mrs. de Jong is 84 years old now. Her 63-year-old neighbour also has atrial fibrillation (AF) and during their weekly coffee appointment, he tells Mrs. de Jong that he received an invitation to join a phase III study for the factor XI inhibitor milvexian, a very promising new type of anticoagulant that might drastically reduce the risk of bleeding, while still providing balanced protection against ischaemic stroke. After hearing this news, Mrs. de Jong is hopeful that a factor XI inhibitor would also help her to get rid of those annoying nose bleeds and bruises on her skin. These got worse after she switched to a non-vitamin K antagonist oral anticoagulant (NOAC) prescribed by her cardiologist six months ago after being hospitalised for heart failure. In fact, these bleeds and bruises sometimes urges her to deliberately stop taking the NOAC tablet for a few days. Right away, she makes an appointment with her general practitioner (GP) to ask if she could

also receive an invitation to participate in this study. Her GP is sceptical because frail older patients like Mrs. de Jong are often excluded from study participation. Nevertheless, the GP visits the website clinicaltrials.gov with details of the study in question and to the GP's positive surprise Mrs. de Jong is eligible to participate. Mrs. de Jong is very pleased and she hopes to be randomised to the intervention arm.

THE 'INVERSE RESEARCH LAW'

The positively surprised reaction of the general practitioner (GP) about a frail old lady not being excluded from research does not emerge out of the blue. So far, almost no randomised controlled trials (RCT) have been conducted in populations with a sufficient number of frail older people, let alone RCTs exclusively focused on this patient group, while in this large and growing population there is a major need for evidence-based and personalised management. Therefore, the management of this population is mainly based on trial and error, generalising evidence from RCTs conducted in younger, non-frail patients or relying on observational data that are affected by confounding that is often difficult and sometimes even impossible to prevent or adjust for. The phenomenon that the availability of evidence is inversely related to the actual need for evidence in society is analogous to the observation that, in clinical practice, people with the greatest needs in healthcare often have the least access to healthcare services. This latter was first put into words by the British GP Julian Tudor Hart in 1971 using the term 'inverse care law'.[30] In this landmark publication he argues that vulnerable people (e.g. frail older people, but also those with a low socioeconomic status) have more health problems and need more medical care, but at the same time face more barriers in obtaining high-quality healthcare. In the areas where they live, there is less access to healthcare and both physicians and nurses have more work with a heavier patient caseload, less staff and equipment, more outdated practice buildings and less hospital support as compared to areas where more vital and younger people with a higher socioeconomic status live. This unequal distribution can further reinforce health and socioeconomic inequalities within society. Thereby, the introduction of the term 'inverse care law' underlines the need to address these health inequalities to ensure that those who need the most care have access to high-quality healthcare. Investing in high-quality healthcare for these vulnerable populations will certainly pay off and is more useful than trying to improve the already good healthcare for the non-vulnerable in society.

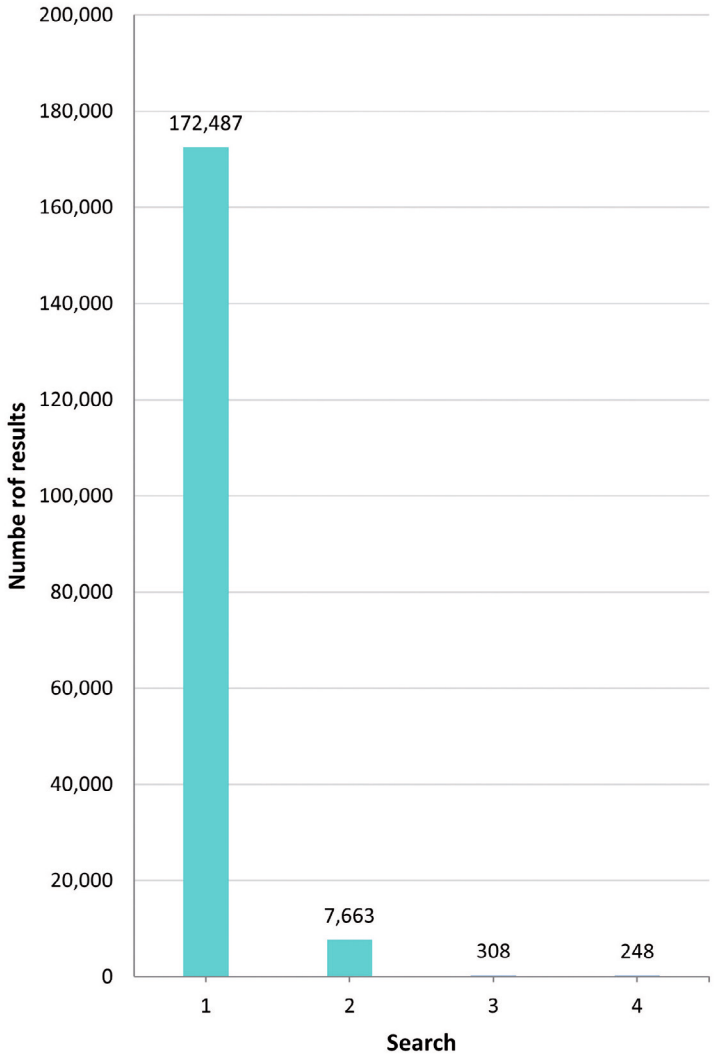
This maldistribution of care is also observed in research where participants in an RCT (one of the highest quality studies according to the evidence-based medicine pyramid) and study populations in similar RCTs are in the vast majority considerably less diverse than society and therefore do not properly reflect day-to-day practice. Therefore, key questions for daily clinical practice and from a societal perspective are regularly not

answered. Historically, study populations consisted mainly of middle-aged Western men with few comorbidities and with a relatively high socioeconomic status. Obviously, homogeneity among study participants has methodological advantages and evidence for these people is also needed, but society is clearly much more diverse than this population group. Moreover, results from these studies cannot and should not be generalised uncritically to population groups that were not included, as has become clear from the results of the FRAIL-AF trial described earlier.[7]

To clarify the maldistribution in research, a quick scoping review was carried out in PubMed yielding the following remarkable results, also shown in Figure 1: of all RCTs recorded in PubMed before the 17th of February 2024, only 0.1% had been performed in frail older patients and 4.4% in older patients. This is anything but a representative percentage when compared to the percentage in Dutch society defined as frail and old (over 4%) or old (about 20%) in 2020.[31–33] Note that these last two percentages are probably even higher if only patients actually receiving healthcare are considered.

The unequal distribution of participants was also seen in the four pivotal non-vitamin K antagonist oral anticoagulant (NOAC) trials.[8–11] The median age of participants in these trials ranged from 70 to 73 years and the mean CHA_2DS_2-VASc score from 2.1 to 2.8 (with the only exception being the ROCKET AF trial where the mean CHA_2DS_2-VASc score was 3.5). These trials were thus conducted in a relatively vital population of barely 70-plus with nearly no comorbidities. Consequently, these pivotal trials did not answer the clinically relevant question whether it is safe for frail older atrial fibrillation (AF) patients to initiate a NOAC or to switch from a vitamin K antagonist (VKA) to a NOAC, while in these patients the prevalence of AF reaches its maximum (38%).[34] The FRAIL-AF trial does provide an answer to this last question, because the study population of the FRAIL-AF trial was very different from the pivotal NOAC trials with a mean age of 83 years and a median CHA_2DS_2-VASc score of 4. Moreover, 88% of FRAIL-AF participants used ≥4 different types of medication, 38% had memory complaints, 17% was unable to walk around the house or to a neighbour, 44% had problems in daily life due to impaired vision, and 55% had problems in daily life due to impaired hearing. Importantly, the fact that the FRAIL-AF population was so different from the pivotal NOAC trials, does not even make it that surprising that the results of the FRAIL-AF trial were so different from the pivotal NOAC trials. The FRAIL-AF trial shows that results (from the pivotal NOAC trials in this example) cannot and should not be generalised to frail older AF patients and, moreover, that it is feasible to conduct an RCT in frail older patients.

FIGURE 1: SEARCHES IN PUBMED INCLUDING THE FILTERS 'HUMANS' AND 'RANDOMISED CONTROLLED TRIAL', PERFORMED ON 16 FEBRUARY 2024.



1: (trial[Title])
2: (trial[Title]) AND ((old[Title]) OR (older[Title]) OR (eld[Title]) OR (elder*[Title]) OR (age[Title]) OR (aged[Title]) OR (ageing[Title]) OR (senior[Title]) OR (geriatric[Title]))*
3: (trial[Title]) AND (frail[Title])*
4: (trial[Title]) AND ((old[Title]) OR (older[Title]) OR (eld[Title]) OR (elder*[Title]) OR (age[Title]) OR (aged[Title]) OR (ageing[Title]) OR (senior[Title]) OR (geriatric[Title])) AND (frail*[Title])*

These are just two examples illustrating that RCTs are too often conducted in the same vital population and that almost no RCTs are performed in specific populations where the greatest need for evidence exists. Since the leading research questions receive little or no attention in high-quality RCTs, it is therefore justified to introduce the term 'inverse research law' analogous to the term 'inverse care law'. As in clinical care, RCTs are often focused on populations that do not have the highest priority of unanswered and clinically relevant questions. This needs to change. The last part of this chapter presents some possible solutions for reversing the 'inverse research law'.

HOW TO REVERSE THE 'INVERSE RESEARCH LAW'?

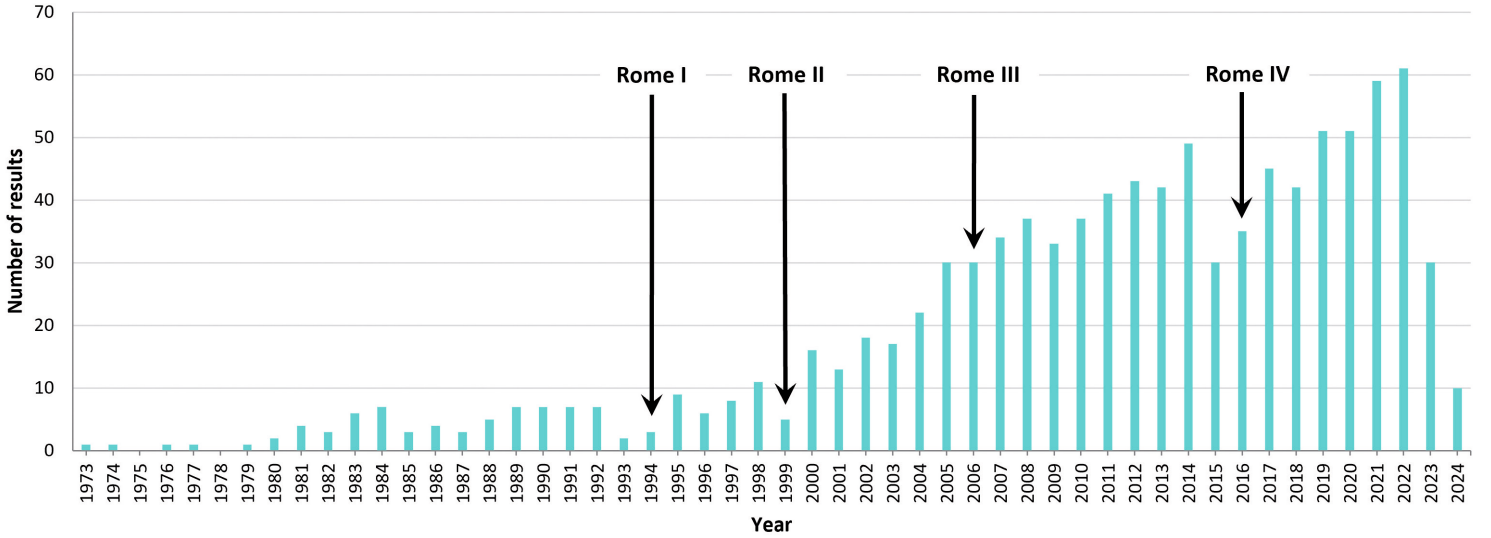
Fortunately, good examples already exist. For instance, the Dutch Heart Foundation has put reversing the 'inverse care law' and the 'inverse research law' on their national cardiovascular agenda for 2024-2034 in order to reduce the cardiovascular burden on patients and society.[35] Three of the seven key challenges on this agenda (i.e. care for all, attention to diversity, and tailored treatment) at least partly reflect the need to also provide evidence for patients who are often not included in research.[36] It also acknowledges the importance to aim at achieving both health and research equity by focusing on underserved and difficult to reach populations, and the need to tailor medical care to the individual needs of these populations. The Dutch Heart Foundation should be complimented for this research agenda, which will hopefully inspire other funding bodies to follow this example. The obvious next question is how we (i.e. both society as a whole and the research community) can achieve reversing the 'inverse research law' described in such a research agenda.

First, it is crucial to establish clarity regarding the specific population in which (additional) research is needed. In the example of frail older patients the concept of frailty is used to define accelerated biological decline, as well as functional decline and social isolation. However, a clear definition for frailty is currently not available, or at least not uniform. The lack of such a clear definition makes it impossible for physicians, researchers, guideline makers, policy makers and regulatory authorities to speak the same language and compare findings from different studies. A uniform and international definition helps determine the future research field and increases the number of RCTs in a specific population as illustrated in the following example. Before there was a uniform and international definition of irritable bowel syndrome, hardly any research was conducted on this highly prevalent functional gastrointestinal disorder. Following the publication of the authority-based diagnostic Rome I criteria in 1994, the number of RCTs on irritable bowel syndrome increased tremendously from 73 RCTs before 1994 to 797 RCTs from 1994 onwards based on a quick scoping search in PubMed using the search term 'irritable bowel syndrome' in the title (see Figure 1).[37] After each update of the Rome criteria (in 1999, 2006 and 2016), the number of

trials received a boost.[38–42] Therefore, it is obvious that a uniform and international definition may boost the reversal of the 'inverse research law'. Hence, providing a clear and internationally accepted definition is a crucial first step, albeit more is needed for substantial reversal.

As a next step, we need to look critically at how research is conducted. At the moment, due to the lack of proper research in specific populations, existing clinical guidelines are largely based on expert opinions which are derived from results of RCTs that are generalised to other populations or from results of observational studies.[43] However, as described in the General Introduction under the heading *Frailty and the consistent lack of evidence* and in the General Discussion under the heading *The 'inverse research law'*, results from RCTs cannot simply be generalised to another population and observational studies often suffer from confounding bias. Therefore, this is not the solution to the reversal of the 'inverse research law'. Another option is to develop an RCT for each research question and for each specific population group. In theory, this would be the best option, except for the fact that conducting so many different RCTs would be incredibly resource intensive. Currently, a lot of attention is given to diversity **within** RCTs to make the study population a reflection of the entire patient population in society. This, however, causes significant heterogeneity, which may eventually lead to difficulties in interpreting study results. The best way to reverse the 'inverse research law' in terms of conducting research is creating diversity **between** RCTs. As mentioned before, the four pivotal NOAC trials were performed in the same population. Testing medicines with a similar mechanism of action four times in a similar population might be considered 'research waste' and exposes more patients to a trial than necessary. Ideally, testing each medicine with a similar mechanism of action in a different population would enormously enrich the evidence, and thus clinical applicability. Imagine a series of trials would be organised differently: one medicine would be tested in men, a second in women and a third in frail older patients. Of course, such a trial strategy is only possible with medicines that have a similar mechanism of action. In addition, it is important that the study populations of the individual RCTs together properly reflect the whole population in society that is affected by the disease. In such a way organised, generalisation of results is based on evidence and no longer on speculations. However, history seems to repeat itself: the fact that the frail and old Mrs. de Jong is eligible to participate in a factor XI inhibitor RCT funded by the pharmaceutical industry appears to be an important development at first sight. But again, the inclusion and exclusion criteria of different RCTs testing a factor XI inhibitor with a similar mechanism of action are very similar.[44–46] As described above, this will most likely lead to the inclusion of very similar populations of patients leading to 'research waste' and unnecessary patient exposure, while leaving society with similar questions for other specific populations. This hampers the reversal of the 'inverse research law'.

FIGURE 2: NUMBER OF TRIALS ON IRRITABLE BOWEL SYNDROME IN PUBMED OVER TIME INCLUDING THE FILTERS 'HUMANS' AND 'RANDOMISED CONTROLLED TRIAL', PERFORMED ON 16 FEBRUARY 2024.



Acknowledging that creating diversity between RCTs, involving consultation between pharmaceutical companies and regulatory authorities to avoid testing medication (with a similar mechanism of action) in the same population, is idealistic and that not all medicines have the same mechanism of action, a more realistic solution to the reversal of the 'inverse research law' should be considered. It would be more feasible to better reflect relevant populations when allocating research funds. In addition, regulatory authorities, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), could play an important role in stimulating RCTs involving adequate numbers of clinically relevant populations. These authorities have taken first steps by developing regulations and guidelines on diversity in trials on medicinal products,[47,48] but these regulations could be more stringent. Pharmaceutical companies could be obliged by these authorities to adequately address diversity to ensure that study populations in RCTs reflect the entire relevant patient population in society. For example, they could require that registration and market access of new medication is conditional on adequate inclusion in RCTs of underserved populations, such as frail elderly. In addition, marketing medication in populations that have not been adequately studied could be prohibited. Similar obligations related to gender have led to an increase in the number of women included in RCTs.

Fourth, and perhaps even the most important point of action in reversing the 'inverse research law', is taking responsibility by researchers themselves to ensure that study populations in RCTs reflect the entire relevant patient population in society. Change starts with each individual: a drop in the ocean may seem small, but if enough drops fall, it creates a wave of change. Moreover, as exemplified by the FRAIL-AF RCT, it is worthwhile and rewarding to create such a wave using a team science approach and it ultimately impacts clinical practice.

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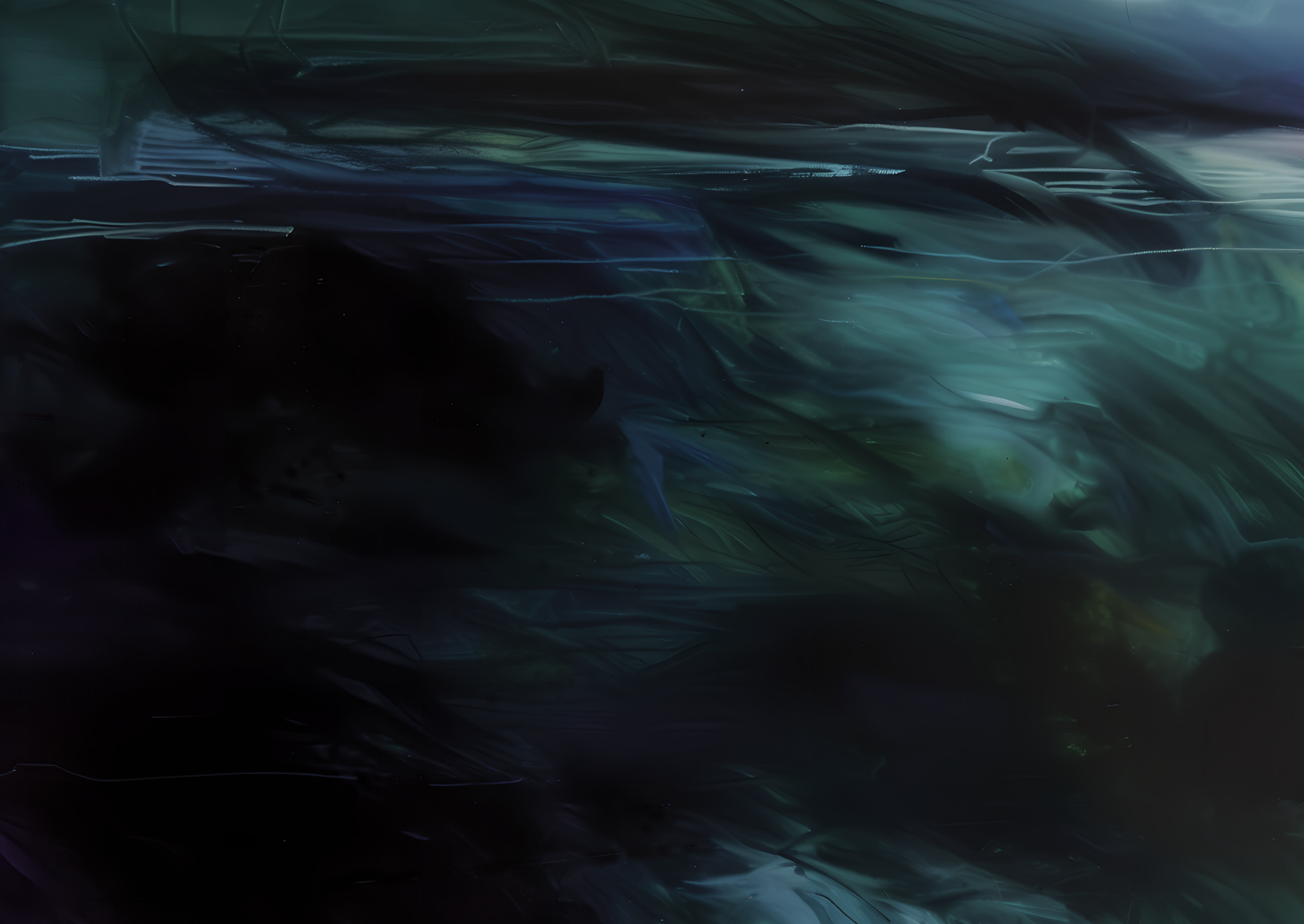

SUMMARY

GENERAL INTRODUCTION

In **Chapter 1**, the general introduction, the case of Mrs. de Jong is introduced to illustrate that there are important gaps in the evidence on the management of atrial fibrillation (AF), notably in frail older patients. Importantly, it is unclear whether frail older patients with AF can safely switch from a vitamin K antagonist (VKA) to a non-VKA oral anticoagulant (NOAC). Both VKAs and NOACs are oral anticoagulants prescribed to reduce the risk of ischaemic stroke in patients with AF. An important side effect of oral anticoagulants, inherent to their action, is an increased risk of bleeding. The CHA_2DS_2-VASc model is widely used to balance the efficacy and safety of oral anticoagulants, though its accuracy remains in debate. Furthermore, the importance of conducting high-quality research, including randomised controlled trials (RCTs), in the frail older population is highlighted in the general introduction. After all, evidence from a relatively young and vital population cannot simply be generalised to frail elderly.

PATHOPHYSIOLOGY OF INCREASED ISCHAEMIC STROKE RISK IN PATIENTS WITH ATRIAL FIBRILLATION

In **Chapter 2**, it is argued that it is not only blood stasis in fibrillating atria that plays a role in the development of emboli that can cause ischaemic stroke, but also the other two aspects of Virchow's triad for thrombogenesis: changes in blood constituents and changes in walls of blood vessels and atria. This supports the view that AF should be considered a systemic cardiovascular disease rather than solely a hearth rhythm disorder. This is in line with the 'Atrial Fibrillation Better Care (ABC) pathway' as incorporated in the most recent guidelines of the European Society of Cardiology,[1] and investigated in practice through, for example, the ALL-IN trial in which was demonstrated that integrated AF care in patients with AF led to a 45% reduction in all-cause mortality.[2] To further improve AF management, more studies should be performed into coagulation mechanisms that are related to the occurrence of AF itself and its association with ischaemic stroke.

SEX- AND AGE SPECIFIC ASSOCIATION OF NEW-ONSET ATRIAL FIBRILLATION WITH MORTALITY IN COVID-19 PATIENTS

Within one month after the occurrence of a respiratory tract infection, such as coronavirus disease 2019 (COVID-19), the risk of cardiovascular disease (including the development of AF) was 1.5-5 times higher.[3] Moreover, in patients hospitalised with COVID-19 during the first wave in 2020 new-onset AF was associated with increased risk of mortality.[4–6] In **Chapter 3** data of a large international multicentre registry study (CAPACITY-COVID) were used to investigate how this increased risk of mortality in

patients hospitalised with COVID-19 is impacted by sex and age.[7] For this purpose, multivariable logistic regression analyses were used.[7] In this study, 5,782 patients were included.[7] 7.3% of these patients developed new AF and/or atrial flutter (AFL) during hospitalisation. This was associated with a two- to three-fold increased risk of in-hospital mortality in men aged 60-72 years, an effect not observed in women.[7] These results improved the identification of subgroups of COVID-19 patients in whom the prognostic impact of new-onset AF and/or AFL on mortality is the most pronounced.

STROKE RATE VARIATION AND ANTICOAGULATION BENEFIT IN ATRIAL FIBRILLATION

Proper AF management with oral anticoagulation starts with identifying patients who do and who do not benefit from this medication. Most importantly stroke risk reduction should outweigh the increased risk of bleeding. In **Chapter 4** a letter to the editor is presented in response to a published article about variation in stroke risk according to the CHA_2DS_2-VAsc model and anticoagulation benefit in patients with AF.[8] The authors of the published article reported relevant uncertainty regarding the CHA_2DS_2-VASc score threshold above which anticoagulant treatment should be initiated.[9] They argued that this uncertainty should receive more attention in AF guidelines.[9] In the letter to the editor, the results of a large systematic review and meta-analysis, which reached a similar conclusion, were presented to support the authors' conclusion. In the meta-analysis, a large heterogeneity was observed in predicted stroke risks, notably for the CHA_2DS_2-VASc scores 1, 2 and 3 which play an important role in deciding on prescribing anticoagulants.[10]

TRENDS IN PREVALENCE AND ANTITHROMBOTIC PRESCRIPTIONS IN PATIENTS WITH ATRIAL FIBRILLATION

Chapter 5 is a descriptive study on the trends in prevalence of AF and the choices in the prescription of antithrombotic therapy.[11] This study used Dutch routine care data from approximately 385,000 patients in the Julius General Practitioners' Network.[11] From 2008 to 2017, 7,459 AF patients were registered.[11] During this period, the prevalence of AF more than tripled: from 0.4% to 1.4%.[11] This increase is due to the ageing of the population, but also to better awareness, detection and registration of AF. Furthermore, this study showed that in AF patients the prevalence of VKA prescriptions decreased from 47% in 2008 to 41% in 2017, while during the same period the prevalence of NOAC prescriptions increased from 0% to 20%.[11] Moreover, it was notable that in 2017, 25% of all AF patients with a CHA_2DS_2-VASc score ≥2 were still not prescribed a prophylactic oral anticoagulant,[11] whereas (also back then) this was recommended in the guidelines.[1,12] Multivariable logistic regression analyses were used

to identify the following patient characteristics that were found to be independently associated with a higher likelihood of receiving a VKA prescription rather than a NOAC prescription in patients with new-onset AF: higher age, heart failure, diabetes mellitus, vascular disease, and dementia.[11]

SWITCHING FROM A VITAMIN K ANTAGONIST TO A NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANT IN FRAIL OLDER PATIENTS WITH ATRIAL FIBRILLATION

It is estimated that 1 in 25 individuals in the Netherlands is currently frail and old.[13,14] AF is particularly common in the older population with a prevalence of 38% in the oldest and frailest population, namely nursing home residents.[15] As shown in Chapter 5, the prevalence of AF in the Netherlands increased from 0.4% to 1.4% between 2008 and 2017.[11] This is partly due to the ageing of the population. The number of frail older patients with AF is expected to increase further in the near future, as the ageing of the population continues in the coming years. Because evidence from RCTs in frail older AF patients is lacking and observational studies are sensitive to confounding bias, the FRAIL-AF trial was set up to investigate whether switching from a VKA to a NOAC compared to continuing a VKA reduces the number of major or clinically relevant non-major bleeding complications in frail older patients with AF. The comprehensive rationale and design of this trial are described in **Chapter 6**.[16] In summary, the FRAIL-AF trial is an investigator-initiated, randomised controlled, pragmatic, multicentre, open-label superiority trial.[16] Frail older patients in an outpatient setting were included.[16] To assess frailty, the validated Groningen Frailty Indicator (GFI) questionnaire was used, which scores frailty on several domains such as mobility, comorbidity, cognition and the psychosocial domain.[16,17] Patients aged 75 years or older with a GFI score of ≥3, managed with a VKA for non-valvular AF, willing to switch from a VKA to a NOAC, and willing and able to provide written informed consent were eligible to participate in the FRAIL-AF trial.[16] Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 were excluded from randomisation.[16] Eight Dutch thrombosis services provided the inclusion of the participants.[16] Patients randomised to the intervention arm switched from a VKA to a NOAC.[16] It was left to the treating physician, often the patient's general practitioner, to decide which of the four NOACs was prescribed.[16] Patients randomised to the control arm continued to receive a VKA (acenocoumarol or phenprocoumon) aiming at an INR target value between 2.0 and 3.0 with monitoring by the Dutch thrombosis services.[16] The primary outcome was the composite of the first major or clinically relevant non-major bleeding complication following the definitions of the International Society on Thrombosis and Haemostasis.[16,18,19] Secondary outcomes were thromboembolic events and all-cause mortality.[16] The follow-up period was one year and all analyses were performed using a Cox regression analysis on an intention-to-treat basis.[16]

The findings of the FRAIL-AF trial are described in **Chapter 7**.[20] 1,330 frail older AF patients were randomised.[20] The mean age of the analysed population was 83 years, 74% had a GFI of ≥4, and the median CHA_2DS_2-VASc score was 4.[20] Most patients in the intervention arm switched to rivaroxaban (50%), followed by apixaban (17%), edoxaban (16%) and dabigatran (9%) and dosing followed the summary of product characteristics in most patients (except for 6.6% of patients in the intervention arm who received an off-label dose reduction).[20] A prespecified interim analysis was planned after at least 160 primary outcome events had occurred.[20] The results of this interim analysis appeared to be completely different from what was expected: the composite primary outcome (i.e. the first major or clinically relevant non-major bleeding complication) occurred in 101 patients in the intervention arm (incidence rate 17.8 events per 100 person-years) and in 62 patients in the control arm (incidence rate 10.5 events per 100 person-years).[20] Thus, switching from a VKA to a NOAC compared to continuing VKA treatment increased the risk of a major or clinically relevant non-major bleeding complication (hazard ratio (HR) for the primary outcome of 1.69 with a 95% confidence interval (CI) of 1.23-2.32).[20] Subsequently, the independent Data Safety Monitoring Board recommended to stop inclusion according to prespecified rules for halting the trial due to futility.[20] In the analysis where the two components of the primary outcome were assessed separately, the observed difference between both treatment arms seemed mainly driven by an increase in clinically relevant non-major bleeding.[20] Regarding secondary outcomes, the occurrence of thromboembolic events and all-cause mortality were similar in the intervention arm (16 thromboembolic events and 44 deaths) and the control arm (13 thromboembolic events and 46 deaths) a HR of 1.26 (95% CI 0.60-2.61) and 0.96 (95% CI 0.64-1.45), respectively.[20] In conclusion, the FRAIL-AF RCT showed that switching from a VKA to a NOAC should not be considered without a clear indication in frail older patients with AF, as switching to a NOAC leads to 69% more bleeding.[20]

CLINICAL CONSEQUENCES OF OFF-LABEL REDUCED DOSING OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION

According to postmarketing observational studies, 20-30% of AF patients receive a reduced NOAC dose without a clear indication, probably aiming to reduce an assumed high risk of bleeding.[21–25] **Chapter 8** is a systematic review and meta-analysis on the clinical consequences (i.e. bleeding, stroke/thromboembolism and all-cause mortality) of this so-called off-label reduced dosing (OLRD) of NOACs compared to on-label non-reduced dosing (OLNRD) of NOACs in patients with AF.[26] The initial search in PubMed and Embase resulted in 10,780 publications and ultimately in the inclusion of 19 articles after applying the predefined inclusion criteria.[26] These 19 observational studies included in total 170,394 patients with AF and reported percentages of OLRD

ranging between 9% and 53%.[26] A meta-analysis of 7 of these 19 studies (with in total 80,725 patients) that met the predefined criteria for the meta-analysis resulted in a pooled HR of OLRD of NOACs compared to OLNRD of NOACs of 1.10 (95% CI 0.95-1.29) for bleeding, 1.04 (95% CI 0.83-1.29) for stroke/thromboembolism, and 1.22 (95% CI 0.81-1.84) for all-cause mortality.[26] Thus, this meta-analysis did not show a reduction in bleeding risk, nor an increased risk of stroke/thromboembolism, nor a significant difference in all-cause mortality in AF patients with OLRD compared to AF patients with OLNRD.[26]

GENERAL DISCUSSION

In **Chapter 9**, the general discussion, the main findings of this thesis and their practical implications are summarised by returning to the case of Mrs. de Jong. In addition, suggestions for future research on NOACs in frail older patients with AF are provided. In the second part of this chapter the 'inverse research law', derived from the 'inverse care law', is explained and discussed in detail. It highlights the paucity of evidence in one of the largest and most difficult to manage populations. The FRAIL-AF trial, which is the centrepiece publication in this thesis, is one of the very few RCTs ever performed in frail older patients.[20] As the FRAIL-AF trial showed that results in frail older patients are different compared to the non-frail populations from the four pivotal NOAC trials,[27–30] the findings of the FRAIL-AF trial emphasises the need for more dedicated RCTs in frail older patients. Thus, besides the important finding of an increased risk of major or clinically relevant non-major bleeding complications in frail older AF patients switching from a VKA to a NOAC compared to those continuing with VKA treatment, another clear message stems from the unexpected results of the FRAIL-AF trial, namely that we need to reverse the 'inverse research law'. Suggestions on how this could be achieved are provided in the last paragraphs of the general discussion.

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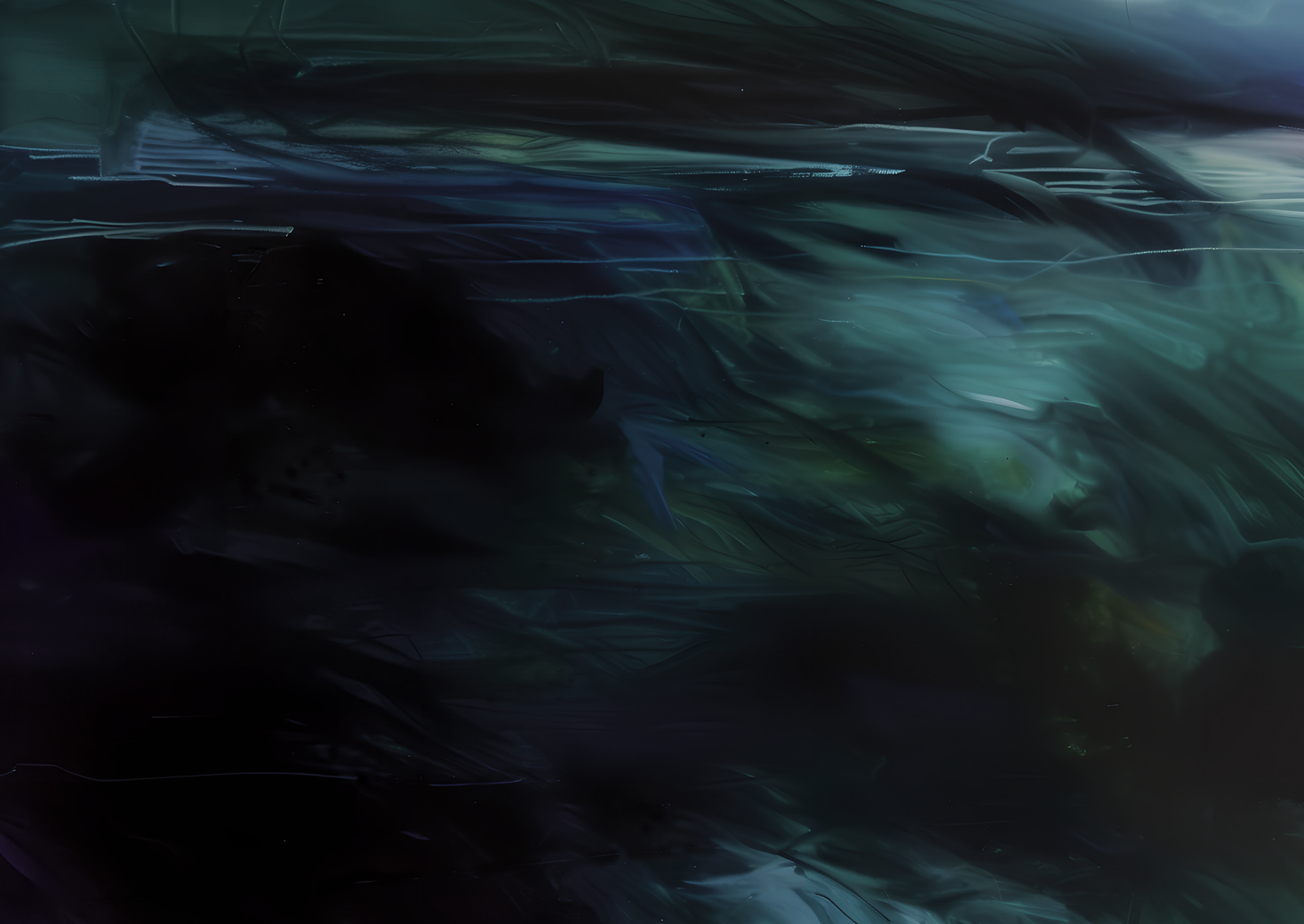

SAMENVATTING

ALGEMENE INLEIDING

In **Hoofdstuk 1**, de algemene inleiding, wordt ter illustratie van belangrijke hiaten in het bewijs over de behandeling van atriumfibrilleren (AF), met name bij kwetsbare oudere patiënten, de casus van mevrouw de Jong geïntroduceerd. Zo is het onduidelijk of kwetsbare oudere patiënten met AF veilig kunnen overstappen van een vitamine K antagonist (VKA) naar een niet-VKA oraal anticoagulans (NOAC). Zowel VKA's als NOAC's zijn orale anticoagulantia die worden voorgeschreven om het risico op een ischemische beroerte bij patiënten met AF te verminderen. Een belangrijke bijwerking van orale anticoagulantia, die inherent is aan de werking, is een verhoogd risico op bloedingen. Het CHA_2DS_2-VASc model wordt veel gebruikt om een balans te vinden tussen de werkzaamheid en veiligheid van orale anticoagulantia, ondanks dat de nauwkeurigheid ervan onderwerp van discussie blijft. Verder wordt in de algemene inleiding het belang benadrukt van het uitvoeren van kwalitatief hoogwaardig onderzoek, waaronder gerandomiseerd gecontroleerd onderzoek, in de kwetsbare oudere populatie. Immers, gevonden bewijs bij een relatief jonge en vitale populatie kan niet simpelweg worden gegeneraliseerd naar kwetsbare ouderen.

PATHOFYSIOLOGIE VAN HET VERHOOGDE RISICO OP ISCHEMISCHE BEROERTE BIJ PATIENTEN MET ATIRUMFIBRILLEREN

In **Hoofdstuk 2** wordt betoogd dat niet alleen bloedstase in fibrillerende atria een rol speelt bij het ontstaan van embolie die een ischemische beroerte kunnen veroorzaken, maar ook de andere twee aspecten van de Trias van Virchow voor trombogenese: veranderingen in bloedbestanddelen en veranderingen in de wanden van bloedvaten en atria. Dit ondersteunt het standpunt dat AF moet worden beschouwd als een systemische cardiovasculaire aandoening in plaats van alleen een hartritmestoornis. Dit is in lijn met het 'Atrial Fibrillation Better Care (ABC) pathway' zoals opgenomen in de meest recente richtlijnen van de European Society of Cardiology,[1] en onderzocht in de praktijk middels bijvoorbeeld het ALL-IN onderzoek waarin werd aangetoond dat een geïntegreerde generalistische benadering van AF patiënten leidde tot een vermindering van de algehele sterfte van 45%.[2] Om de behandeling van AF verder te verbeteren moet er meer onderzoek worden uitgevoerd naar stollingsmechanismen die gerelateerd zijn aan het optreden van AF zelf en de associatie ervan met ischemische beroerte.

GESLACHTS- EN LEEFTIJDSSPECIFIEKE ASSOCIATIE VAN NIEUW ONTSTAAN ATRIUMFIBRILLEREN MET MORTALITEIT BIJ COVID-19 PATIËNTEN

Binnen een maand na het optreden van een luchtweginfectie, zoals het coronavirus (COVID-19), is het risico op hart- en vaatziekten (waaronder het ontwikkelen van AF) 1,5 tot 5 keer hoger.[3] Bovendien was bij patiënten die met COVID-19 werden opgenomen in het ziekenhuis tijdens de eerste golf in 2020, nieuw ontstaan AF geassocieerd met een verhoogd risico op mortaliteit.[4–6] In **Hoofdstuk 3** werden gegevens van een groot internationaal multicenter registeronderzoek (CAPACITY-COVID) gebruikt om te onderzoeken hoe dit verhoogde risico op mortaliteit bij in het ziekenhuis opgenomen patiënten met COVID-19 wordt beïnvloed door geslacht en leeftijd.[7] Voor dit doel werden multivariabele logistische regressieanalyses gebruikt.[7] In dit onderzoek werden 5.782 patiënten geïncludeerd.[7] 7.3% van deze patiënten ontwikkelde nieuw AF en/of atriumflutter (AFL) tijdens de ziekenhuisopname. Dit werd geassocieerd met een twee- tot driemaal verhoogd risico op sterfte in het ziekenhuis bij mannen van 60-72 jaar, een effect dat niet werd waargenomen bij vrouwen.[7] Deze resultaten hebben de identificatie van subgroepen van COVID-19 patiënten verbeterd bij wie de prognostische impact van nieuw ontstaan AF en/of AFL op mortaliteit het meest uitgesproken is.

VARIATIE IN HET AANTAL BEROERTES EN VOORDEEL VAN ANTISTOLLING BIJ ATRIUMFIBRILLEREN

Een goede behandeling van AF met orale anticoagulantia begint met het identificeren van patiënten die wel en die geen baat hebben bij deze medicatie. Het belangrijkste is dat de vermindering van het risico op een beroerte opweegt tegen het verhoogde risico op bloedingen. In **Hoofdstuk 4** wordt een ingezonden brief gepresenteerd waarin een reactie op een gepubliceerd artikel is opgenomen over variatie in het risico op een beroerte volgens het CHA_2DS_2-VAsc model en het voordeel van antistolling bij patiënten met AF.[8] De auteurs van het gepubliceerde artikel rapporteerden dat er onzekerheid bestaat over de drempelwaarde van de CHA_2DS_2-VASc score waarboven behandeling met anticoagulantia moet worden gestart.[9] Ze stelden dat deze onzekerheid meer aandacht zou moeten krijgen in AF richtlijnen.[9] In de ingezonden brief werden de resultaten van een grote systematische review en meta-analyse, waarin een vergelijkbare conclusie werd getrokken, aangehaald om de conclusie van de auteurs te ondersteunen. In de meta-analyse was een grote heterogeniteit zichtbaar in voorspelde risico's op een beroerte, met name bij de CHA_2DS_2-VASc scores 1, 2 en 3 welke een belangrijke rol spelen bij de beslissing over het voorschrijven van anticoagulantia.[10]

TRENDS IN PREVALENTIE EN ANTITROMBOTISCHE VOORSCHRIFTEN BIJ PATIËNTEN MET ATRIUMFIBRILLEREN

Hoofdstuk 5 is een beschrijvend onderzoek naar de trends in de prevalentie van AF en de keuzes in het voorschrijven van antitrombotische therapie.[11] Voor dit onderzoek is gebruik gemaakt van de Nederlandse routinezorggegevens van ongeveer 385.000 patiënten in het Julius Huisartsen Netwerk.[11] In de periode van 2008 tot en met 2017 waren 7.459 AF patiënten geregistreerd.[11] Gedurende deze periode is de prevalentie van AF meer dan verdrievoudigd: van 0,4% naar 1,4%.[11] Deze toename is te wijten aan de vergrijzing van de bevolking, maar ook aan een betere bewustwording, detectie en registratie van AF. Daarnaast is uit dit onderzoek gebleken dat bij AF patiënten de prevalentie van VKA voorschriften is gedaald van 47% in 2008 naar 41% in 2017, terwijl in dezelfde periode de prevalentie van NOAC voorschriften is gestegen van 0% naar 20%.[11] Bovendien was het opvallend dat in 2017 25% van alle AF patiënten met een CHA_2DS_2-VASc score ≥2 nog steeds geen profylactisch oraal anticoagulans kreeg voorgeschreven,[11] terwijl dit (ook toen) wel werd aanbevolen in de richtlijnen.[1,12] Multivariabele logistische regressieanalyses werden gebruikt voor de identificatie van de volgende patiëntkenmerken die onafhankelijk geassocieerd bleken te zijn met een hogere kans op het ontvangen van een VKA voorschrift in plaats van een NOAC voorschrift bij patiënten met nieuw ontstaan AF: hogere leeftijd, hartfalen, diabetes mellitus, vaatziekte en dementie.[11]

OVERSTAPPEN VAN EEN VITAMINE K ANTAGONIST NAAR EEN NIET-VITAMINE K ANTAGONIST ORAAL ANTICOAGULANS BIJ KWETSBARE OUDERE PATIËNTEN MET ATRIUMFIBRILLEREN

Naar schatting is momenteel 1 op de 25 Nederlanders kwetsbaar en oud.[13,14] AF komt met name veel voor in de oudere populatie met een prevalentie van 38% in de oudste en meest kwetsbare populatie, namelijk verpleeghuisbewoners.[15] Zoals blijkt uit Hoofdstuk 5 is de prevalentie van AF in Nederland gestegen van 0,4% naar 1,4% tussen 2008 en 2017.[11] Dit is deels te verklaren door de vergrijzing van de bevolking. Naar verwachting zal het aantal kwetsbare oudere patiënten met AF in de nabije toekomst verder toenemen, omdat de vergrijzing van de bevolking de komende jaren door zal zetten. Aangezien bewijs van gerandomiseerde gecontroleerde onderzoeken bij kwetsbare oudere AF patiënten ontbreekt en observationele onderzoeken gevoelig zijn voor vertekening door confounding, werd het FRAIL-AF onderzoek opgezet om te onderzoeken of het overstappen van een VKA naar een NOAC in vergelijking met het voortzetten van een VKA het aantal grote of klinische relevante niet-grote bloedingscomplicaties vermindert bij kwetsbare oudere patiënten met AF. De uitgebreide rationale en opzet van dit onderzoek worden beschreven in **Hoofdstuk 6**.[16] Samengevat is het FRAIL-AF onderzoek een door de onderzoeker geïnitieerd,

gerandomiseerd gecontroleerd, pragmatisch, multicenter, niet-geblindeerd superioriteitsonderzoek.[16] In het onderzoek werden kwetsbare oudere patiënten in een ambulante setting geïncludeerd.[16] Voor het beoordelen van kwetsbaarheid werd de gevalideerde Groningen Frailty Indicator (GFI) vragenlijst gebruikt, die kwetsbaarheid scoort op verschillende domeinen zoals mobiliteit, comorbiditeit, cognitie en het psychosociale domein.[16,17] Patiënten van 75 jaar of ouder met een GFI-score van ≥3 die werden behandeld met een VKA voor niet-valvulair AF, bereid waren om over te stappen van een VKA naar een NOAC en bereid en in staat waren om schriftelijke geïnformeerde toestemming te geven kwamen in aanmerking om mee te doen aan het FRAIL-AF onderzoek.[16] Patiënten met een geschatte glomerulaire filtratiesnelheid (eGFR) <30 mL/min/1.73 m² werden uitgesloten van randomisatie.[16] Acht Nederlandse trombosediensten zorgden voor de inclusie van de deelnemers.[16] Patiënten die werden gerandomiseerd naar de interventiegroep stapten over van een VKA naar een NOAC.[16] De keuze voor een van de vier NOAC's werd overgelaten aan de behandelend arts, vaak de huisarts van de patiënt.[16] Patiënten die werden gerandomiseerd naar de controlegroep bleven een VKA (acenocoumarol of fenprocoumon) gebruiken, gericht op een INR waarde tussen 2,0 en 3,0 met monitoring door de Nederlandse trombosediensten.[16] De primaire uitkomst was de samenstelling van de eerste grote of klinisch relevante niet-grote bloedingscomplicatie volgens de definities van de International Society on Thrombosis and Haemostasis.[16,18,19] Secundaire uitkomsten waren trombo-embolieën en algehele sterfte.[16] De follow-up periode was één jaar en alle analyses werden uitgevoerd met behulp van een Cox regressieanalyse op basis van de aan de deelnemers toegewezen interventie.[16]

De bevindingen van het FRAIL-AF onderzoek worden beschreven in **Hoofdstuk 7**.[20] 1.330 kwetsbare oudere AF patiënten werden gerandomiseerd.[20] De gemiddelde leeftijd van de geanalyseerde populatie was 83 jaar, 74% had een GFI van ≥4 en de mediane CHA_2DS_2-VASc score was 4.[20] De meeste patiënten in de interventiegroep stapten over op rivaroxaban (50%), gevolgd door apixaban (17%), edoxaban (16%) en dabigatran (9%) en de dosering volgde de samenvatting van de productkenmerken bij de meeste patiënten (met uitzondering van 6,6% van de patiënten in de interventiegroep die een off-label verlaagde dosering kregen).[20] Een van tevoren gespecifieerde tussentijdse analyse was gepland nadat ten minste 160 voorvallen met de primaire uitkomst waren opgetreden.[20] De resultaten van deze tussentijdse analyse bleken volledig anders te zijn dan verwacht: de samengestelde primaire uitkomst (d.w.z. de eerste grote of klinisch relevante niet-grote bloedingscomplicatie) trad op bij 101 patiënten in de interventiegroep (incidentiecijfer 17,8 voorvallen per 100 persoonsjaren) en bij 62 patiënten in de controlegroep (incidentiecijfer 10,5 voorvallen per 100 persoonsjaren).[20] Daaruit bleek dat het overstappen van een VKA naar een NOAC in vergelijking met het voortzetten van de VKA behandeling het risico op een grote of klinisch relevante niet-grote bloedingscomplicatie verhoogde (hazard ratio (HR) voor de primaire uitkomst van 1,69 met een 95% betrouwbaarheidsinterval (BI)

van 1,23-2,32).[20] De onafhankelijke Data Safety Monitoring Board adviseerde daarop om de inclusie te stoppen volgens vooraf gespecifieerde regels voor het stopzetten van het onderzoek wegens futiliteit.[20] In de analyse waarin de twee componenten van de primaire uitkomst afzonderlijk werden beoordeeld, leek het waargenomen verschil tussen beide behandelingsgroepen voornamelijk te worden veroorzaakt door een toename van klinisch relevante niet-grote bloedingen.[20] Wat betreft secundaire uitkomsten waren het optreden van trombo-embolieën en algehele sterfte vergelijkbaar in de interventiegroep (16 trombo-embolische voorvallen en 44 sterfgevallen) en de controlegroep (13 trombo-embolische voorvallen en 46 sterfgevallen) een HR van 1,26 (95% BI 0,60-2,61) en 0,96 (95% BI 0,64-1,45), respectievelijk.[20] De conclusie is dat het FRAIL-AF gerandomiseerde gecontroleerde onderzoek heeft aangetoond dat overstappen van een VKA naar een NOAC niet moet worden overwogen zonder een duidelijke indicatie bij kwetsbare oudere patiënten met AF, omdat overstappen naar een NOAC leidt tot 69% meer bloedingen.[20]

KLINISCHE GEVOLGEN VAN HET OFF-LABEL VERLAAGD DOSEREN VAN NIET-VITAMINE K ANTAGONIST ORALE ANTICOAGULANTIA BIJ PATIËNTEN MET ATRIUMFIBRILLEREN

Volgens postmarketing observationele onderzoeken krijgt 20-30% van de AF patiënten een verlaagde NOAC dosering zonder een duidelijke indicatie, waarschijnlijk om een verondersteld hoog risico op bloedingen te verminderen.[21–25] **Hoofdstuk 8** is een systematische review en meta-analyse over de klinische gevolgen (d.w.z. bloedingen, beroertes/trombo-embolieën en algehele sterfte) van deze zogenaamde off-label verlaagde dosering (OLVD) van NOAC's in vergelijking met de on-label niet-verlaagde dosering (OLNVD) van NOAC's bij patiënten met AF.[26] De initiële zoekactie in PubMed en Embase resulteerden in 10.780 publicaties en uiteindelijk in de inclusie van 19 artikelen na toepassing van de vooraf gedefinieerde inclusiecriteria.[26] Deze 19 observationele onderzoeken includeerden in totaal 170.394 patiënten met AF en rapporteerden percentages van OLVD variërend tussen 9% en 53%.[26] Een meta-analyse van 7 van deze 19 onderzoeken (met in totaal 80.725 patiënten) die voldeden aan de vooraf gedefinieerde criteria voor de meta-analyse resulteerde in een gecombineerde HR van OLVD van NOAC's in vergelijking met OLNVD van NOAC's van 1,10 (95% BI 0,95-1,29) voor bloedingen, 1,04 (95% BI 0,83-1,29) voor beroertes/trombo-embolieën en 1,22 (95% BI 0,81-1,84) voor algehele sterfte.[26] Deze meta-analyse toonde dus geen verlaging van het bloedingsrisico, noch een verhoogd risico op beroerte/trombo-embolische voorvallen, noch een significant verschil in algehele sterfte bij AF patiënten met OLVD in vergelijking met AF patiënten met OLNVD.[26]

ALGEMENE DISCUSSIE

In **Hoofdstuk 9**, de algemene discussie, worden de belangrijkste bevindingen van dit proefschrift en hun praktische implicaties samengevat door terug te keren naar de casus van mevrouw de Jong. Daarnaast worden er suggesties gedaan voor toekomstig onderzoek naar NOAC's bij kwetsbare oudere patiënten met AF. In het tweede deel van dit hoofdstuk wordt de 'inverse onderzoekswet', afgeleid van de 'inverse zorgwet', uitgelegd en in detail besproken. Het benadrukt het gebrek aan bewijs in een van de grootste en moeilijkst te behandelen populaties. Het FRAIL-AF onderzoek, de centrale publicatie in dit proefschrift, is een van de zeer weinige gerandomiseerde gecontroleerde onderzoeken ooit uitgevoerd bij kwetsbare oudere patiënten.[20] Aangezien uit het FRAIL-AF onderzoek is gebleken dat resultaten bij kwetsbare oudere patiënten verschillen van de niet-kwetsbare populaties uit de vier belangrijke NOAC trials,[27–30] benadrukken de bevindingen van het FRAIL-AF onderzoek de noodzaak van meer specifieke gerandomiseerde gecontroleerde onderzoeken bij kwetsbare oudere patiënten. Naast de belangrijke bevinding van een verhoogd risico op grote of klinisch relevante niet-grote bloedingscomplicaties bij kwetsbare oudere AF patiënten die overstappen van een VKA naar een NOAC in vergelijking met degenen die continueren met VKA behandeling, komt er dus nog een duidelijke boodschap voort uit de onverwachte resultaten van het FRAIL-AF onderzoek, namelijk dat we de 'inverse onderzoekswet' moeten omkeren. Suggesties over hoe dit kan worden bereikt, worden gegeven in de laatste alinea's van de algemene discussie.

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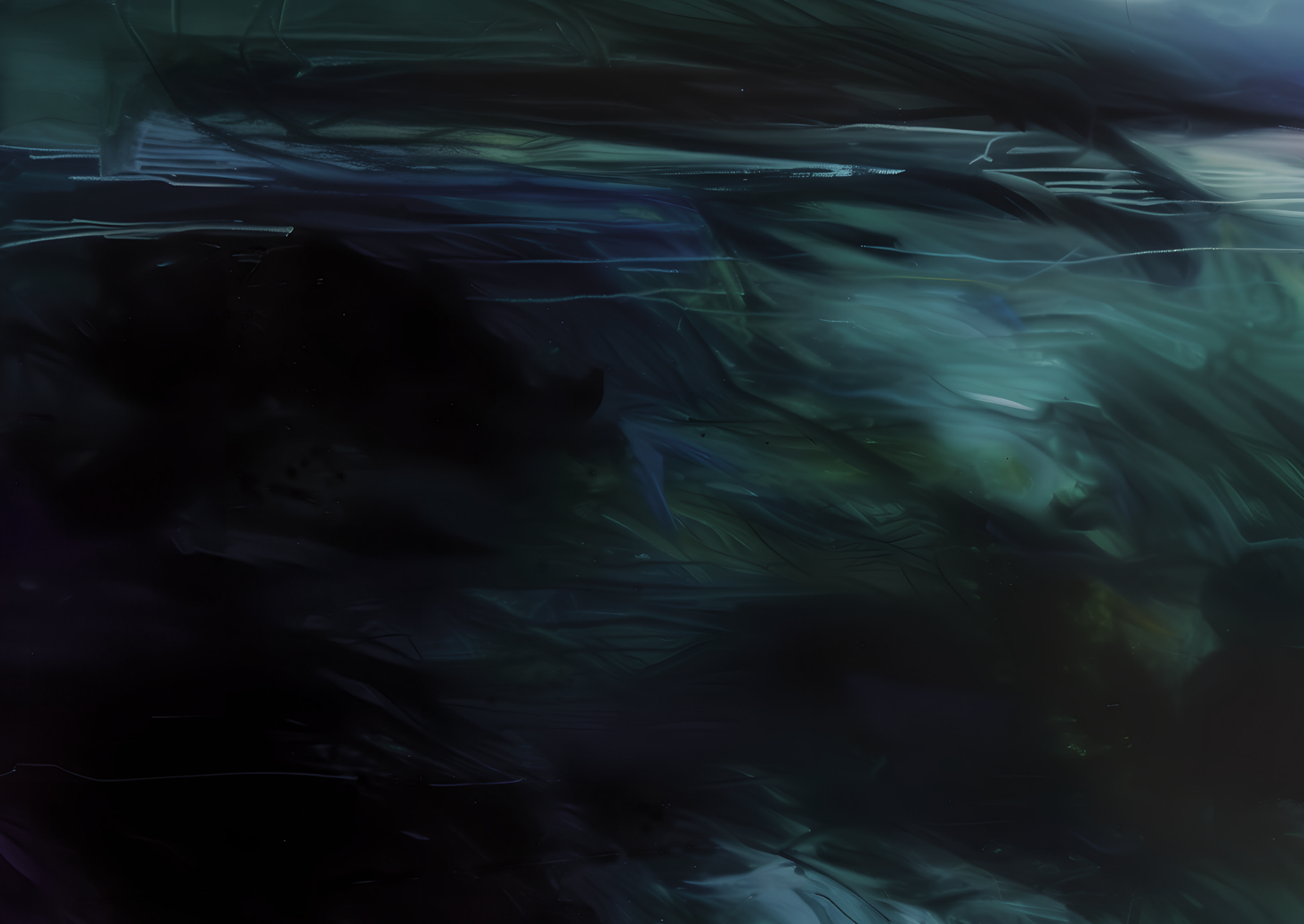

DANKWOORD

DANKWOORD

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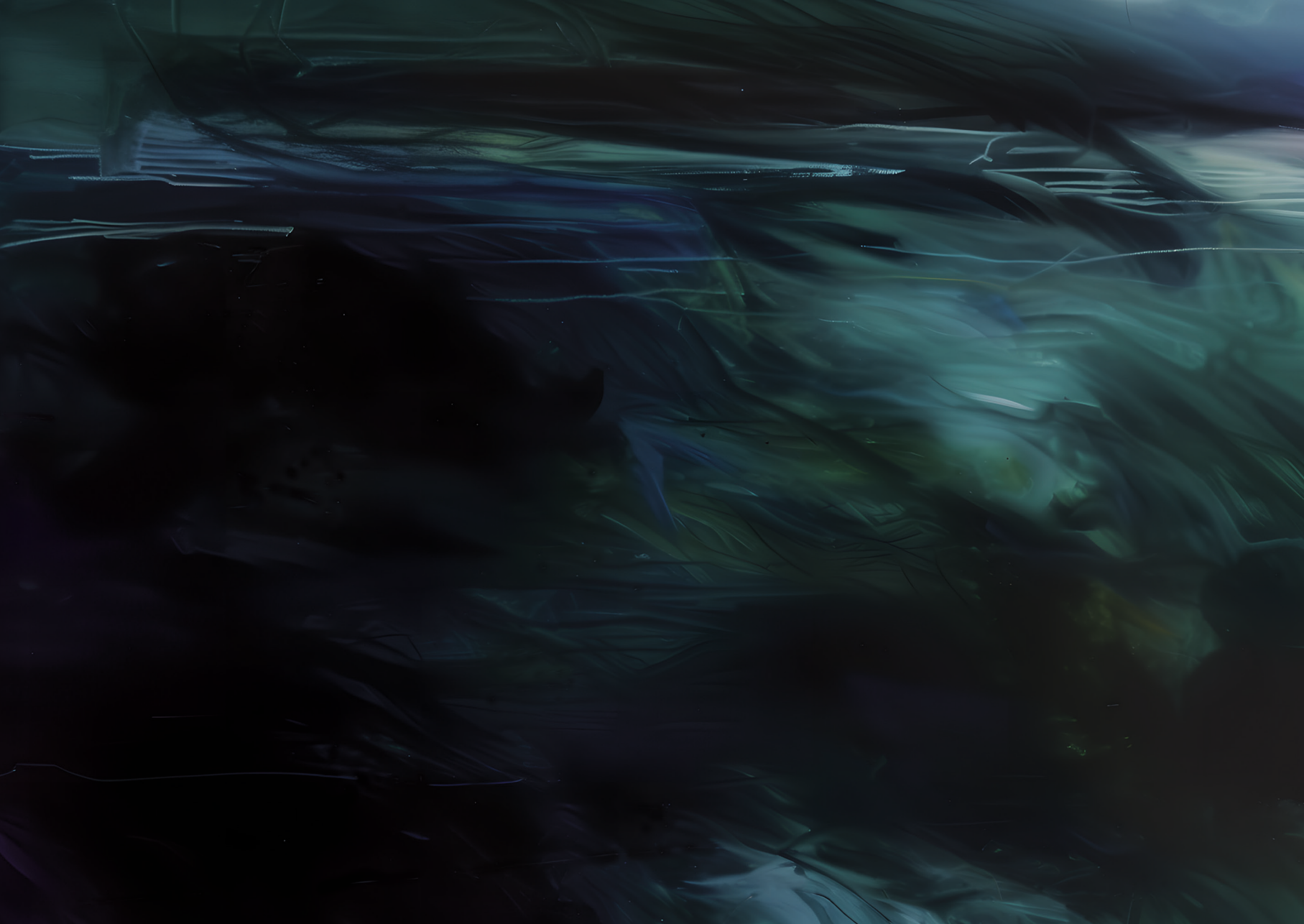
Linda Joosten
Weert, maart 2024



ABOUT THE AUTHOR

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Linda Petronella Theodora Joosten was born in Weert, the Netherlands, on the first of November 1991. She obtained her medical degree at Utrecht University in 2016.

In 2017, she started her PhD trajectory under the supervision of prof. dr. F.H. Rutten, prof. dr. A.W. Hoes, dr. G.J. Geersing and dr. S. van Doorn at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht, Utrecht University, which resulted in this thesis about the management of patients with atrial fibrillation. She combined her PhD trajectory with the Postgraduate Master of Epidemiology at Utrecht University and with the General Practitioner Training at the University Medical Center Utrecht, Utrecht University. In 2021, she finished the Postgraduate Master of Epidemiology after specialising in Clinical Epidemiology. She participated in the working group of the Dutch College of General Practitioners (NHG) for the revision of the NHG Guideline on atrial fibrillation in 2022 and 2023. In 2023, she completed her General Practitioner Training. Currently, Linda is working as a general practitioner in Weert.

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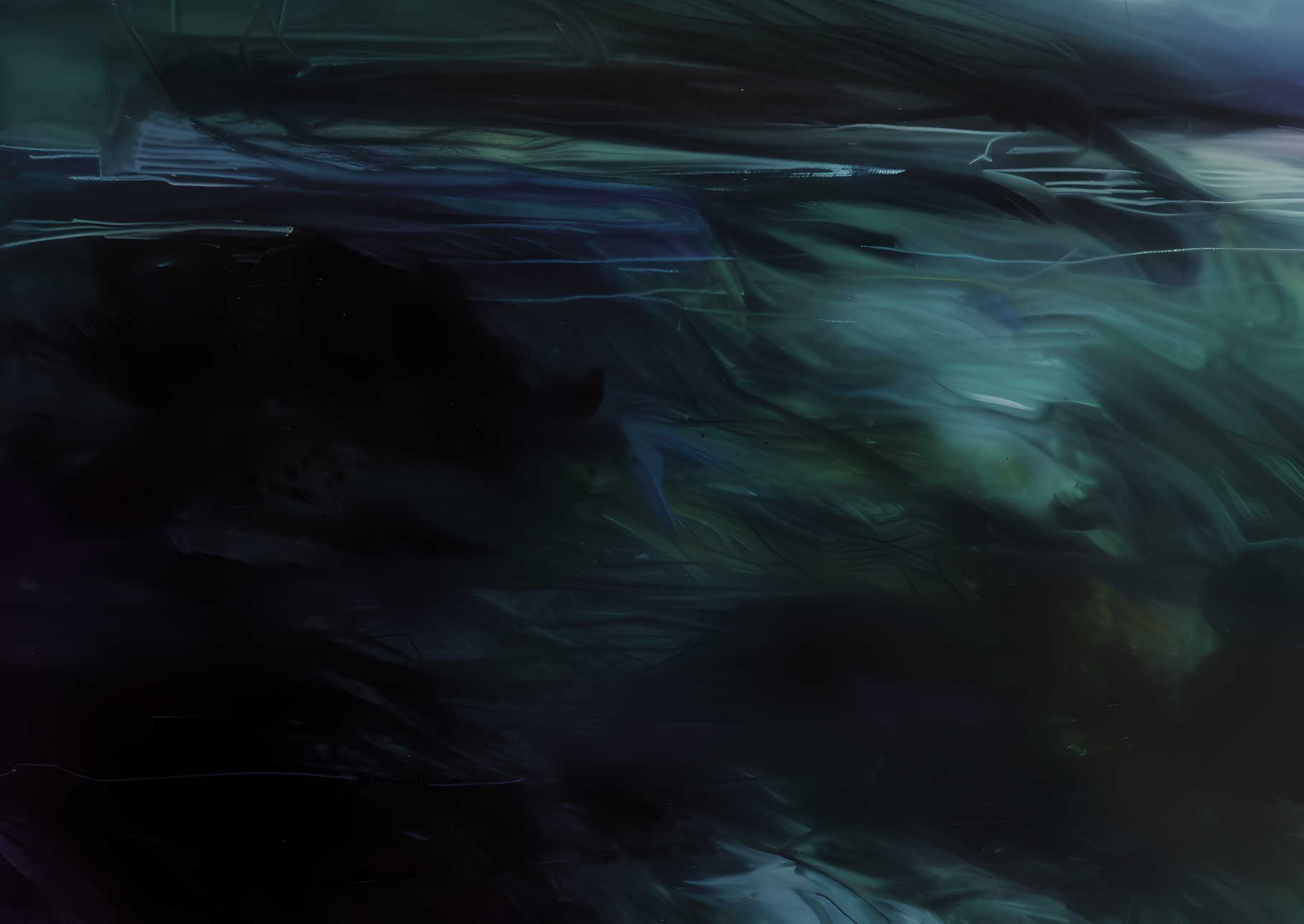

PUBLICATIONS AND CONFERENCE PRESENTATIONS

PUBLICATIONS BASED ON STUDIES PRESENTED IN THIS THESIS

- **Joosten LPT**, van Doorn S, van de Ven PM, Köhlen BTG, Nierman MC, Koek HL, Hemels MEW, Huisman MV, Kruip M, Faber LM, Wiersma NM, Buding WF, Fijnheer R, Adriaansen HJ, Roes KC, Hoes AW, Rutten FH, Geersing GJ. 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. Circulation. 2024;149(4):279-89. doi: 10.1161/CIRCULATIONAHA.123.066485.
- **Joosten LPT**, van Maanen R, van den Dries CJ, Rutten FH, Hoes AW, Granger CB, Hemels MEW, Geersing GJ, van Doorn S. Clinical consequences of off-label reduced dosing of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. Open Heart. 2023;10(1):e002197. doi: 10.1136/openhrt-2022-002197.
- **Joosten LPT**, Offerhaus JA, van Smeden M, Linschoten M, Bleijendaal H, Tieleman R, Wilde AAM, Rutten FH, Geersing GJ, Remme CA. Sex- and age specific association of new-onset atrial fibrillation with in-hospital mortality in hospitalised COVID-19 patients. Int J Cardiol Heart Vasc. 2022;39:100970. doi: 10.1016/j.ijcha.2022.100970.
- **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 primary care. Neth Heart J. 2022;30(10):459-65. doi: https://doi.org/10.1007/s12471-022-01667-x.
- **Joosten LPT**, van Doorn S, Hoes AW, Nierman MC, Wiersma NM, Koek HL, Hemels MEW, Huisman MV, Roes KC, van den Bor RM, Buding WF, Rutten FH, Geersing GJ. 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. doi: 10.1136/bmjopen-2019-032488.
- **Joosten LPT**, van Doorn S, Rutten FH, Geersing GJ. Stroke Rate Variation and Anticoagulation Benefit in Atrial Fibrillation. Ann Intern Med. 2019;170(11):816-817. doi: 10.7326/L19-0129.

ADDITIONAL PUBLICATIONS

- **Joosten LPT**, van Doorn S, Hemels MEW, Huisman MV, Rutten FH, Geersing GJ. Cumarine of DOAC bij kwetsbare ouderen met atriumfibrilleren? Ned Tijdschr Geneeskd. 2024;168:D8026. [Dutch]
- **Joosten LPT**. Vastzittende vishaak. In: Eekhof JAH, Bruggink SC, Kruis AL. Bonten TN, Petrus AHJ. Kleine Kwalen in de huisartsenpraktijk. Houten: Bohn Stafleu van Loghum; 2024. P. 881-886. [Dutch]

- Boelman L, Geersing GJ, Hemels MEW, Jongerius S, **Joosten LPT**, Olk H, Ruigrok S, Schep-Akkerman AE, Schoenmakers M, van Doorn S, Verheij AAA, Wiersma Tj. Herziening NHG-Standaard Atriumfibrilleren. [Internet]. 2023 [cited 2024 Feb 15]. Available from: https://richtlijnen.nhg.org/standaarden/atriumfibrilleren. [Dutch]
- Van Royen F, **Joosten LPT**, van Smeden M, Slottje P, Rutten FH, Geersing GJ, van Doorn S. Cardio-embolic vulnerability predicts hospitalisation in primary care clinically suspected and confirmed COVID-19 patients: a model development and validation study. PLOS ONE. 2022;17(4):e0266750. doi: 10.1371/journal.pone.0266750.
- **Joosten LPT**, van Eerde EJB, Rutten FH, Geersing GJ. Ontwikkelingen in prevalentie van atriumfibrilleren en antitrombotica voorschriften. In: de Boer AR, van Dis I, Visseren FLJ, Vaartjes I, Bots ML. Hart- en vaatziekten in Nederland 2019, cijfers over incidentie, prevalentie, ziekte en sterfte. Den Haag: Hartstichting; 2019. P. 119-132. [Dutch]
- **Joosten LPT**, Trinks-Roerdink E. Antistolling bij patiënten met atriumfibrilleren. Huisarts Wet. 2019;62(9). doi: 10.1007/s12445-019-0237-1. [Dutch]
- **Joosten LPT**, Wiersma NM. Het FRAIL-AF onderzoek: Optimale anticoagulantia bij kwetsbare ouderen. Tijdschrift voor trombose en antistolling. 2018;46(3):23. [Dutch]
- **Joosten LPT**, Geersing GJ. Welke DOAC bij patiënten met atriumfibrilleren? Ned Tijdschr Geneeskd. 2018;162:D2589. [Dutch]

NATIONAL CONFERENCE PRESENTATIONS

- NHG-wetenschapsdag, Rotterdam, 6 September 2024
  - Oral presentation: Resultaten FRAIL-AF studie: Veiligheid van het switchen van een VKA naar een NOAC bij kwetsbare ouderen met AF. [Dutch]
- Applicatiecursus FNT, Hoevelaken, 30 November and 15 December 2023
  - Oral presentation: Resultaten FRAIL-AF studie: Veiligheid van het switchen van een VKA naar een NOAC bij kwetsbare ouderen met AF. [Dutch]
- HartVaatHAG Dubbelcongres, Veenendaal, 12 October 2023
  - Oral presentation: Stoppen met antistolling. [Dutch]
- Nationale Antistollingsdag, Zeist, 2 November 2021
  - Oral presentation: Anticoagulantia bij ouderen: Praktische inzichten. [Dutch]
- NHG-wetenschapsdag, Maastricht (online), 11 February 2021
  - Oral presentation: Ontwikkelingen in prevalentie van atriumfibrilleren en antitromboticavoorschriften. [Dutch]
- Applicatiecursus FNT, Hoevelaken, 15 November 2018
  - Oral presentation: FRAIL-AF onderzoek: Optimale anticoagulantia bij kwetsbare ouderen. [Dutch]

- NHG-wetenschapsdag, Amsterdam, 8 June 2018
  - Oral presentation: De FRAIL-AF studie: Het switchen van VKA naar NOAC bij kwetsbare ouderen met atriumfibrilleren. [Dutch]
- Symposium Kenniscentrum Trombosezorg Saltro, Utrecht, 2 November 2017
  - Oral presentation: FRAIL-AF onderzoek: Optimale anticoagulantia bij kwetsbare ouderen. [Dutch]
- Jaarcongres HartVaatHAG, Utrecht, 29 September 2017
  - Pitch and poster: De FRAIL-AF studie: Het switchen van VKA naar NOAC bij kwetsbare ouderen met atriumfibrilleren. [Dutch]
- Connect-AF, Arnhem, 28 March 2017
  - Oral presentation: FRAIL-AF studie: Switchen van anticoagulantiatherapie bij kwetsbare ouderen met atriumfibrilleren. [Dutch]

INTERNATIONAL CONFERENCE PRESENTATIONS

- ESC 2023, Amsterdam, 25-28 August 2023
  - Oral presentation at a hot line session, ESC TV, ask the trialist, 6 video interviews: 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.
- ISTH 2022, London, 9-13 July 2022
  - Poster: Sex- and age specific association of new-onset atrial fibrillation with in-hospital mortality in hospitalised COVID-19 patients.
  - Poster: Atrial fibrillation: trends in prevalence and antithrombotic prescriptions in primary care.
- ISTH 2019, Melbourne, 6-10 July 2019
  - Poster: Design of the FRAIL-AF Trial: Safety of Switching from VKA to DOAC in Frail Elderly with Atrial Fibrillation.
  - Poster: Off-label Dose Reduction of Direct Oral Anticoagulants in Atrial Fibrillation: A Systematic Review and Meta-analysis.
- WONCA, Kraków, 24-27 May 2018
  - Oral presentation: Design of the FRAIL-AF study: Safety of switching anticoagulant management (from VKA to DOAC) in frail elderly patients with atrial fibrillation: a randomised controlled trial.
  - Workshop: Thrombosis in primary care: Diagnostics, Prognostics and Treatment.
- Europrevent, Ljubljana, 19-21 April 2018
  - Poster: FRAIL-AF study: Switching from VKA to NOAC in frail elderly patients with atrial fibrillation.

AWARDS

- NHG-Wetenschapsdag, Rotterdam, 6 September 2024: NHG-Wetenschapssprijs 2024 for best article written by a general practitioner or general practitioner in training, titled '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'.
- LOVAH-Congres, 's Hertogenbosch, 5 April 2024: Kees Esser Academiseringsprijs 2024 for best article written by a general practitioner in training, titled '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'.
- Summer school huisartsopleiding Utrecht, Utrecht, 4 August 2020: Frank Almekindersprijs 2020 for best evidence based medicine report, titled 'Toegevoegde waarde van een positieve PCR-test op het aantonen van SARS-CoV-2 in de huisartsenpraktijk'. [Dutch]
- ISTH 2019, Melbourne, 7 July 2019: ISTH 2019 Congress Top Poster Winner for poster, titled 'Off-label Dose Reduction of Direct Oral Anticoagulants in Atrial Fibrillation: A Systematic Review and Meta-analysis'.
- Jaarcongres HartVaatHAG, Utrecht, 29 September 2017: HartVaatHAG Onderzoeksprijs 2017 for best pitch, titled 'De FRAIL-AF studie: Het switchen van VKA naar NOAC bij kwetsbare ouderen met atriumfibrilleren'. [Dutch]