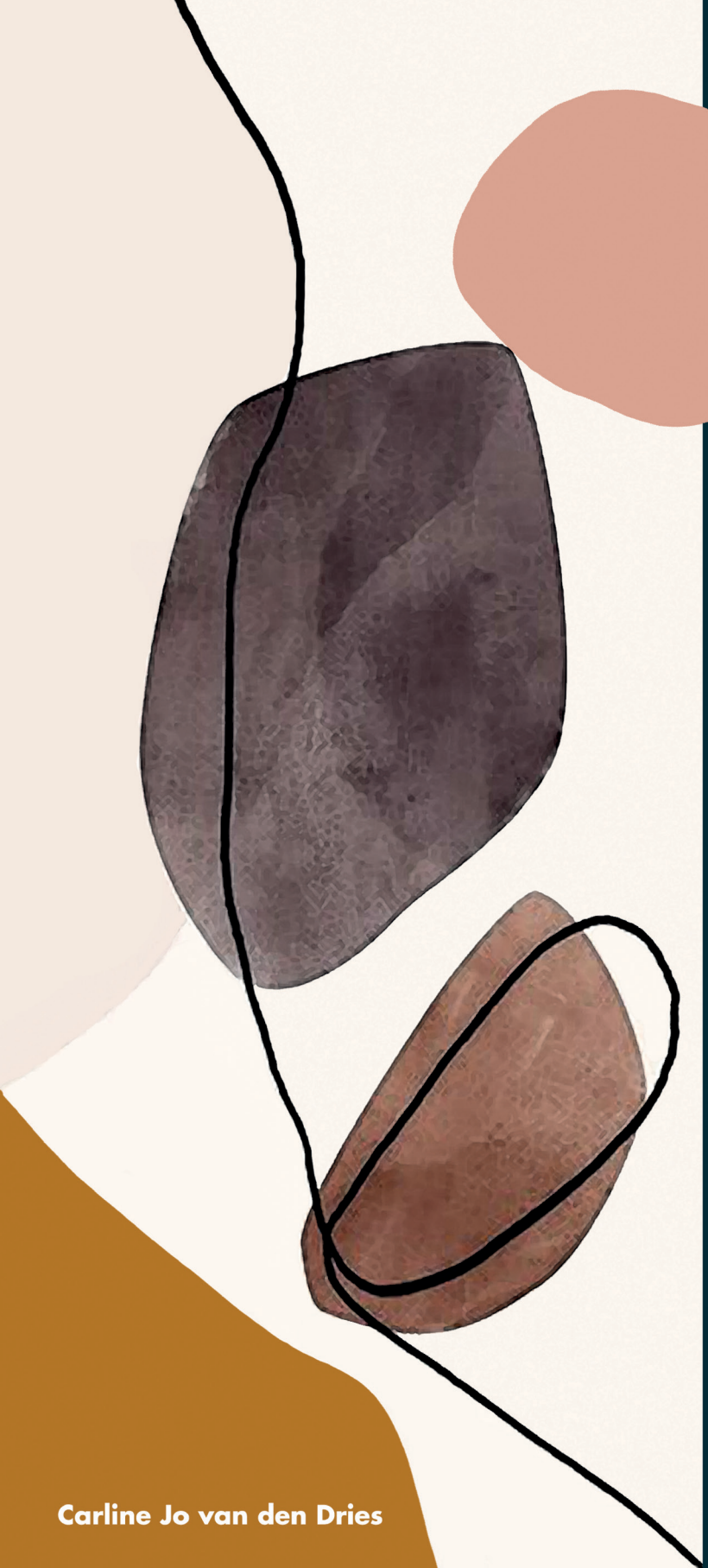

MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION IN PRIMARY CARE

Carline Jo van den Dries

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COLOFON

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MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION IN PRIMARY CARE

MANAGEMENT VAN PATIËNTEN MET ATRIUMFIBRILLEREN IN DE EERSTE LIJN

(met een samenvatting in het Nederlands)

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	Prof. dr. A.W. Hoes
Copromotoren:	Dr. G.J. Geersing
	Dr. S. van Doorn

CONTENTS

GENERAL INTRODUCTION

THE CASE OF MS. WILLEMS

Ms. Willems is an 84-year old woman who lives in a small village in the Netherlands. She was diagnosed with atrial fibrillation (AF), a heart rhythm disorder, more than 10 years ago. In the beginning, she had paroxysmal AF and when she had complaints of palpations she was treated with an electrocardioversion to restore sinus rhythm. After a couple of years however, the cardioversions were no longer successful and her atrial fibrillation became permanent. Her cardiologist concluded that her condition was 'stable' and referred her back to her general practitioner (GP) 7 years ago. Mrs. Willems was happy she did not need to go to the cardiologist anymore, because her son always needed to take half a day off from work to take her to the hospital once a year. Besides AF, she also suffers from mild cognitive impairment, COPD, high blood pressure, diabetes and renal failure, for which she takes a total of 7 drugs. Amongst these drugs is a vitamin K antagonist (oral anticoagulant) to prevent an ischaemic stroke, a possible and severe complication of atrial fibrillation. Every couple of weeks she goes to the anticoagulation clinic where her International Normalized Ratio (INR) level is checked and the dosage of the vitamin K antagonist adjusted where appropriate. For her diabetes, she visits the practice nurse of her GP twice a year and her GP once a year. She also visits a nephrologist in the academic hospital twice a year, who monitors her renal function.

It is on a cold Friday afternoon when Ms. Willems feels ill. She has been coughing since a few days, is short of breath and now also has a fever. She calls her GP, who visits her and diagnoses a pneumonia. The GP prescribes an antibiotic and plans to visit her again after the weekend. But when the GP reads her mail on Monday morning, she sees that Ms. Willems had been admitted to the hospital because of a severe stomach bleeding. It appeared her INR level was very high. Moreover, the pneumonia did not recover as was hoped, partly because at admission it appeared that Ms. Willems also had mild heart failure with preserved ejection fraction, leading to increased symptoms of shortness of breath due to pulmonary congestion. The GP asks herself: could I have prevented this complication? Should I have contacted the anticoagulation clinic for an extra INR measurement? Why wasn't I aware that she also had heart failure? Should I have given more attention to her atrial fibrillation? Normally, patients or their families should contact the anticoagulation clinic themselves in case of fever or other changes that could cause the INR to change. In addition, the anticoagulation clinic should automatically receive a message from the pharmacy when an antibiotic or other drug that interacts with a vitamin K antagonist is initiated. But because of the weekend, this message came a few days later. How can we best organise care for these frail, elderly patients like Ms. Willems?

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and occurs most frequently among the elderly. The most feared complication of AF is the occurrence of an ischaemic stroke. If left untreated, the risk of an ischaemic stroke is increased 5-fold.[1] To reduce this risk, AF patients are often treated with oral anticoagulants, which have been shown to reduce the risk of an ischaemic stroke by 60%.[2] Apart from anticoagulant therapy, AF management also involves heart rate or heart rhythm control.[3] Importantly, however, AF is more than a heart rhythm disorder with an increased risk of stroke, as it often interacts with multiple comorbidities, especially in the elderly.[4–7] Therefore, care for comorbidities like hypertension, heart failure and COPD, forms an important and integral part of AF management.

Currently, there are two critical developments in the field of AF management that constitute the overall background and motivation for the studies described in this thesis. The first development is the **ongoing AF epidemic**. The second is a **shift in the prescription of oral anticoagulants** used for stroke prevention: from the traditional vitamin K antagonists (VKA), towards non-vitamin K antagonist oral anticoagulants (NOACs, also known as direct oral anticoagulants (DOACs)) of which currently four drugs are available: dabigatran, apixaban, rivaroxaban and edoxaban.

1. The AF epidemic

AF prevalence is rapidly increasing, largely attributable to increased detection of AF, increased incidence of AF and increasing life expectancy.[8,9] By the year 2060, AF is expected to affect 17.9 million people in Europe, more than twice the prevalence in 2010.[10] AF patients are often affected by multiple comorbidities. As a result, multiple health care providers are typically involved. Moreover, AF is also associated with impaired quality of life, increased mortality and frequent hospitalisations, both for cardiovascular and – importantly – non-cardiovascular reasons.[6,11,12] These frequent hospital admissions are an important driver of AF-associated costs, having a dramatic impact on health care resources. To deal with this properly, organisational changes in AF management are warranted.[13] One of the possible solutions to deal with this AF epidemic is *integrated and multidisciplinary care*, as for instance recommended by the 2016 ESC Guidelines on the management of atrial fibrillation.[3]

But what does such integrated care actually entail? A review of the literature in 2009 yielded about 175 definitions and the concept of integrated care has been described as "an imprecise hodgepodge".[14,15] The lack of a common definition is not surprising

as integrated care interventions are typically multifaceted and highly dependent on the targeted patient population and setting. However, the key element has been aptly described by Goodwin as follows: "at its simplest, integrated care is an approach to overcome care fragmentations".[16]

Overcoming such care fragmentations seems desirable, especially in patients with AF and multimorbidity. Indeed, studies evaluating integrated care by specialised AF nurses in secondary and tertiary care hospitals have shown promising results, but included only newly diagnosed AF patients that typically are first managed in a hospital care setting.[17–19] Many elderly AF patients however, have chronic or permanent AF and are referred back to primary care by their cardiologist once a 'stable' situation has been reached, exemplified by the case of Ms. Willems described above. Therefore, orchestrating integrated AF management with primary care 'in the lead' could have important practical and clinical benefits for older patients, like Ms. Willems, with AF and multimorbidity. Additionally, this could be instrumental to mitigate the impact of the AF epidemic and notably help to reduce its associated healthcare costs. Therefore, the ALL-IN study, which forms the heart of this thesis, was set up to investigate if such integrated care can be safely and cost-effectively performed in primary care.

2. Shift from VKA to NOAC use

Since more than a decade, different classes of oral anticoagulant drugs to prevent strokes in AF patients are available. For many years, vitamin K antagonists (VKAs) have been the cornerstone therapy in anticoagulation management. Since 2008, when the first NOAC dabigatran entered the market, NOACs have become an increasingly popular alternative to VKAs worldwide.[20–23] Although the shift started a bit later in the Netherlands, the majority of new-users were prescribed a NOAC since 2016, and since 2019 NOACs have outnumbered VKA prescriptions when taking all prescriptions into account.[24,25] The four available pivotal randomised clinical trials all demonstrated that the efficacy of NOACs in terms of stroke prevention is comparable to VKAs.[26–29] Regarding the safety of NOACs in terms of bleeding, a meta-analysis of the four trials showed a markedly reduced risk ratio of intracranial haemorrhage (relative risk (RR) 0.48, 95% CI 0.39–0.59), albeit with an increased risk of gastro-intestinal bleeding (RR 1.25, 95% CI 1.01–1.55).[30] But there are also practical advantages, as NOACs do not require INR monitoring or subsequent dose adjustments as they have fewer food and drug interactions compared to VKA treatment.

The large shift from VKA to NOAC use raises a multitude of clinical questions, for example: what are the results of NOACs compared to VKAs in real life? Do clinicians

adhere to the guidelines when choosing the NOAC dosage? And if not, how problematic is this? Are NOACs safe also in specific subgroups like frail elderly AF patients who often use multiple concomitant drugs, like Ms. Willems?

Questions also arise from an organisational point of view: what are the consequences for the anticoagulation clinics? What if the small anticoagulation clinic locations like in the village of Ms. Willems have to close their doors because of a decrease in patients managed with VKAs? How do we then keep anticoagulation monitoring accessible for AF patients, for example in those who cannot, or prefer not to, be treated with a NOAC but require lifelong treatment with a VKA?

Although this thesis does not provide an answer to all of these questions, the objectives of the studies described in this thesis are strongly related to these questions and challenges.

OUTLINE AND OBJECTIVES OF THIS THESIS

The first three chapters are about the ALL-IN trial. The ALL-IN trial is a cluster-randomised, pragmatic non-inferiority trial to evaluate if integrated care for AF patients can be safely and (cost)effectively organised in primary care. In **Chapter 1**, we describe the rationale and design of the ALL-IN trial. **Chapter 2** shows the results regarding the clinical outcomes of this trial. In **Chapter 3** the question is answered whether organizing integrated AF care in primary care is cost-effective.

Chapters four to six consist of studies providing real-world evidence of anticoagulant treatment with NOACs. **Chapter 4** describes a systematic review and meta-analysis of observational studies, to determine how frequent doctors prescribe an off-label reduced NOAC dose. In **Chapter 5**, the clinical impact of off-label NOAC dose reduction is assessed, using observational primary care data from the United Kingdom Clinical Practice Research Datalink (CPRD). **Chapter 6** describes a population based cohort study, also using CPRD data, on the influence of the number of concomitant drugs prescribed on the safety and efficacy of NOACs versus VKAs.

In the final chapter, the findings of the studies described in this thesis are discussed and suggestions for future AF management and future AF research are provided.

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INTEGRATED MANAGEMENT OF ATRIAL FIBRILLATION INCLUDING TAILORING OF ANTICOAGULATION IN PRIMARY CARE – STUDY DESIGN OF THE ALL-IN CLUSTER RANDOMISED TRIAL

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ABSTRACT

Introduction: In our ageing society, we are at the merge of an expected epidemic of atrial fibrillation (AF). AF management requires an integrated approach, including rate or rhythm control, stroke prevention with anticoagulation and treatment of important comorbidities such as heart failure or type 2 diabetes. As such, primary care seems to be the logical health care setting for the chronic management of patients with AF. However, primary care has not yet played a dominant role in AF management, which has been in fact more fragmented between different healthcare providers. This fragmentation might have contributed to high healthcare costs. To demonstrate the feasibility of managing AF in primary care, studies are needed that evaluate the safety and (cost-)effectiveness of integrated AF management in primary care.

Methods and analysis: The ALL-IN trial is a multicenter, pragmatic, cluster randomized, non-inferiority trial performed in primary care practices in a suburban region in the Netherlands. We aim to include a minimum of 1000 patients with AF aged 65 years or more from around 18 to 30 practices. Duration of the study is two years. Practices will be randomised to either the intervention arm (providing integrated AF management, involving a trained practice nurse and collaboration with secondary care) or the control arm (care as usual). The primary endpoint is all-cause mortality. Secondary endpoints are cardiovascular mortality, (non)-cardiovascular hospitalisation, major adverse cardiac events, stroke, major bleeding, clinically relevant non-major bleeding, quality of life and cost-effectiveness.

Ethics and dissemination: The protocol was approved by the Medical Ethical Committee of the Isala Hospital Zwolle, the Netherlands. Patients in the intervention arm will be asked informed consent for participating in the intervention. Results are expected in 2019 and will be disseminated through both national and international journals and conferences.

Trial registration: This trial is registered at the Netherlands Trial Register (NTR5532).

Strengths and limitations of this study

- This is the first randomised clinical trial to evaluate integrated care for patients with atrial fibrillation (AF) in primary care.
- Patient relevant outcomes, such as all-cause mortality, hospitalisation and quality of life, will be evaluated.
- A possible limitation is the lack of contrast between intervention and care as usual due to cardiovascular risk disease management programs that improve the cardiovascular risk profile of community-dwelling adults.
- The multifaceted concept makes it difficult to assess the contribution of each individual component of the intervention on the outcome.

INTRODUCTION

With the ageing population and the increasing disease burden of atrial fibrillation (AF), both clinically and economically, a change in the organisation of care for patients with AF seems imperative.[1] From 2010 to 2060, the number of patients with AF is expected to more than double, to amount to the alarming number of almost 18 million people in Europe.[2] Most of these patients are old, or even very old.[3]

Currently, in many healthcare settings, care for these elderly patients with AF is fragmented between cardiologists, general practitioners (GPs) as well as specialised anticoagulation clinics. However, most patients with AF have multiple comorbidities, with each disease requiring adequate attention in relation to their possible impact on health-related quality of life, mortality, and also treatment goals for AF.[4–6] For instance, common comorbidities in elderly patients with AF such as hypertension, type 2 diabetes, heart failure and ischaemic cardiovascular diseases, are all more or less 'thrombogenic' and increase the risk of stroke and premature death by thromboembolic events.[7,8] This influences the need to prescribe anticoagulation, and perhaps even the intensity of the required dosage, for example, if impaired renal function concurrently exists or in the case of an intercurrent infection. Also, there is a mutually reinforcing relationship between AF and many other conditions, leading to (prolonged) hospitalisation if not recognised or treated in time.[9–11] Importantly, the relative and absolute risks of many of these conditions or their associated hospitalisation, especially heart failure, are much larger than the risks of stroke.[12,13] In addition, AF may worsen heart failure or chronic obstructive pulmonary

disease (COPD), and vice versa.[14,15] Hence, AF is not merely a cardiac arrhythmia, yet rather an exponent of multiple cardiac and non-cardiac illnesses all more or less leading to accelerated ageing of the heart.[8,16] This calls for an integrated approach to AF management.

Such integrated AF care clearly requires good communication and cooperation between patients, GPs, cardiologists and the anticoagulation clinics. The best way to deliver this type of care for patients with chronic AF is however less clear. For instance, the latest guideline from the European Society of Cardiology on AF calls for integrated management of AF, and states that 'more research is needed into the best way of delivering integrated AF care'.[17]

A systematic review and meta-analysis of integrated care in AF by Gallagher *et al* showed reduced all-cause mortality (OR 0.51, 95% CI 0.32 to 0.80) and reduced cardiovascular hospitalisation (OR 0.58, 95% CI 0.44 to 0.77).[18] The three studies included in this meta-analysis all involved cardiac nurses from AF clinics at tertiary care hospitals.[19–21] Currently, an increasing number of patients are treated at these specialised AF clinics. However, in the era of rapidly evolving knowledge in understanding AF, the focus of AF-treatment is evolving as well: rhythm control (including ablation) in symptomatic AF, to integrative management for the large group of older, frail patients with AF, with treatment being focussed on rate control and treatment of concurring comorbidity.[22,23] If integrated AF care could be performed equally effective and safe in primary care, this could have important clinical benefits for older patients with AF and multi-morbidity, but could also help to reduce healthcare costs, especially in view of the increasing prevalence of AF.

For more than a decade, 'small-team based integrated disease management' exists in primary care, with GPs and dedicated practice nurses specialised in the disease management of diabetes, COPD and cardiovascular risk management.[24–27] As an example, a large nurse-coordinated cardiovascular disease prevention programme has been shown to improve blood pressure control and lifestyle.[28] Such structured integrated care does not yet exist for patients with AF in primary care. Hence, we want to evaluate a newly developed integrated management program for the elderly patients with chronic AF in primary care, with cooperative care of the GP and practice nurse in a cluster randomised non-inferiority trial: the ALL-IN study. We will compare case management of AF in primary care with usual care that mainly involves cardiologists and anticoagulation clinics.

OBJECTIVES

To evaluate whether integrated AF management in primary care is non-inferior to usual care in terms of all-cause mortality (primary outcome), and also in terms of cardiovascular mortality, cardiovascular and non-cardiovascular hospitalisations, major adverse cardiac events (MACE), stroke, major bleeding, clinically relevant non-major bleeding (CRNMB), quality of life and cost-effectiveness (all secondary outcomes).

METHODS AND ANALYSIS

Study design

This is a multicentre, prospective, open label, cluster randomised pragmatic trial in patients with AF aged 65 years or more, managed in primary care in the Netherlands. The participating primary care practices are affiliated to three centres (hospitals): the Isala hospital in Zwolle, the Röpcke Zweers Hospital in Hardenberg and the Deventer Hospital in Deventer. The duration of follow-up will be 24 months.

Randomisation

Randomisation of primary care practices will be stratified according to cluster size, defined as the total number of patients in the primary care practice aged 65 years and older. Primary care practices are randomised to the intervention or the control (care as usual) arm, following a computerised block randomisation with a 1:1 allocation ratio. If, during the subsequent randomisation of practices within approximately one year, an unequal distribution of patients across the intervention and control arm appears (e.g., due to cluster effects or the modified informed consent procedure, in which only patients in the intervention arm need to provide informed consent, see below), an adaptive design with a 2:1 allocation ratio will be applied allowing the randomisation module to allocate more practices to the intervention arm, if applicable. As this is a pragmatic trial, there is no blinding for index or control treatment.

Study population

Inclusion criteria

Participating primary care practices need to be willing and able to provide integrated management to their patients with AF. Patients aged 65 years or more with documented AF in the primary care practice (by an ECG or specialist's letter to the GP) are eligible for participation if they do not meet any of the following exclusion criteria.

Exclusion criteria

1. An internal cardioverter defibrillator or a cardiac resynchronisation therapy device
2. Cardiac resynchronisation treatment, cardiac ablation or cardiac surgery < 3 months prior to inclusion or one of these procedures planned
3. Heart valve surgery in the past or a rheumatic mitral valve stenosis
4. Pulmonary vein isolation in the past or being planned
5. Being legally incapable of providing informed consent
6. Life expectancy shorter than 3 months
7. Participation in another randomised trial on AF

Sample size calculation

To our knowledge, the currently only available randomised controlled trial on the effectiveness of nurse-led care versus care as usual (in the cardiology outpatient clinic setting) in patients with AF is from Hendriks *et al.*[19] Based on their results (*cardiovascular* mortality 1.1% intervention vs 3.9% care as usual; all-cause mortality is not specifically reported by Hendriks *et al*), we anticipate that *all-cause* mortality, our primary endpoint, will occur in 8% of the patients receiving usual care versus 4% in those receiving the intervention with integrated AF management. Our study uses a non-inferiority design, as its first purpose is to demonstrate that integrated AF management can be performed safely in a primary care setting. Based on non-inferiority with a margin of 1%, chosen on clinical grounds, using an α of 0.05 (one sided, as any improvement on all-cause mortality is desirable) and a power of 80% we need approximately 300 patients with AF in each study arm. However, as this study follows a cluster randomised design, adjustment for clustering is needed. The amount of clustering is unknown, but as the outcomes of this study are likely driven by individual-level characteristics rather than cluster-level characteristics, we expect little clustering.[29] Nevertheless, using an intra-cluster coefficient (ICC) of 0.005, the inflation factor (or design effect, DE) can be calculated as follows: $DE=1 + ((m-1)*ICC)$, where m is the total number of participants in each cluster. Given the known AF prevalence of 1%-2% in the general population, and a total number of about 2350 patients registered within each practice (i.e., the defining cluster), we would expect about 30 patients with AF in each practice. If we define m=30 patients with AF per cluster, the DE=1.145. This thus would inflate the total sample size to 343 patients in each treatment arm, leading to about 23 clusters. However, if the number of patients with AF in each cluster (i.e. m) is lower or higher in each practice, which could be the case indeed, the DE would change accordingly, and thereby also the number of clusters needed. For instance, if m=20, DE would change to 1.095, inflating our sample size to 329 patients, thereby requiring 33 clusters. Similarly, if m=50, DE would change to

1.245, with a sample size of 374 patients per cluster, and requiring only 15 clusters for the whole study. Yet, given these uncertainties on the exact number of patients with AF who are eligible in each practice, the number of patients who will provide informed consent for the intervention, the uncertainty around the amount of clustering, as well as considering 10% loss to follow-up, we (conservatively) aim to include between 18 and 30 primary care practices in each study arm with a minimum of 500 patients with AF per arm.

This sample size would also be sufficient to demonstrate superiority for the secondary outcome cardiovascular hospitalisation, considering the same effect size as reported by Hendriks *et al* (HR 0.60). In that case, based on an α of 0.05 (two sided), a power of 80% and an ICC of 0.005, we would need at least 357 patients in each arm, estimating that cardiovascular hospitalisation will occur in 25% vs 16.5% of patients in the control arm and intervention arm, respectively.

Study procedures

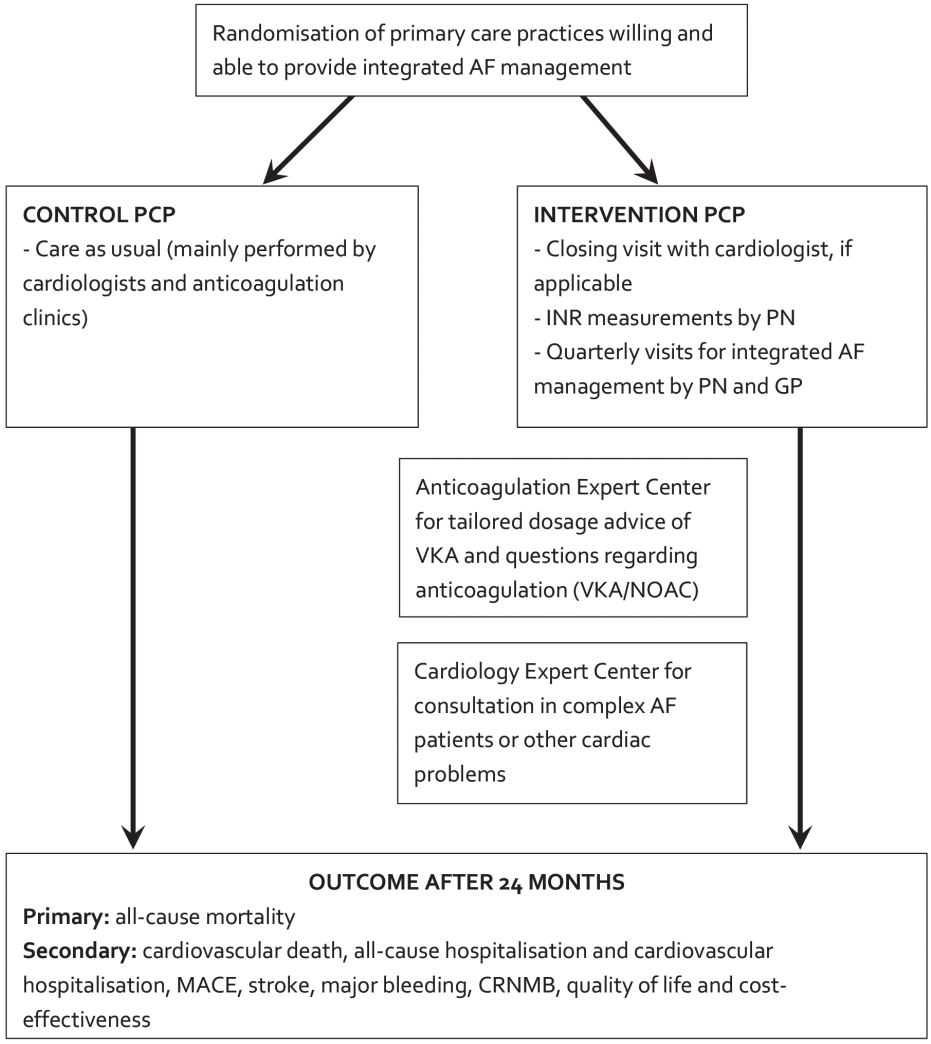
The study design is shown in figure 1. First, primary care practices willing to participate will be randomized. After randomisation, the researchers will identify eligible patients with AF by searching the GPs' electronic patient files of all patients aged 65 years or more, labelled with the Internal Classification of Primary Care code K78 (AF/flutter). Next, baseline data of these patients will be collected. Subsequently, patients will receive either integrated AF management (intervention arm) or care as usual (control arm), based on the randomisation allocation of their primary care practice.

Intervention under study

After providing informed consent for participating in the intervention, patients who used to receive care by a cardiologist will get a 'closing visit'. With this closing visit, the cardiologist is notified that the patient will receive integrated AF care in primary care without routine cardiology outpatient visits for AF, if appropriate. Also, the cardiologist can give final instructions on AF-treatment. These patients will still receive cardiologist's care if needed for other cardiac diseases, that is, pacemaker or valvular dysfunction.

Integrated AF management will be performed by the practice nurse under supervision of the GP. This integrated AF management encompasses (1) case management of anticoagulation in primary care, (2) quarterly check-ups for AF and its related comorbidities and (3) easy-access consultation with cardiologists and thrombosis experts.

FIGURE 1. FLOWCHART OF THE ALL-IN STUDY DESIGN



AF, atrial fibrillation; CRNMB, clinically relevant non-major bleeding; GP, general practitioner; MACE, major adverse cardiac events; NOAC, non-VKA oral anticoagulant; PCP, primary care practice; PN, practice nurse; VKA, vitamin K antagonist.

Case management of anticoagulation in primary care

Patients treated with a vitamin K antagonist (VKA) are offered tailored anticoagulation monitoring with International Normalised Ratio (INR) measurements using point-of-care INR measurement, performed by a trained practice nurse or GPs assistant at the practice, or if necessary at the patient's home. They will communicate the INR

value and relevant medical information (e.g. fever, diarrhoea, medication changes) to the Anticoagulation Expert Centre of the Dutch Thrombosis Service through an online portal. The same day, the practice nurse will receive the recommended dosage calendar for the subsequent time period from the Anticoagulation Expert Centre. Importantly, primary care practices are the first to know when a change in clinical condition occurs that might influence the anticoagulation status, and are instructed to then perform an extra INR-measurement, for instance when fever or (progression of) heart failure occurs. Patient education about when to contact the practice is also part of the intervention. Patients will only have one or two easy-access practice nurses to address their anticoagulation issues with, in contrast to the situation at the anticoagulation clinics where they often see many different faces.

For patients treated with a non-VKA oral anticoagulant (NOAC), adherence and other aspects of the NOAC therapy will be part of the quarterly routine primary care visits, as detailed in Quarterly check-ups for AF and its related comorbidities section. Each participating primary care practice will receive financial reimbursement in order to facilitate the aforementioned individualised anticoagulant case management.

Quarterly check-ups for AF and its related comorbidities
Patients will visit the primary care practice every 3 months (three times the practice nurse and once a year the GP). With a standardised protocol (based on guidelines from the Dutch College of General Practitioners, including the guideline for AF[30]), patients will be checked for their health condition and the management of AF, including evaluation of all cardiac and non-cardiac comorbidities. Blood pressure, heart rate and body weight are measured, and when in doubt of adequate rate control because of a possible pulse deficit, an ECG is made to know the actual heart rate. Special attention will be paid to lifestyle, drug compliance (notably for the NOACs), monitoring of kidney function (at least once a year), and the early detection of heart failure. Hereto, practice nurses are instructed to ask about dyspnoea, orthopnoea and check for peripheral oedema. If necessary, treatment will be adjusted. In case of an intercurrent illness, the GP can easily signal (and intervene on) the interaction of the illness with AF and the patient's anticoagulant status. The practice nurses will be trained in the management of AF, including education about the causes, signs and symptoms, and treatment of AF.

Easy access consultation with Cardiology and Anticoagulation Expert Centres
The GP and the practice nurse will have easy access to consultation of the Cardiology Expert Centre and Anticoagulation Expert Centre of the hospital in their region. Consultation is possible through a separate email address and/or telephone number.

Physicians and nurses from the expert centres are involved in the training of the practice nurses, also to get acquainted with each other and hopefully lower the threshold for the GP or practice nurse to contact the expert centres. Also, evaluation meetings between the practices and the expert centres will be organised twice a year, with educational purposes and to make further agreements. Patients may also be referred promptly to secondary care if necessary. In that case, patients will not drop out of the study, but continue to participate in the intervention, as the need for the main aspects of the integrated management remains, i.e. close follow-up and care for both cardiac and in particular also non-cardiac comorbidity, as well as close anticoagulation monitoring.

Control group

In the control arm, patients will receive care as usual. Essentially, this implies partly fragmented care with at least the absence of an integrated approach looking at all AF and anticoagulation management-related aspects in a holistic manner with a coordinating role in primary care. It generally consists of a routine visit to the cardiologist once a year. In stable elderly patients with AF, the cardiologist may or may not have already ended routine follow-up though, depending on patient and physician preference. Usually, these patients only visit the GP on demand, without routine visits or regular check-ups on the disease burden associated with AF. Some of these patients are seen by the practice nurse in case of type 2 diabetes, COPD or hypertension, yet again without paying specific attention to AF. INR checks and adjustment of the dosage are organised by the anticoagulation clinics, on average once every 3 weeks. To define usual care, the following characteristics will be collected: (1) the proportion of patients (still) seen regularly by a cardiologist for routine care visits in the outpatient department; (2) the proportion of patients seen by a practice nurse in primary care of routine follow-up for type 2 diabetes, COPD or hypertension; and finally (3) the average number of INR measurements performed for each patient managed with a VKA.

Data collection

Baseline data collection

All data will be collected from the GP's electronic patient files. We will collect: (1) the individual's CHA_2DS_2-VASc score (history of congestive heart failure, hypertension, age≥75 (doubled), diabetes, stroke or Transient Ischaemic Attack (TIA) (doubled) – vascular disease, age 65-74 and female sex),(2) the individual's HAS-BLED score (history of hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile INR values, elderly, and concomitant drugs and/or alcohol excess),(3)

medication use, (4) the most recent laboratory results, and (5) type of AF at baseline (paroxysmal or non-paroxysmal).

Outcome assessment
After 24 months of follow-up we will collect data on the primary endpoint all-cause mortality and the secondary endpoints cardiovascular mortality, cardiovascular and non-cardiovascular hospitalisation, MACE, stroke, major bleeding, CRNMB, HRQoL and cost-effectiveness. HRQoL will be measured with the 12-item Short Form Health Survey (SF12) and the 5-level EuroQol 5D questionnaire (EQ5D-5L), at baseline, after 1 year and after 24 months. The EQ5D-5L is used to calculate quality-adjusted life-years (QALYs) in both arms. Actual health care expenses will be calculated from data in the GPs' electronic patient files (e.g., hospitalisation). An independent committee adjudicates the causes of death based on all available patients' data, blinded for the allocation of the study arm of the patients.

Data analysis
The aim of the main analysis is to compare the cumulative incidence of the primary endpoint (all-cause mortality) in 2 years in both study arms, that is, the study patients in the control group receiving usual care and the study patients in the index group that provided informed consent to undergo the intervention. As is recommended in non-inferiority trials, we will perform an intention-to-treat analysis and a per protocol analysis.[31] As is common in cluster randomised trials, those patients undergoing the intervention in the index clusters may differ from eligible study patients in the control clusters, as it is likely that providing informed consent for the intervention is selective. As this could introduce bias, we will collect information on the outcomes of patients who were eligible in the intervention arm, but preferred not to undergo the intervention. This will allow us to compare this group with both the intervention and control group patients on essential determinants such as age, sex, and comorbidities, and to judge whether we had selective study participation for those providing informed consent to receive integrated AF management. It also allows us to adjust for any selection bias introduced by such selective study participation.

Kaplan Meier and survival analysis will be used to analyse the primary and secondary outcomes. To account for the clustered design, a frailty model will be used, with the cluster being the random effect. For the dichotomous outcomes, risk differences and ratios (with 95% CIs) between the two groups will be calculated, using a multilevel generalised linear model including the random cluster effect. For the continuous outcome HRQoL, the differences in means (95% CI), after 12 and 24 months of

follow-up, will be calculated using a linear mixed effects model, again including the random cluster effect. Cost-effectiveness will be assessed in terms of the incremental cost-effectiveness ratio (ICER), which is the difference in average cost between the intervention arm and control arm, divided by the difference in QALYs between the two arms. The ICER thus represents the incremental cost per QALY gained by following the intervention instead of care as usual.

ETHICS AND DISSEMINATION

Informed consent

For this cluster randomised trial, we will follow a modified informed consent procedure.[32] In the intervention arm, all eligible patients are personally invited by their GP to participate and they need to provide full written informed consent before participating in the intervention. In the control arm, informed consent is only required for filling out the HRQoL questionnaires, without directly revealing the true purpose of our study to control group patients.

As to be expected, not all eligible patients will provide informed consent, probably the very old and frail patients with AF in particular. This may induce selection bias. To address this issue and to adjust for it, we will gather information on determinants relevant for the baseline thromboembolic risk plus outcome assessment on *all* eligible patients in an encrypted manner for both the intervention arm and the control arm. For this specific reason, we obtained a waiver for informed consent from the Medical Ethics Committee. Patients' privacy will be cared for throughout the study and during data handling.

Safety monitoring

An independent Data and Safety Monitoring Board (DSMB) will be installed to assess the progress of the study and in particular the occurrence of the three most relevant serious adverse events: death, stroke and major bleeding ('major' according to the International Society on Thrombosis and Haemostasis' definition[33]).

Dissemination policy

Results of the trial are expected in 2019 and will be disseminated through peer-reviewed publications and presentations at (inter)national conferences.

DISCUSSION

With the ALL-IN cluster randomised trial, we will evaluate structured, integrated management of patients with AF in primary care. This is characterised by (1) a key role for the practice nurse, (2) special attention for comorbidities and (anticoagulant) drug adherence and (3) easy access to the Cardiology and Anticoagulation Expert Centers. We hypothesise that such an integrated primary care approach will be at least non-inferior (in terms of all-cause mortality) to usual care by cardiologists, anticoagulation clinics and GPs. Transition of care from the hospital to the community is deemed necessary, for example, by insurance companies and policymakers, because of the ageing of the population and the growing health care cost, but a formal evaluation of the safety and efficacy prior to such transitions is often lacking.[27] This study deliberately therefore uses a non-inferiority design, as it is pivotal that such transition of integral care for patients with AF to primary care is safe in terms of all-cause mortality. However, we hypothesise that by regularly monitoring these patients with regard to early signs of heart failure, for example, cardiovascular hospitalisation could be prevented. As stated earlier, the sample size would allow us to potentially demonstrate superiority for this endpoint.

We chose our exclusion criteria in a way that our study population includes the somewhat more 'stable' patients with AF, who are probably older and have more often permanent AF than those generally treated in secondary or tertiary care. However, we want to emphasise that this is not a low-risk population, as cardiac and non-cardiac comorbidity are frequent and the risk of mortality and hospitalisation is very high in elderly patients with AF.[12,13]

A possible limitation of this study is that the rise in prescription of NOACs in patients with AF might somewhat impact the generalizability of this study over time. In 2014, around 9% of all patients treated with oral anticoagulants in the Netherlands were receiving a NOAC.[34] This percentage is expected to increase in the coming years. However, prescription of NOACs is allowed for in this study, and we expect that the uptake of NOACs in fact may be enhanced due to study participation, predominantly thus for patients with AF receiving integrated AF care in the intervention arm. Second, evaluating a multifaceted intervention means that it will be difficult to examine which elements of the intervention are responsible for a certain observed effect. Finally, many primary care practices have disease management programs for cardiovascular risk and type 2 diabetes, and also those in the control arm. Therefore, usual care could already be of high quality regarding the management of cardiovascular risk factors.

This can diminish contrast between the intervention and care as usual. Nevertheless, in this pragmatic trial, care as usual is the best comparator to evaluate the safety and (cost-)effectiveness of the intervention. Moreover, the existing primary care disease management programmes do not involve special attention for AF or management of anticoagulant therapy.

To conclude, this will be the first study to structurally and prospectively evaluate integrated care for patients with AF in primary care. If proven safe and effective, widespread implementation of this strategy should be aimed for.

CONTRIBUTORS

RO, GJG, KGMM, FHR, CJD and AWH designed the study. RO, CJD, SJCML and AE contributed to the implementation of the intervention and AE and SJCML established the Cardiology and Anticoagulation Expert Centres of the Isala hospital, respectively. CJD drafted the first version of the manuscript. All authors critically reviewed and revised the manuscript before providing final approval.

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COMPETING INTERESTS

None declared.

ETHICS APPROVAL

The Medical Research Ethics Committee of the Isala hospital Zwolle, the Netherlands, provided approval of the study on 1 August, 2015.

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INTEGRATED MANAGEMENT OF ATRIAL FIBRILLATION IN PRIMARY CARE - RESULTS OF THE ALL-IN CLUSTER RANDOMISED TRIAL

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ABSTRACT

Aims: To evaluate whether integrated care for atrial fibrillation (AF) can be safely orchestrated in primary care.

Methods and results: The ALL-IN trial was a cluster randomized, open-label, pragmatic non-inferiority trial performed in primary care practices in the Netherlands. We randomised 26 practices: 15 to the integrated care intervention and 11 to usual care. The integrated care intervention consisted of (i) quarterly AF check-ups by trained nurses in primary care, also focusing on possibly interfering comorbidities, (ii) monitoring of anticoagulation therapy in primary care, and finally (iii) easy-access availability of consultations from cardiologists and anticoagulation clinics. The primary endpoint was all-cause mortality during 2 years of follow-up. In the intervention arm, 527 out of 941 eligible AF patients aged ≥ 65 years provided informed consent to undergo the intervention. These 527 patients were compared with 713 AF patients in the control arm receiving usual care. Median age was 77 (interquartile range 72-83) years. The all-cause mortality rate was 3.5 per 100 patient-years in the intervention arm vs. 6.7 per 100 patient-years in the control arm [adjusted hazard ratio (HR) 0.55; 95% confidence interval (CI) 0.37 to 0.82]. For non-cardiovascular mortality, the adjusted HR was 0.47 (95% CI 0.27 to 0.82). For other adverse events, no statistically significant differences were observed.

Conclusion: In this cluster randomised trial, integrated care for elderly AF patients in primary care showed a 45% reduction in all-cause mortality when compared with usual care.

INTRODUCTION

Integrated care has been proposed as a solution for the increasing disease burden of atrial fibrillation (AF) and is recommended in the 2016 European Society of Cardiology (ESC) guidelines on the management of AF (class IIa recommendation, level of evidence B).[1] The motive for integrated care is grounded on the view that AF is not merely an isolated heart rhythm disorder with an increased risk of stroke, but more, in general, a 'hypercoagulable state' caused by (or associated with) the presence of multiple underlying and interacting comorbidities.[2] Consequently, notably for elderly AF patients, management is evolving towards a more integrated care including also management of comorbidities.

A meta-analysis of studies investigating integrated care coordinated by tertiary care hospitals showed a reduction in all-cause mortality and cardiovascular hospitalisation.[3] More recently, the RACE 4 trial confirmed that integrated, nurse-led care reduced cardiac mortality and hospitalisation, yet *only* when provided in experienced AF clinics.[4] Hence, it is yet unknown whether such integrated care could be safely orchestrated in *primary care*, a setting characterised by non-specialist doctors and nurses and AF patients being typically older, frailer and suffering from multimorbidity. When proven safe, integrated AF care in primary care can be instrumental in managing the ever-increasing prevalence of AF and the associated burden and mortality, especially among the elderly.[5,6]

Therefore, the aim of our study was to assess whether integrated care for AF organised in primary care is non-inferior compared to usual care as performed by cardiologists and anticoagulation clinics.

METHODS

Setting

This study was conducted in the setting of Dutch primary care, a setting characterised by small teams with one or more general practitioners (GPs), closely working together with practice nurses and assistants, providing care for about 2200 patients enlisted per GP. The coverage of practices across the country is high, with 75% of people living within 1 km of a GP practice.[7] Another important characteristic is that the GP serves as a gatekeeper to secondary care.

Trial design

The ALL-IN trial was a cluster randomized, pragmatic, non-inferiority trial in primary care. Full details on the study design and protocol have been previously reported.[8] In brief, primary care practices located in the region of three affiliated secondary care hospitals (Zwolle, Deventer, and Hardenberg) in the Netherlands could be included if they were willing and able to provide integrated care. Given the uncertainty of whether primary care could safely orchestrate such integrated care, our aim was to demonstrate that management of AF in primary care was at least as safe and effective as current care provided (mainly) in secondary care. Therefore, this study was designed as a non-inferiority study regarding the primary outcome of all-cause mortality. During the design, conduct, and reporting of this study, we closely adhered to the CONSORT 2010 statement extension for cluster trials.[9] The trial was registered at the Netherlands Trial Register (NL5407).

Randomisation and participants

Randomisation occurred at the level of primary care practices (clusters), performed by an independent researcher through off-site computerised block randomisation stratified by practice size. Because of cluster randomisation, one practice (including all eligible patients within this practice) was allocated to either the intervention arm or the control arm. Randomisation at this practice level was necessary to prevent contamination of the intervention and thus dilution of any true effect, as it is practically impossible for a GP and his/her practice nurse to provide integrated care to one AF patient while refraining from doing so to the next.

After randomisation, *all* patients within the participating practices with documented AF and aged 65 years or older were assessed at the practices for eligibility using their electronic medical records. The following exclusion criteria were applied: (i) presence of an internal cardioverter-defibrillator or a cardiac resynchronisation therapy device; (ii) cardioversion, cardiac ablation, or cardiac surgery <3 months prior to inclusion or being planned; (iii) heart valve surgery in the past; (iv) a rheumatic mitral valve stenosis; (v) pulmonary vein isolation in the past or being planned; (vi) being legally incapable of providing informed consent; (vii) a life expectancy shorter than 3 months; and finally (viii) participation in another randomised trial on AF.

Informed consent and ethics

All eligible patients from practices randomised to the intervention were informed on study purposes and asked for written informed consent before undergoing the intervention. In the control arm, informed consent was only asked for filling out quality

of life questionnaires (secondary outcome, see below). The Medical Ethics Committee provided a waiver of informed consent for the collection of *anonymised* baseline and outcome data for *all* eligible patients in both arms, yet all strictly under the auspices of the treating GP. It was decided that to ensure the scientific validity of the trial such a waiver of informed consent for anonymised data collection was necessary, for three reasons: (i) to enable the assessment of otherwise undetectable possible selection bias caused by providing informed consent *for participation* after randomisation, inherent to cluster randomised trials, (ii) to enhance the generalizability of our findings, especially to frail elderly AF patients, and (iii) informing all eligible patients in the control practices would involve providing information and education on AF and its risks, thus inducing a risk of contamination. Moreover, no additional examinations for anonymised data collection were needed and thus no additional risk was imposed to patients. This approach is increasingly applied in cluster randomised trials to ensure its merits to science and society.[10–12]

Index intervention and usual care

Details of the intervention and a comparison with usual care are shown in the Supplementary material, *Appendix Section A*. The aspects included in our intervention largely overlap with the aspects mentioned in the 2016 ESC guidelines for the management of AF (except for the use of decision support software). Additionally, the primary care setting enabled our intervention to be even broader, as it involved also care for non-cardiovascular comorbidities that likely interact with AF, such as diabetes, infectious diseases, and chronic obstructive lung disease.

In short, the intervention consisted of three pivotal items: (i) quarterly AF check-ups by the practice nurse on symptoms and comorbidities, notably assessment of early signs and symptoms of heart failure and also patient education (for checklist, see Supplementary material, *Appendix section A*), (ii) case management of anticoagulant treatment, including international normalized ratio (INR) measurements performed by the intervention practice in those treated with a vitamin K antagonist (VKA), special attention to drug compliance, and monitoring of kidney function in patients using a non-vitamin K antagonist oral anticoagulant (NOAC), and (iii) easy-access consultation of anticoagulation clinics and/or cardiologists, thus truly enabling 'shared care and responsibility' between primary care, anticoagulation clinics, and cardiology care. When patients needed to be referred to secondary care or needed additional check-ups by a cardiologist (in case of other cardiac conditions or pacemaker), they continued their participation in the intervention arm. Practice nurses in the intervention practices received a 3 hr training at the start of the intervention with education on signs and

symptoms of AF and heart failure, rate and rhythm control, anticoagulant treatment, and an explanation of the most important recommendations of the guidelines on AF.[1,13] In addition, we organised three meetings throughout the 2-year follow-up period for both practice nurses and GPs to (i) share experiences and 'best practices', (ii) discuss complex patients, and (iii) provide additional education on topics based on existing questions of the practice nurses. Decisions regarding pharmacotherapy and referral to cardiology care were left to the GPs, guided by the Dutch College of General Practitioners' guidelines on AF.[13]

Usual care could vary per patient, but for most patients, it involved a once yearly consultation of a cardiologist or AF nurse at the outpatient cardiology department of the affiliated hospital. Some patients may already have been discharged from treatment by their cardiologist and for those patients, the GP was the first person to contact in case of signs or symptoms related to AF or other conditions. However, this occurs on an '*ad hoc* basis', initiated by the patient. For patients using a VKA, anticoagulation clinics affiliated to the local hospital performed the INR measurements and created the dosage calendar, yet without involvement of the GP. For patients using a NOAC, no structured control was in place in the control group.

Data collection and outcomes

Data on comorbid conditions and medication use for all eligible patients were automatically derived at baseline from the electronic medical records using International Classification of Primary Care (ICPC) codes and Anatomical Therapeutic Chemical (ATC) codes, respectively.

All patients were followed for at least 2 years. The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular and non-cardiovascular mortality, cardiovascular and non-cardiovascular hospitalisation, major adverse cardiac events (MACE), stroke, major bleeding, clinically relevant non-major bleeding (CRNMB), health-related quality of life (HRQoL), and cost-effectiveness. For major and clinically relevant non-major bleeding, the definitions of the International Society on Thrombosis and Haemostasis (ISTH) were used.[14,15] Definitions of the other outcomes are described in the Supplementary material, *Appendix Section B*. An independent adjudication committee, blinded for treatment allocation, adjudicated all causes of death. HRQoL was assessed by the 12-item Short-Form Health Survey (SF-12), measured at baseline and after 1 year and 2 years of follow-up.[16] The SF-12 consists of a physical health component score (PCS) and a mental health component score (MCS), both ranging from 0 to 100 with higher scores indicating better HRQoL.

Results of the cost-effectiveness analyses will be published separately. Except for the SF-12, all follow-up data were manually retrieved by the researchers from the primary care electronic medical records (i.e. from hospital discharge letters and reports from consultations). As all patients participating in the intervention needed to have this clearly noted in their files, researchers could not be blinded for treatment allocation during data collection.

Sample size calculation and statistical analysis

We anticipated that all-cause mortality (primary outcome) would occur more frequently in our older and frailer primary care study population than in the population studied by Hendriks *et al.*,[17] where 2.5% of patients died of a cardiovascular reason. We estimated mortality to occur in 8% of participants in the usual care arm of the trial during 24 months of follow-up. Assuming a 1% margin (absolute risk, one-sided) for non-inferiority and accounting for clustering (with an estimated intra-cluster correlation coefficient (ICC) of 0.005), we (conservatively) needed to include 500 patients in each arm to demonstrate non-inferiority for our primary outcome. In a post-hoc analysis, considering the outcome all-cause mortality as a binary event in the absence of appropriate methods to calculate the true ICC with time-to-event data, the estimate of the observed ICC appeared to be 0.008. Like we assumed beforehand, albeit with a slightly smaller ICC of 0.005, this ICC indeed indicates very little clustering. This sample size allowed us to demonstrate superiority *if* the hazard ratio (HR) of the effect size of the intervention would be 0.60 or lower. A possible superiority analysis was thus pre-planned and described in our protocol paper albeit that at study initiation we expected superiority to occur only for the secondary outcome hospitalisation.[8]

In the main analyses we compared the outcomes of all eligible patients in the control arm with the outcomes of the patients in the intervention arm who provided informed consent to receive integrated AF care, as described and pre-planned in our protocol.[8] Because individual informed consent for participating in the intervention was asked after randomisation of practices, differences in baseline characteristics between study arms might still occur. Therefore, we a priori defined to adjust for age, sex, and the Frailty Index (FI).[18] The FI is a validated frailty indicator based on ICPC and ATC codes from routine electronic healthcare data.[19] For each patient, the FI score (ranging from 0 to 1, with higher values indicating more frailty) was calculated by dividing the number of health deficits present, by the total fixed number of 36 pre-specified health deficits (including for example heart failure, cancer, renal impairment, and polypharmacy).

For the outcomes mortality, MACE, ischaemic stroke, and major bleeding, we used random effects Cox proportional hazard regression models with the clusters (practices) introduced as a frailty term to account for clustering and adjusting for age, sex, and FI. Scaled Schoenfeld residuals were plotted to visually assess the proportional hazards assumption and Martingale residuals were checked for the continuous covariates age and FI.[20,21] As traditional Cox models would analyse only the *first* event, we used negative binomial regression adjusted for age, sex, FI and length of follow-up (as an offset variable) for the analyses of the frequently *recurrent* outcome events hospitalisation and CRNMB. Finally, HRQoL and in particular changes in the PCS and MCS of the SF-12 between baseline, 1 year and 2 years of follow-up were analysed using linear mixed models, with a random intercept for the patient level and the practice level, and adjusted for age, sex, FI, and baseline PCS or MCS.

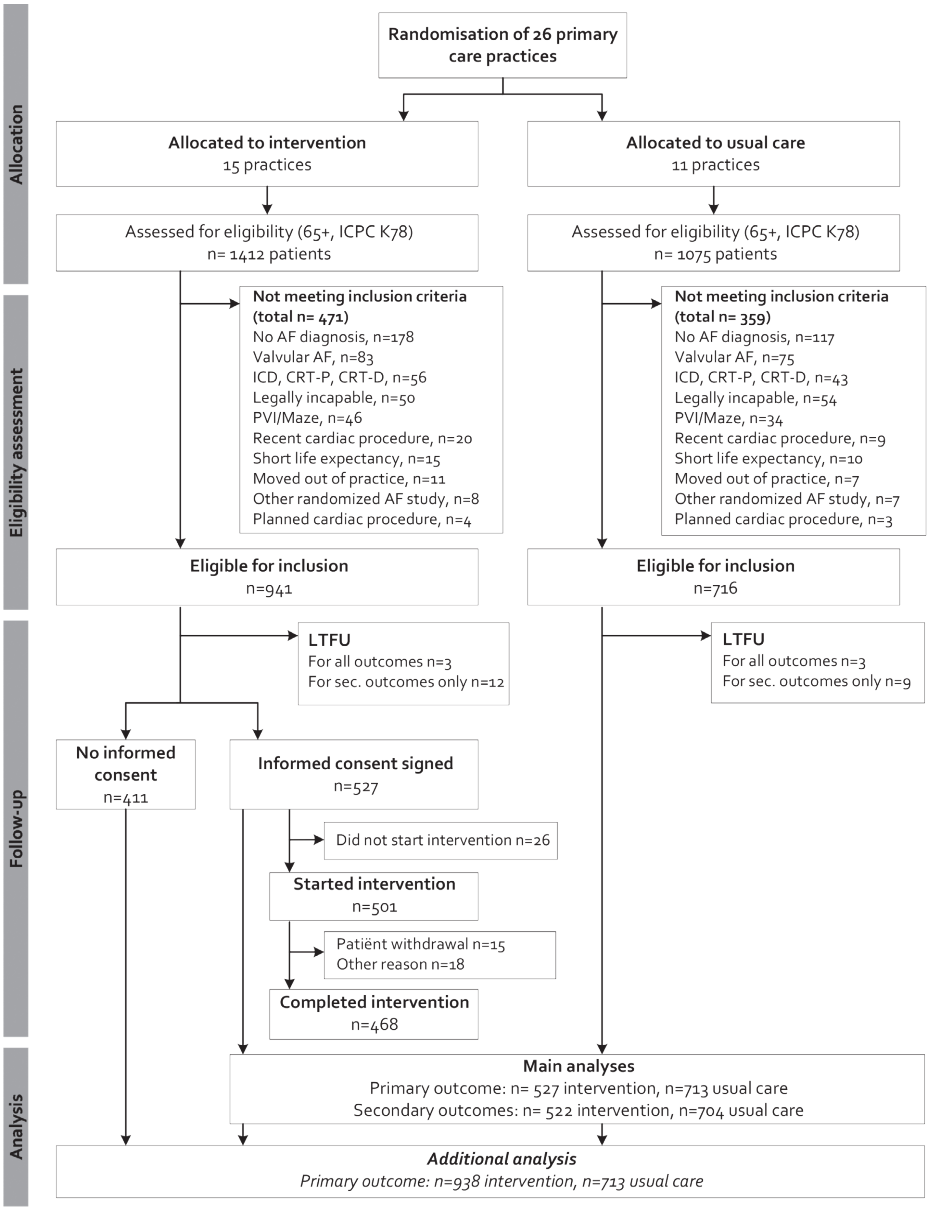
Finally, to assess the robustness of our findings and the impact of potential selection bias due to asking informed consent for the intervention after randomisation, we performed a pre-planned, additional analysis for our primary outcome comparing *all* eligible control patients to *all* eligible intervention patients, including also those patients who did not sign informed consent to undergo the intervention. Survival analyses were performed in *R* version 3.4.1.[22] with package *survival* version 2.42-3 [23], and quality of life questionnaires were analysed in SAS for Windows, version 9.4.

RESULTS

Baseline characteristics

A total of 119 practices were informed about the trial, of which 26 practices decided to participate. Between October 2015 and January 2017, these 26 practices were randomised (see flowchart, *Figure 1*). Within these 26 practices, 1657 (66.6%) out of 2487 AF patients were eligible for inclusion. Fifteen practices were randomised to the intervention arm, involving 32 GPs and 28 practice nurses. In these intervention practices, 527 (56.0%) of the eligible patients provided informed consent for participation in the intervention and were included in our main analyses. The median cluster size in the intervention arm was 29 patients (interquartile range (IQR) 25-46). In the control arm, all eligible patients (n=716) were analysed and median cluster size was 53 patients (IQR 45-75). All practices completed at least 2 years of follow-up, ending between April 2018 and March 2019. The uptake and persistence of performing the intervention were high; there was no drop-out of intervention practices and 93% of the patients who started the intervention completed it.

FIGURE 1. FLOWCHART OF THE ALL-IN CLUSTER RANDOMISED TRIAL



CRT-P/D, cardiac resynchronisation therapy pacemaker/defibrillator; ICD, implantable cardioverter defibrillator; ICPC K78, International Classification of Primary Care code for atrial fibrillation; LTFU, lost to follow-up; PVI, pulmonary vein isolation.

TABLE 1. BASELINE CHARACTERISTICS OF INCLUDED PATIENTS

		Integrated care (n = 527)	Usual care (n = 713)	*P*-value
Age (years), median (IQR)		76 (71-81)	78 (73-84)	<0.001
Female sex		239 (45.4)	374 (52.5)	0.016
Years since AF diagnosis, median (IQR)		4.3 (2.1-7.4)	4.0 (2.0-8.4)	0.177
Quality of life	*Median PCS (IQR)*	42.6 (33.6-50.4)	40.6 (32.7-48.7)	0.351
	Median MCS (IQR)	52.8 (45.5-57.4)	52.3 (44.0-57.4)	0.376
Hypertension		311 (59.0)	389 (54.6)	0.132
Diabetes mellitus		131 (24.9)	185 (25.9)	0.712
Prior stroke/TIA		84 (15.9)	95 (13.3)	0.225
Coronary artery disease		93 (17.6)	120 (16.8)	0.764
Prior myocardial infarction		36 (6.8)	50 (7.0)	0.991
Heart failure		72 (13.7)	136 (19.1)	0.015
Peripheral vascular disease		36 (6.8)	48 (6.7)	1.000
Prior venous thromboembolism		25 (4.7)	30 (4.2)	0.754
Chronic renal impairment		59 (11.2)	110 (15.4)	0.039
Chronic obstructive pulmonary disease		73 (13.9)	99 (13.9)	1.000
History of cancer		95 (18.0)	131 (18.4)	0.935
Pacemaker		34 (6.5)	62 (8.8)	0.171
Frailty index, median (IQR)		0.14 (0.11-0.22)	0.17 (0.11-0.19)	0.577
Polypharmacy (≥5 chronic drugs)		134 (25.4)	140 (19.6)	0.018
Anticoagulant use	*VKA*	390 (74.0)	571 (80.1)	0.014
	NOAC	84 (15.9)	80 (11.2)	0.019
	None	53 (10.1)	62 (8.7)	0.473
	Undertreatment	44 (8.3)	45 (6.3)	0.203
Antiplatelet therapy		48 (9.1)	51 (7.2)	0.250
Beta-blockers		378 (71.7)	522 (73.2)	0.606
Calcium channel antagonists		150 (28.5)	182 (25.5)	0.276
Digoxin		97 (18.4)	137 (19.2)	0.775
Class I and III antiarrhythmic drugs		32 (6.1)	52 (7.3)	0.464
Diuretics		198 (37.6)	341 (47.8)	<0.001
RAAS-inhibitors		279 (52.9)	400 (56.1)	0.295

Numbers are counts (%) unless stated otherwise. The frailty index consists of the presence or absence of 36 health deficit items (scale 0-1, higher value indicating more frailty), see text. [a]Undertreatment was defined as no oral anticoagulant prescription in the 12 months prior to baseline, despite a CHA_2DS_2-VASc score of 2 or more and in the absence of only a single AF episode following cardiac surgery. IQR, interquartile range; MCS, mental health component score (scale 0-100, higher score indicating better HRQoL); NOAC, non-vitamin K antagonist oral anticoagulant; PCS, physical health component score (scale 0-100, higher score indicating better HRQoL); RAAS, renin-angiotensin-aldosterone system; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Baseline characteristics are shown in Table 1. Median age was 77 years. Some differences in baseline characteristics between both groups were observed, although not consistently in favour of one of the treatment arms. At baseline, 78% of all included patients used a VKA. The proportion of patients not receiving anticoagulant therapy despite having an indication was low in both arms (8.3% vs. 6.3% in the intervention and control arm, respectively). Baseline characteristics of patients in the intervention arm who did not give informed consent to undergo the intervention are shown in the Supplementary material, *Appendix Section C*, as are the baseline characteristics per practice.

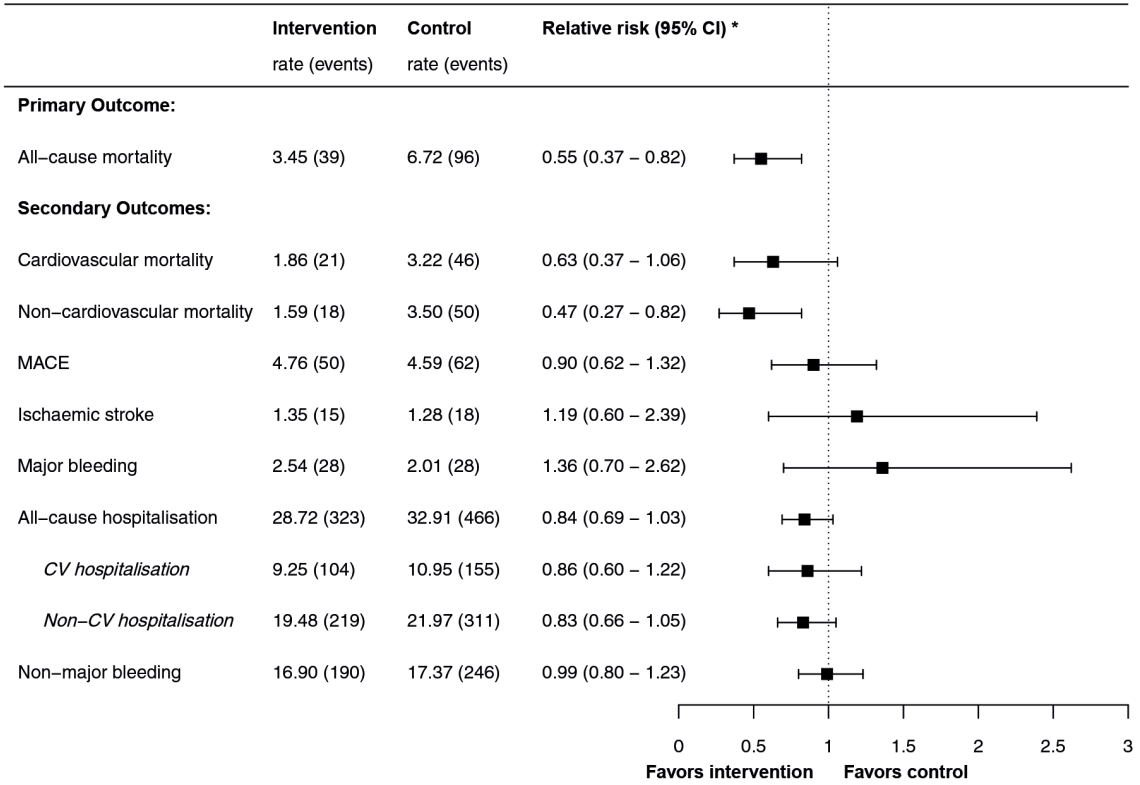
Primary outcome

During a median follow-up time of 2.3 years in the intervention arm and 2.2 years in the control arm, 39 patients in the intervention arm and 96 patients in the control arm died (7.4% and 13.5%, respectively). Incidence rates and crude and adjusted HRs are presented in the Supplementary material, *Appendix Section D*. The HR for all-cause mortality, after adjustment for age, sex, and FI, was 0.55 (95% confidence interval (CI) 0.37 to 0.82, *Figure 2*). The cumulative event plot is shown in *Figure 3*. When we repeated the analysis including the 411 patients who did not sign informed consent for participation in the intervention arm, the effect was attenuated but a reduction in all-cause mortality was still observed (adjusted HR 0.81 (95% CI 0.61 to 1.07)), though the CI overlapped with 1.0.

Secondary outcomes

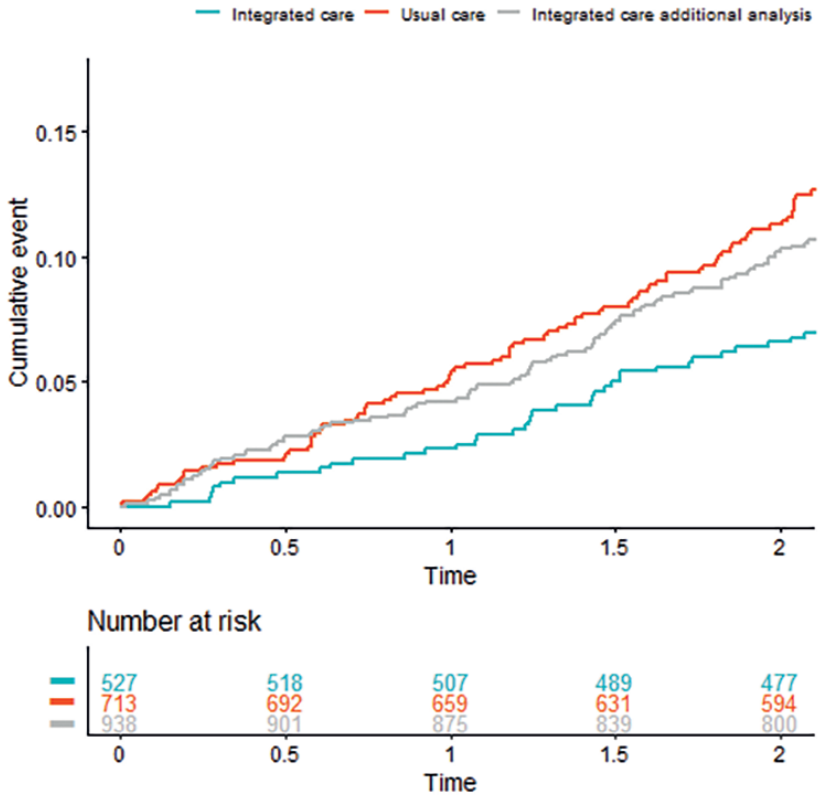
Figure 2 shows the results of Cox survival analyses for the secondary outcomes cardiovascular mortality, non-cardiovascular mortality, MACE, ischaemic stroke, and major bleeding, and the results of the negative binomial regression analyses for the *recurrent* events hospitalisation and CRNMB. Event rates, crude and adjusted HRs, and incidence rate ratios (IRR) are displayed in the Supplementary material, *Appendix Section D*. As for cause-specific mortality, risk reduction of non-cardiovascular mortality in intervention practices was more pronounced than risk reduction of cardiovascular mortality (adjusted HR for non-cardiovascular mortality 0.47 (95% CI 0.27 to 0.82), compared to adjusted HR 0.63 (95% CI 0.37 to 1.06) for cardiovascular mortality). A table with the occurrence of the different cardiovascular and non-cardiovascular causes of death is shown in the Supplementary material, *Appendix Section E*.

FIGURE 2. FOREST PLOT OF COX REGRESSION ANALYSES OF PRIMARY AND SECONDARY OUTCOMES, AND RECURRENT EVENTS ANALYSES OF HOSPITALISATION AND CLINICALLY RELEVANT NON-MAJOR BLEEDING



Rates are incidence rates per 100 person years. *Relative risks are adjusted hazard ratios, except for the recurrent events hospitalisations and clinically relevant non-major bleeding which are adjusted incidence rate ratios (adjusted for age, sex, frailty index and accounted for clustering). CV, cardiovascular.

FIGURE 3. CUMULATIVE EVENT PLOT ALL-CAUSE MORTALITY



The red and blue lines represent the cumulative events for all-cause mortality of the 713 patients in the usual care arm and the 527 patients who gave informed consent in the intervention arm, respectively (main analysis). The grey line represents the integrated care arm when including also the 411 patients who did not sign informed consent to participate in the intervention (additional analysis).

Hospitalisations occurred frequently in both treatment arms: during follow-up, in total 38% of patients had at least one hospital admission and 16% had at least two hospital admissions. Non-cardiovascular hospitalisation occurred twice as frequently as cardiovascular hospitalisation. The number of all-cause hospital admissions was 16% lower in the intervention arm, albeit the 95% CI overlapped with 1.0 (adjusted IRR 0.84; 95% CI 0.69 to 1.03). This effect was similar for cardiovascular and non-cardiovascular hospitalisations.

No statistically significant differences were observed for the outcomes MACE, CRNMB, ischaemic stroke, and major bleeding. However, numbers of events for ischaemic stroke and major bleeding were particularly small. Changes between baseline and

follow-up in HRQoL were minimal in both arms. The intervention arm experienced a 0.95 point decrease on the physical health component score (ranging from 0 to 100) over 2 years of follow-up vs. a 1.51 point decrease in the control arm (P = 0.130). For the mental health component score, this was a 2.04 vs. 0.75 points decrease (P = 0.517).

Although we did not have complete data on number of consultations and medication changes, we observed that the mean number of GP consultations per patient during 2.2 years of follow-up was 24.2 in the intervention arm and 15.2 in the usual care arm (data available from 19 out of 26 practices). In the intervention arm, 10.2% of patients switched from VKA to NOAC, compared to 5.9% in the usual care arm (data available from 11 out of 26 practices).

DISCUSSION

Statement of principal findings

In this large cluster randomised trial, we studied the effect of integrated care for AF patients in primary care. Compared to usual care, this integrated care approach delivered by GPs and practice nurses significantly reduced all-cause mortality by 45% (95% CI 0.37 to 0.82).

Strengths and weaknesses of the study

This is the first study showing effectiveness of structured AF management in primary care. Our results are generalizable to the large majority of AF patients who are on average of high age and preferably managed close to their homes. Our intervention may also be implemented in more rural areas, as it is predominantly provided by nurses and offers a more accessible alternative to the often greater travel distance to the nearest hospital. Other strengths are the low number of patients lost to follow-up and the high compliance rate in the intervention arm. For full appreciation, however, the following issues and limitations need to be discussed.

First, selection bias could have occurred, which is inherent to using a cluster randomised design with interventions delivered on an individual patient level.[18,24] As such, we anticipated the potential of such bias and performed pre-specified, adjusted analyses for age, sex, and frailty, which did not substantially change the effect estimate (crude vs. adjusted HR 0.51 (95% CI 0.33 to 0.76) and 0.55 (95% CI 0.37 to 0.82), respectively). Moreover, a cluster randomised design is the best option to assess the effects of integrated care interventions, because randomisation at the patient level would have

led to considerable contamination. Finally, in the additional analysis free from any potential selection bias and including the 411 patients who did not sign informed consent for participation in the intervention, the effect on mortality was attenuated (as expected, as almost half of these patients did not participate in the intervention) but remained in favour of the intervention (HR 0.81, 95% CI 0.61 to 1.07).

Second, we did not have information on echocardiographic parameters, NT-proBNP levels, and type of AF (paroxysmal, persistent, or permanent). This information could be informative in understanding why and in whom integrated AF care is most beneficial and should be incorporated in future studies.

Finally, the substitution of care from cardiologist to primary care was less than expected: 41% of intervention patients and 48% of the control patients had routine cardiologist control visits during follow-up. Thus, it is likely that many intervention patients received extra care due to the intervention, on top of care from cardiologists or instead of no previous AF-care. This could explain part of the observed effect and also exemplifies that modern, integrated AF management should be shared care between primary care, cardiologists and coagulation experts, across clinical boundaries.

Comparison with existing literature

Previous research, notably the RACE 4 study and the study by Hendriks *et al.*,[3,4,17] studied the effect of integrated care in secondary or tertiary care. In *hospital care*, patients typically differ from those managed in primary care, as is reflected in the baseline characteristics. For instance, our primary care study population was on average 10 years older than the population studied in a systematic review on integrated AF care in tertiary care (mean age 77.4 vs. 66.9 years)[3] and more often suffered from comorbidities. Furthermore, contrary to many younger patients in the hospital setting who receive rhythm control therapy (e.g. ablation procedures), treatment in our study population was typically focused on chronic disease management. Such differences notwithstanding, Hendriks *et al.*[17] found a similar reduction in their primary outcome, i.e. a 35% reduction of the risk of the composite outcome of cardiovascular hospitalisation and cardiovascular death. Our findings are also in line with the exploratory analysis of the RACE 4 trial showing a favourable effect of nurse-led care, albeit only in experienced centres (HR 0.52; 95% CI 0.37 to 0.71). As the authors state, this emphasizes the importance of training and a focus on team-based integrated care approaches.[4]

Clinical implications

As with any so-called 'complex intervention', an interesting question is *which aspect* of the intervention mostly explains the reduction in mortality. While our study was not set-up to address this question, we can hypothesise about the main drivers of the effect. In general, we believe that the protocolled primary care approach including training of practice nurses in AF management and early recognition of clinical deterioration or complications, such as heart failure, was paramount for the observed effect on all-cause mortality. This is exemplified by the fact that *urgent* hospitalisation occurred less frequently in our intervention arm, which was shown in a post-hoc exploratory analysis (adjusted IRR 0.79; 95% CI 0.63 to 1.00).

Additionally, repeated focus on cardiovascular risk management, including management of hypertension and lipid levels, may have contributed. Comprehensive and structured management seem to be important drivers of the beneficial effects, as these were common aspects of both our study and the previously mentioned studies on integrated AF care that also showed positive results.[4,17] The RACE 3 trial showed, as a proof of concept, that addressing classical cardiovascular risk factors has beneficial effects on 'AF progression', defined as the proportion of time in sinus rhythm.[25]

Furthermore, the beneficial effect in our study was more pronounced for non-cardiovascular mortality, likely because cardiovascular and non-cardiovascular causes of death are often interrelated. For example, a patient dying from pneumonia might have survived if his underlying heart failure or AF had been better controlled. Moreover, during the INR check-ups, patients were routinely asked about factors like pain or fever. Therefore, it can be hypothesised that during the INR check-ups, patients also mentioned symptoms of non-cardiovascular nature that might have led to, for instance, earlier detection of cancer or pneumonia. As can be seen in the Supplementary material, *Appendix E*, the benefit was evenly distributed across the different causes of death (except for death from major bleeding, for which no benefit was observed).

Finally, the easy accessibility of the primary care practice for patients[26] and the integrated anticoagulation monitoring with direct feedback of the INR value, all contributing to patient education and adherence, could have been beneficial. The absence of an effect on ischaemic stroke and bleeding outcomes suggests that the reduction in all-cause mortality is unlikely to be explained by better anticoagulation management in the intervention arm. Prompted by this observation, the largest of the three involved anticoagulation clinics performed a post hoc analysis of the time in therapeutic range of patients using a VKA in their region, which was similar between

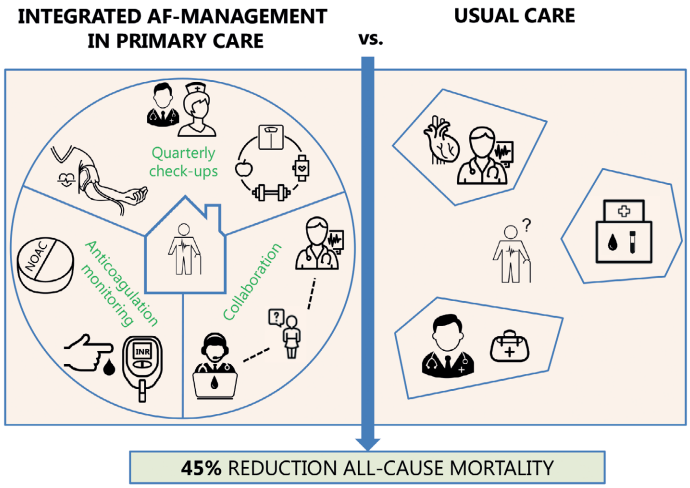
intervention and control patients (68.2% vs. 68.1%, respectively), thus strengthening this conclusion. Of note, the relatively low proportion of patients receiving NOAC treatment is at least partly due to the fact that GPs in the Netherlands were not allowed to initiate a NOAC before August 2016. In addition, the 2017 Dutch College of General Practitioners' guidelines on AF does not encourage to switch stable AF patients from VKA to NOAC and recommend to be reticent in prescribing NOACs to frail elderly patients given the lack of evidence from randomised trials for this population.[13] However, background information on NOAC use was provided to the intervention practices as part of the education and more patients switched to NOAC treatment in the index arm compared to the control arm (10.2% vs. 5.9%, respectively, based on data of 11 out of 26 practices). Further research is needed to explore the specific and relative components of integrated AF care that contribute most in reducing clinical adverse outcomes. Also, a thorough cost-effectiveness analysis is warranted, which we plan to publish separately.

Currently, no benefit on mortality has yet been shown in AF trials investigating single-faceted interventions, like anti-arrhythmic drugs or ablation techniques (except in AF patients with severe heart failure).[27–29] Although these interventions importantly do impact HRQoL, our findings offer extra arguments for the view that AF is not merely a hearth rhythm disorder, but rather part of a systemic condition.[2] Although the exact underlying substrate and pathophysiology are currently being unravelled, a focus on integrated care with treatment of underlying comorbidities like obesity and hypertension seems beneficial, especially in elderly patients.[30–32]

Conclusion

In this cluster randomised pragmatic trial, we observed a reduction of 45% on all-cause mortality by providing integrated care for elderly AF patients primarily in primary care, compared to usual care.

TAKE HOME FIGURE OF THE ALL-IN TRIAL



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CONFLICT OF INTEREST

GJG and FHR report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer, and Daiichi Sankyo. All other authors report no competing interests.

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APPENDIX A

DETAILED DESCRIPTION OF THE INTERVENTION IN COMPARISON TO USUAL CARE

	Integrated care intervention in primary care	Usual care
Description	**1. Quarterly follow-up visits:** Proactive, structured face-to-face check-ups for AF treatment and treatment and prevention of cardiovascular and non-cardiovascular comorbidities, according to a check-list (see appendix) based on Dutch primary care guidelines on AF and ESC guidelines. Visits included special attention to detection of signs of heart failure, adequate rate control, evaluation of the need for laboratory testing or ECG (available within the primary care practices), lifestyle improvement and patient education/empowerment. **2. Tailored anticoagulation monitoring:** *In VKA patients:* regular INR measurements in the primary care practice or if necessary at home. The INR value was measured from a capillary blood sample with the Coaguchek® and communicated together with information on important interacting factors (e.g. fever, pain, medication or dietary changes) to the anticoagulation clinic through an online portal. The anticoagulation clinic acted like a 'back-office' and created the dosage calendar that was sent back to the primary care practice or to the patient. Some patients measured the INR themselves at home. *In NOAC patients:* adherence, patient education, and kidney function monitoring were part of the checklist of the quarterly follow-up visits. **3. Close collaboration with specialists:** Cardiologists and anticoagulation clinics were easily accessible for consultation. At the start of follow-up, cardiologists were asked to evaluate if the patient could be discharged from outpatient cardiology care or not. If not, cardiology care was complementary to the integrated care intervention in primary care.	Variable and delivered by different health care professionals (cardiologists, specialised AF nurses, anticoagulation clinics, general practitioners, practice nurses), without one designated coordinator (see text). Some patients did not receive any care during follow-up. In VKA patients, INR measurements were performed by anticoagulation clinics by venepuncture. Some patients measured the INR themselves at home.

CONTINUED

	Integrated care intervention in primary care	Usual care
When and how much	Prescheduled quarterly follow-up visits to the primary care practice (3 times a year with practice nurse, once yearly with GP). In addition, VKA-patients received INR measurements, about 20 times a year.	Usually ad-hoc visits to the GP when symptoms have developed. In some patients pre-planned visits to the cardiology outpatient service once or twice a year. VKA-patients received INR measurements, on average about 20 times a year.
Who provided AF care	The practice nurse, supervised by the GP, was the predominant deliverer of integrated AF care. To ensure continuity during holidays for example, practice assistants were also trained to perform INR measurements.	Variable (cardiologists, specialised AF nurses, GPs, practice nurses, anticoagulation clinic personnel, or no one).
Training	At the start of the trial, participating practice nurses, assistants and general practitioners received 4 hours of training, given by the corresponding author, cardiologists, and the anticoagulation clinic. Education included treatment of AF and its related comorbidities, anticoagulation monitoring (including information on when to perform extra INR measurements) and referral criteria. Evaluation meetings were organised 3 times during the 2 year follow-up, to share knowledge, practical issues and interesting or complicated cases.	No specific training about AF. In the Netherlands, practice nurses have a post-bachelor degree in chronic disease management of diabetes, COPD and cardiovascular risk management, yet without specific attention to AF.
Initiator/ coordinator of care	The practice nurse.	Usually the patient (and/or cardiologist when treated in out-patient cardiology clinic, and/or anticoagulation clinic).

CONTINUED

	Integrated care intervention in primary care	Usual care
Scope of care	Holistic.	AF-focused.
Location of care delivery	Primary care practice (or when necessary at the patient's home).	Variable (out-patient cardiology clinic, anticoagulation clinic, primary care practice).
Responsibility	Shared responsibility, but primarily the GP (although anticoagulation clinics remained responsible for the VKA dosing calendar).	Often unclear or variable (cardiologist, GP, anticoagulation clinic).
Patient education	Information on AF, complications, importance of adherence to anticoagulants and when to contact the primary care practices were given to all eligible patients by the GP during the recruitment visit. In large practices we organised an information evening together with the practice. All eligible patients received a 15 page booklet with information on AF and the trial. Importantly, patients actively participating in the intervention received education (especially on the importance of VKA/NOAC adherence) repeatedly during follow-up visits.	No specific patient education was provided.
Communication	Easy access communication was encouraged between patients, GPs and practice nurses within the practices; with the anticoagulation clinic through the online portal; and with cardiologists and specialised AF nurses in secondary care through telephone or pre-existing digital and secured communication systems.	No specific agreements were made regarding communication.
Clinical example of short lines of communication	A 90-year old AF patient is visited at home by her GP because of pneumonia. The GP prescribes an antibiotic and asks the practice nurse to perform an extra INR measurement that same day, which appeared to be too high. After consulting the anticoagulation clinic, vitamin K was prescribed and a short-term follow-up INR measurement was planned.	Some VKA users know that they should contact the anticoagulation clinic when they feel ill, but many patients only contact their GP. Out-of-range INR levels are then only detected during regular INR measurements, or worse, when a bleeding occurs.

GP, general practitioner; ESC, European Society of Cardiology; ECG, electrocardiography; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; INR, International Normalized Ratio; COPD, chronic obstructive pulmonary disease.

Checklist quarterly follow-up visits

During each quarterly follow-up visit:

- Measurements (also to compare with previous measurements):
  - *Blood pressure:* systolic target value <140 mmHg. In patients aged 80 or over: <150-160 mmHg. Always measure manually instead of digitally in patients with AF.
  - *Heart frequency:* target value < 90 bpm at rest, or <110 bpm at mild exertion.
  - *Body weight:* stable? Increasing weight can be an early sign of heart failure.
- Physical complaints? Ask/check specifically for:
  - *dyspnea*
  - *orthopnea (shortness of breath when lying down)*
  - *decreased exercise tolerance*
  - *palpitations*
  - *dizziness/fainting*
  - *fluid retention/peripheral edema*
  - *chest pain*
  - *neurological symptoms (TIA/stroke)*
  - *bleeding/hematomas*
- Ask for adherence to drugs (especially in NOAC patients) and side effects from drugs.
- Can pharmacological therapy be optimized? For example: lowering heart frequency/blood pressure, indication for proton pump inhibitor or NOAC dose reduction in case of decreased kidney function.
- Has the indication for oral anticoagulation changed? For example, did the CHA_2DS_2-VASc score increase from 1 to 2 or more?
- Can lifestyle be improved? For example regarding alcohol intake, salt intake, smoking, exercise, stress.
- Can care for comorbidity be improved? For example hypertension, diabetes, heart failure, COPD, OSAS.
- Are there any invasive procedures planned that require temporary discontinuation of anticoagulation?
- In patients with an impaired kidney function and a NOAC: check kidney function every 6 months.
- In patients using amiodarone: check thyroid-stimulating hormone (TSH) and liver enzymes every 6 months
- Are there any questions for the cardiologist or anticoagulation clinic?

Extra during yearly GP visit:

- Physical examination:
  - Auscultation heart and lungs: increased or new heart murmur? Crackles?
  - Peripheral edema?
- Indication for laboratory testing?
  - NOAC: kidney function (at least once yearly, but in case of pre-existent MDRD<60 ml/min of dabigatran every 6 months)
  - Digoxin: kidney function and potassium, digoxin level if indicated.
  - Amiodaron: thyroid-stimulating hormone (TSH) and liver enzymes every 6 months. Once yearly a chest X-ray to check for interstitial fibrosis.
  - If indicated: Hemoglobin, glucose, cholesterol spectrum, liver enzymes, (NT-pro)BNP.
- Indication for echocardiographic examination?
- Indication for ECG/holter monitoring? In case of a pulse deficit, adequate rate-control can is better assessed by ECG or holter monitoring than by manually checking the pulse.

In particular during first visit:

- Explain to the patient what atrial fibrillation entails
- Explain about the increased risk of stroke, the need for anticoagulation and the importance of adherence.
- Explain about factors that might trigger paroxysms of AF and about the importance of a healthy lifestyle.
- Explain about rate control (or in some patients: rhythm control).
- Explain when the patient should contact the practice (in case of symptoms of a TIA/stroke, bleeding, dyspnea or fluid retention/edema)

APPENDIX B

Outcome definitions

Cardiovascular death: death due to acute myocardial infarction, heart failure, systemic embolism, intracranial bleeding (all fatal major bleedings were in fact intracranial), ischaemic stroke, severe arrhythmic events, or sudden death without any further information.

Non-cardiovascular death: malignancy (direct or indirect), infection and other causes of death not classified as cardiovascular.

Cardiovascular hospitalisation: hospital admission with at least one overnight stay for heart failure, ischaemic stroke or transient ischaemic attack (TIA), MACE (including acute coronary syndrome, acute arrhythmic events and cardiac tamponade), pericarditis, systemic embolism, major bleeding, life-threatening adverse effects of cardiovascular drugs, or invasive cardiac therapy (for instance valvular surgery, ablation therapy, or pacemaker implantation).

MACE: acute coronary syndrome (myocardial infarction or instable angina pectoris), acute arrhythmic events (including electric cardioversion or cardioversion through administration of intravenous antiarrhythmic drugs) or cardiac tamponade.

Stroke: ischaemic stroke as concluded in the imaging report or discharge letter by a neurologist.

APPENDIX C

BASELINE CHARACTERISTICS INCLUDING PATIENTS WHO DID NOT SIGN INFORMED CONSENT FOR THE INTERVENTION

	Integrated care		Usual care (n = 713)
	No informed consent (n = 411)	With informed consent (n = 527)	
Age, median (IQR)	78 (72-84)	76 (71-81)	78 (73-84)
Female sex	217 (52.8)	239 (45.4)	374 (52.5)
Hypertension	261 (63.5)	311 (59.0)	389 (54.6)
Diabetes mellitus	98 (23.8)	131 (24.9)	185 (25.9)
Previous stroke/TIA	65 (15.8)	84 (15.9)	95 (13.3)
Coronary artery disease	90 (21.9)	93 (17.6)	120 (16.8)
Myocardial infarction	41 (10.0)	36 (6.8)	50 (7.0)
Congestive heart failure	76 (18.5)	72 (13.7	136 (19.1)
Peripheral vascular disease	35 (8.5)	36 (6.8)	48 (6.7)
Previous venous thromboembolism	18 (4.4)	25 (4.7)	30 (4.2)
Chronic renal impairment	51 (12.4)	59 (11.2)	110 (15.4)
COPD	41 (10.0)	73 (13.9)	99 (13.9)
History of cancer	98 (23.8)	95 (18.0)	131 (18.4)
Pacemaker	52 (12.9)	34 (6.5)	62 (8.8)
Frailty Index, median (IQR)	0.17 (0.11-0.22)	0.14 (0.11-0.22)	0.17 (0.11-0.19)
Polypharmacy (≥5 chronic drugs)	96 (23.4)	134 (25.4)	140 (19.6)
Anticoagulant use *VKA*	297 (72.3)	390 (74.0	571 (80.1)
NOAC	51 (12.4)	84 (15.9)	80 (11.2)
None	63 (15.3)	53 (10.1)	62 (8.7)
*Undertreatment**	52 (12.7)	44 (8.3)	45 (6.3)
Antiplatelet therapy	34 (8.3)	48 (9.1)	51 (7.2)
Beta-blockers	266 (64.7)	378 (71.7)	522 (73.2)

CONTINUED

	Integrated care		Usual care (n = 713)
	No informed consent (n = 411)	**With informed consent (n = 527)**	
Calcium channel antagonists	97 (23.6)	150 (28.5)	182 (25.5)
Digoxin	85 (20.7)	97 (18.4)	137 (19.2)
Class I and III antiarrhythmic drugs	19 (4.6)	32 (6.1)	52 (7.3)
Diuretics	169 (41.1)	198 (37.6)	341 (47.8)
RAAS-inhibitors	212 (51.6	279 (52.9)	400 (56.1)

Numbers are counts(%) unless stated otherwise. IQR = interquartile range; TIA = transient ischaemic attack; VKA = vitamin K antagonist; NOAC = non vitamin K antagonist oral anticoagulant, RAAS = Renin-angiotensin-aldosterone system. The Frailty Index consists of the presence or absence of 36 health deficit items, see text. Undertreatment was defined as no oral anticoagulant prescription in the 12 months prior to baseline, despite a CHA_2DS_2-VASc score of 2 or more and in the absence of only a single AF episode following cardiac surgery.

* Undertreatment is defined as patients not using anticoagulants, while indicated

BASELINE CHARACTERISTICS PER CONTROL PRACTICE

Control practice number		1	2	3	4	5
N patients		53	74	47	24	75
Age (median, IQR)		79 (73-85)	78.5 (73-83)	79 (74.5-82)	79 (70-83.3)	82 (76.5-86.5)
Female sex		33 (62.3)	42 (56.8)	30 (63.8)	16 (66.7)	47 (62.7)
Hypertension		28 (52.8)	40 (54.1)	27 (57.4)	12 (50.0)	64 (85.3)
Diabetes mellitus		21 (39.6)	15 (20.3)	10 (21.3)	7 (29.2)	27 (36.0)
Prior stroke/TIA		11 (20.8)	15 (20.3)	3 (6.4)	3 (12.5)	11 (14.7)
Coronary artery disease		10 (18.9)	14 (18.9)	12 (25.5)	1 (4.2)	26 (34.7)
Prior myocardial infarction		3 (5.7)	9 (12.2)	1 (2.1)	0 (0.0)	13 (17.3)
Heart failure		15 (28.3)	17 (23.0)	15 (31.9)	1 (4.2)	25 (33.3)
Peripheral vascular disease		3 (5.7)	7 (9.5)	1 (2.1)	0 (0.0)	12 (16.0)
Prior venous thromboembolism		2 (3.8)	5 (6.8)	1 (2.1)	1 (4.2)	1 (1.3)
Chronic renal impairment		4 (7.5)	18 (24.3)	6 (12.8)	1 (4.2)	18 (24.0)
Chronic obstructive pulmonary disease		3 (5.7)	9 (12.2)	10 (21.3)	2 (8.3)	15 (20.0)
History of cancer		9 (17.0)	17 (23.0)	8 (17.0)	8 (33.3)	13 (17.3)
Pacemaker		5 (10.0)	7 (9.9)	3 (6.4)	2 (8.3)	7 (9.3)
Frailty Index, median (IQR)		0.14 (0.11-0.19)	0.17 (0.11-0.19)	0.14 (0.08-0.17)	0.17 (0.14-0.19)	0.22 (0.17-0.29)
Polypharmacy (≥5 chronic drugs)		2 (3.8)	9 (12.2)	30 (63.8)	15 (62.5)	36 (48.0)
Anticoagulant use	*VKA*	46 (86.8)	66 (89.2)	42 (89.4)	19 (79.2)	61 (81.3)
	NOAC	2 (3.8)	4 (5.4)	1 (2.1)	1 (4.2)	5 (6.7)
	None	5 (9.4)	4 (5.4)	4 (8.5)	4 (16.7)	9 (12.0)

CONTINUED

Control practice number	1	2	3	4	5
Antiplatelet therapy	3 (5.7)	3 (4.1)	3 (6.4)	3 (12.5)	12 (16.0)
Beta-blockers	40 (75.5)	54 (73.0)	37 (78.7)	14 (58.3)	54 (72.0)
Calcium channel antagonists	16 (30.2)	17 (23.0)	11 (23.4)	11 (45.8)	19 (25.3)
Digoxin	12 (22.6)	12 (16.2)	8 (17.0)	1 (4.2)	10 (13.3)
Class I and II antiarrhythmic drugs	8 (15.1)	5 (6.8)	3 (6.4)	1 (4.2)	13 (17.3)
Diuretics	29 (54.7)	41 (55.4)	25 (53.2)	13 (54.2)	42 (56.0)
RAAS-inhibitors	34 (64.2)	42 (56.8)	25 (53.2)	12 (50.0)	42 (56.0)

Control practice number (continued)	6	7	8	9	10	11
N patients	72	81	44	157	45	41
Age (median, IQR)	77 (71-81.3)	79 (72-86)	75.5 (70-79.5)	76 (73-83)	80 (72-84)	74 (71-81)
Female sex	38 (52.8)	37 (45.7)	22 (50.0)	71 (45.2)	20 (44.4)	18 (43.9)
Hypertension	25 (34.7)	37 (45.7)	38 (86.4)	70 (44.6)	31 (68.9)	17 (41.5)
Diabetes mellitus	12 (16.7)	21 (25.9)	12 (27.3)	44 (28.0)	10 (22.2)	6 (14.6)
Prior stroke/TIA	11 (15.3)	13 (16.0)	1 (2.3)	20 (12.7)	5 (11.1)	2 (4.9)
Coronary artery disease	12 (16.7)	14 (17.3)	6 (13.6)	22 (14.0)	2 (4.4)	1 (2.4)
Prior myocardial infarction	7 (9.7)	6 (7.4)	1 (2.3)	8 (5.1)	0 (0.0)	2 (4.9)
Heart failure	9 (12.5)	20 (24.7)	5 (11.4)	14 (8.9)	9 (20.0)	6 (14.6)
Peripheral vascular disease	5 (6.9)	3 (3.7)	5 (11.4)	8 (5.1)	2 (4.4)	2 (4.9)
Prior venous thromboembolism	2 (2.8)	4 (4.9)	3 (6.8)	8 (5.1)	1 (2.2)	2 (4.9)

CONTINUED

Control practice number (continued)		6	7	8	9	10	11
Chronic renal impairment		21 (29.2)	10 (12.3)	7 (15.9)	13 (8.3)	6 (13.3)	6 (14.6)
Chronic obstructive pulmonary disease		9 (12.5)	13 (16.0)	7 (15.9)	15 (9.6)	7 (15.6)	9 (22.0)
History of cancer		10 (13.9)	14 (17.3)	7 (15.9)	28 (17.8)	8 (17.8)	9 (22.0)
Pacemaker		7 (9.7)	9 (11.1)	4 (9.1)	14 (9.0)	1 (2.3)	3 (7.3)
Frailty Index, median (IQR)		0.14 (0.11-0.22)	0.17 (0.14-0.22)	0.17 (0.11-0.22)	0.14 (0.08-0.19)	0.11 (0.08-0.17)	0.11 (0.08-0.17)
Polypharmacy (≥5 chronic drugs)		38 (52.8)	2 (2.5)	1 (2.3)	5 (3.2)	1 (2.2)	1 (2.4)
Anticoagulant use	*VKA*	63 (87.5)	73 (90.1)	28 (63.6)	118 (75.2)	30 (66.7)	25 (61.0)
	NOAC	3 (4.2)	4 (4.9)	7 (15.9)	31 (19.7)	9 (20.0)	13 (31.7)
	None	6 (8.3)	4 (4.9)	9 (20.5)	8 (5.1)	6 (13.3)	3 (7.3)
Antiplatelet therapy		6 (8.3)	9 (11.1)	2 (4.5)	8 (5.1)	1 (2.2)	1 (2.4)
Beta-blockers		53 (73.6)	58 (71.6)	26 (59.1)	122 (77.7)	35 (77.8)	29 (70.7)
Calcium channel antagonists		15 (20.8)	19 (23.5)	12 (27.3)	37 (23.6)	14 (31.1)	11 (26.8)
Digoxin		17 (23.6)	20 (24.7)	9 (20.5)	33 (21.0)	12 (26.7)	3 (7.3)
Class I and II antiarrhythmic drugs		4 (5.6)	2 (2.5)	4 (9.1)	9 (5.7)	1 (2.2)	2 (4.9)
Diuretics		25 (34.7)	42 (51.9)	20 (45.5)	69 (43.9)	17 (37.8)	18 (43.9)
RAAS-inhibitors		28 (38.9)	47 (58.0)	24 (54.5)	99 (63.1)	23 (51.1)	24 (58.5)

BASELINE CHARACTERISTICS PER INTERVENTION PRACTICE

Intervention practice		1	2	3	4	5	6	7
N patients with informed consent		48	68	16	25	51	38	21
Age, median (IQR)		71 (75.5-80)	70.8 (75-80)	72.8 (77.5-84.5)	72 (79-81)	68.5 (75-79)	73.3 (76.5-80.8)	71 (75-80)
Female sex		21 (43.8)	29 (42.6)	10 (62.5)	14 (56.0)	22 (43.1)	13 (34.2)	11 (52.4)
Hypertension		37 (77.1)	32 (47.1)	11 (68.8)	14 (56.0)	36 (70.6)	18 (47.4)	6 (28.6)
Diabetes mellitus		12 (25.0)	12 (17.6)	8 (50.0)	9 (36.0)	13 (25.5)	11 (28.9)	6 (28.6)
Prior stroke/TIA		2 (4.2)	17 (25.0)	5 (31.2)	2 (8.0)	4 (7.8)	3 (7.9)	4 (19.0)
Coronary artery disease		7 (14.6)	7 (10.3)	4 (25.0)	3 (12.0)	3 (5.9)	10 (26.3)	5 (23.8)
Prior myocardial infarction		5 (10.4)	3 (4.4)	2 (12.5)	1 (4.0)	1 (2.0)	3 (7.9)	3 (14.3)
Heart failure		6 (12.5)	6 (8.8)	4 (25.0)	6 (24.0)	7 (13.7)	11 (28.9)	2 (9.5)
Peripheral vascular disease		3 (6.2)	3 (4.4)	0 (0.0)	1 (4.0)	4 (7.8)	0 (0.0)	1 (4.8)
Prior venous thromboembolism		1 (2.1)	1 (1.5)	2 (12.5)	0 (0.0)	1 (2.0)	2 (5.3)	1 (4.8)
Chronic renal impairment		7 (14.6)	4 (5.9)	2 (12.5)	0 (0.0)	5 (9.8)	4 (10.5)	4 (19.0)
Chronic obstructive pulmonary disease		11 (22.9)	4 (5.9)	1 (6.2)	3 (12.0)	6 (11.8)	7 (18.4)	1 (4.8)
History of cancer		8 (16.7)	10 (14.7)	4 (25.0)	4 (16.0)	12 (23.5)	8 (21.1)	3 (14.3)
Pacemaker		2 (4.3)	3 (4.4)	4 (25.0)	2 (8.0)	2 (3.9)	1 (2.6)	0 (0.0)
Frailty Index, median (IQR)		0.08 (0.11-0.17)	0.08 (0.11-0.17)	0.22 (0.31-0.38)	0.11 (0.14-0.19)	0.11 (0.14-0.19)	0.11 (0.17-0.19)	0.11 (0.14-0.19)
Polypharmacy (≥5 chronic drugs)		10 (20.8)	2 (2.9)	10 (62.5)	19 (76.0)	10 (19.6)	18 (47.4)	10 (47.6)
Anticoagulant use	*VKA*	41 (85.4)	55 (80.9)	11 (68.8)	25 (100.0)	35 (68.6)	31 (81.6)	19 (90.5)
	NOAC	4 (8.3)	5 (7.4)	3 (18.8)	0 (0.0)	7 (13.7)	5 (13.2)	2 (9.5)
	None	3 (6.2)	8 (11.8)	2 (12.5)	0 (0.0)	9 (17.6)	2 (5.3)	0 (0.0)

CONTINUED

Intervention practice	1	2	3	4	5	6	7
Antiplatelet therapy	7 (14.6)	5 (7.4)	3 (18.8)	3 (12.0)	3 (5.9)	4 (10.5)	1 (4.8)
Beta-blockers	40 (83.3)	54 (79.4)	9 (56.2)	24 (96.0)	31 (60.8)	29 (76.3)	19 (90.5)
Calcium channel antagonists	11 (22.9)	26 (38.2)	6 (37.5)	4 (16.0)	11 (21.6)	14 (36.8)	7 (33.3)
Digoxin	11 (22.9)	14 (20.6)	7 (43.8)	9 (36.0)	10 (19.6)	5 (13.2)	4 (19.0)
Class I and III antiarrhythmic drugs	0 (0.0)	5 (7.4)	1 (6.2)	1 (4.0)	0 (0.0)	2 (5.3)	3 (14.3)
Diuretics	24 (50.0)	26 (38.2)	12 (75.0)	14 (56.0)	12 (23.5)	15 (39.5)	6 (28.6)
RAAS-inhibitors	26 (54.2)	41 (60.3)	11 (68.8)	17 (68.0)	25 (49.0)	23 (60.5)	15 (71.4)

Intervention practice (continued)	8	9	10	11	12	13	14	15
N patients with informed consent	40	27	61	24	27	8	29	44
Age, median (IQR)	72 (76-82.3)	67 (72-79)	73 (77-81)	67 (70-73.3)	72 (77-81)	75.8 (78.5-79)	72 (77-83)	72.8 (78-84)
Female sex	20 (50.0)	11 (40.7)	31 (50.8)	8 (33.3)	12 (44.4)	1 (12.5)	15 (51.7)	21 (47.7)
Hypertension	25 (62.5)	17 (63.0)	39 (63.9)	18 (75.0)	16 (59.3)	2 (25.0)	19 (65.5)	21 (47.7)
Diabetes mellitus	8 (20.0)	3 (11.1)	18 (29.5)	6 (25.0)	8 (29.6)	2 (25.0)	8 (27.6)	7 (15.9)
Prior stroke/TIA	9 (22.5)	4 (14.8)	13 (21.3)	1 (4.2)	4 (14.8)	1 (12.5)	6 (20.7)	9 (20.5)
Coronary artery disease	3 (7.5)	5 (18.5)	17 (27.9)	11 (45.8)	4 (14.8)	1 (12.5)	5 (17.2)	8 (18.2)
Prior myocardial infarction	3 (7.5)	1 (3.7)	4 (6.6)	3 (12.5)	4 (14.8)	0 (0.0)	1 (3.4)	2 (4.5)
Heart failure	2 (5.0)	3 (11.1)	6 (9.8)	2 (8.3)	7 (25.9)	2 (25.0)	3 (10.3)	5 (11.4)
Peripheral vascular disease	1 (2.5)	5 (18.5)	4 (6.6)	3 (12.5)	5 (18.5)	1 (12.5)	1 (3.4)	4 (9.1)
Prior venous thromboembolism	1 (2.5)	1 (3.7)	3 (4.9)	2 (8.3)	6 (22.2)	2 (25.0)	0 (0.0)	2 (4.5)

CONTINUED

Intervention practice (continued)		8	9	10	11	12	13	14	15
Chronic renal impairment		3 (7.5)	8 (29.6)	7 (11.5)	2 (8.3)	5 (18.5)	2 (25.0)	4 (13.8)	2 (4.5)
Chronic obstructive pulmonary disease		4 (10.0)	2 (7.4)	11 (18.0)	4 (16.7)	6 (22.2)	4 (50.0)	2 (6.9)	7 (15.9)
History of cancer		5 (12.5)	6 (22.2)	8 (13.1)	7 (29.2)	4 (14.8)	2 (25.0)	3 (10.3)	11 (25.0)
Pacemaker		8 (20.0)	1 (3.7)	7 (11.5)	0 (0.0)	1 (3.7)	0 (0.0)	2 (6.9)	1 (2.5)
Frailty Index, median (IQR)		0.08 (0.10-0.17)	0.11 (0.17-0.25)	0.14 (0.22-0.28)	0.14 (0.19-0.24)	0.13 (0.19-0.25)	0.08 (0.15-0.23)	0.08 (0.14-0.19)	0.11 (0.14-0.19)
Polypharmacy (≥5 chronic drugs)		2 (5.0)	11 (40.7)	33 (54.1)	1 (4.2)	1 (3.7)	2 (25.0)	3 (10.3)	2 (4.5)
Anticoagulant use	*VKA*	25 (62.5)	17 (63.0)	44 (72.1)	13 (54.2)	20 (74.1)	5 (62.5)	23 (79.3)	26 (59.1)
	NOAC	11 (27.5)	5 (18.5)	11 (18.0)	4 (16.7)	6 (22.2)	1 (12.5)	5 (17.2)	15 (34.1)
	None	4 (10.0)	5 (18.5)	6 (9.8)	7 (29.2)	1 (3.7)	2 (25.0)	1 (3.4)	3 (6.8)
Antiplatelet therapy		0 (0.0)	3 (11.1)	8 (13.1)	3 (12.5)	1 (3.7)	1 (12.5)	1 (3.4)	5 (11.4)
Beta-blockers		32 (80.0)	17 (63.0)	34 (55.7)	16 (66.7)	22 (81.5)	3 (37.5)	13 (44.8)	35 (79.5)
Calcium channel antagonists		16 (40.0)	9 (33.3)	12 (19.7)	8 (33.3)	8 (29.6)	2 (25.0)	6 (20.7)	10 (22.7)
Digoxin		4 (10.0)	3 (11.1)	3 (4.9)	4 (16.7)	10 (37.0)	2 (25.0)	5 (17.2)	6 (13.6)
Class I and III antiarrhythmic drugs		4 (10.0)	4 (14.8)	8 (13.1)	1 (4.2)	1 (3.7)	0 (0.0)	0 (0.0)	2 (4.5)
Diuretics		18 (45.0)	8 (29.6)	12 (19.7)	6 (25.0)	12 (44.4)	4 (50.0)	9 (31.0)	20 (45.5)
RAAS-inhibitors		24 (60.0)	13 (48.1)	27 (44.3)	9 (37.5)	12 (44.4)	4 (50.0)	10 (34.5)	22 (50.0)

APPENDIX D

COX REGRESSION ANALYSES OF PRIMARY AND SECONDARY OUTCOMES

	Intervention n= 527	Usual care n= 713	Intervention vs usual care	
	IR per 100 py (n. events)	IR per 100 py (n. events)	Crude HR* (95% CI, p)	Adjusted HR** (95% CI, p)
All-cause mortality	3.45 (39)	6.72 (96)	0.51 (0.33-0.76, 0.001)	0.55 (0.37-0.82, 0.003)
Cardiovascular mortality	1.86 (21)	3.22 (46)	0.56 (0.33-0.94, 0.028)	0.63 (0.37-1.06, 0.080)
Non-cardiovascular mortality	1.59 (18)	3.50 (50)	0.44 (0.26-0.76, 0.003)	0.47 (0.27-0.82, 0.008)
MACE	4.67 (50)	4.59 (62)	1.00 (0.69-1.46, 0.990)	0.90 (0.62-1.32, 0.600)
Ischaemic stroke	1.35 (15)	1.28 (18)	1.06 (0.54-2.11, 0.860)	1.19 (0.60-2.39, 0.620)
Major bleeding	2.54 (28)	2.01 (28)	1.30 (0.73-2.30, 0.380)	1.36 (0.70-2.63, 0.360)

IR, incidence rate; HR, hazard ratio. *Accounted for clustering only. **Adjusted for age, sex, frailty index (consisting of 36 health deficits, see text) and accounted for clustering.

RECURRENT EVENTS ANALYSES OF HOSPITALISATION AND CRNMB (COUNT DATA)

	Intervention n= 522	Usual care n= 704	Intervention vs usual care	
	IR per 100 patient years (total n. of events)	IR per 100 patient years (total n. of events)	Crude IRR* (95% CI, p)	Adjusted IRR** (95% CI, p)
All-cause hospitalisation	28.72 (323)	32.91 (466)	0.85 (0.72-0.99, 0.043)	0.84 (0.69-1.03, 0.091)
Cardiovascular hospitalisation	9.25 (104)	10.95 (155)	0.82 (0.57-1.18, 0.286)	0.86 (0.60-1.22, 0.400)
Non-cardiovascular hospitalisation	19.48 (219)	21.97 (311)	0.87 (0.69-1.09, 0.227)	0.83 (0.66-1.05, 0.121)
CRNMB	16.90 (190)	17.37 (246)	0.97 (0.77-1.23, 0.813)	0.99 (0.80-1.23, 0.936)

IR, incidence rate; IRR, incidence rate ratio. *Adjusted for length of follow-up and accounted for clustering only. **Adjusted for age, sex, frailty index (consists of 36 health deficits, see text), length of follow-up and accounted for clustering.

APPENDIX E

DISTRIBUTION OF CARDIOVASCULAR AND NON-CARDIOVASCULAR CAUSES OF DEATH

Cause of death	Intervention (n=527)	Usual care (n=713)
Total cardiovascular	*21 (4.0%)*	*46 (6.5%)*
Heart failure	8 (1.5%)	21 (2.9%)
Acute coronary syndrome	3 (0.6%)	8 (1.1%)
Ischaemic stroke	1 (0.2%)	4 (0.6%)
Major bleeding (all intracranial)	6 (1.1%)	5 (0.7%)
Other cardiovascular	3 (0.6%)	8 (1.1%)
Total non-cardiovascular	*18 (3.4%)*	*50 (7.0%)*
Malignancy	7 (1.3%)	15 (2.1%)
Infection	6 (1.1%)	18 (2.5%)
Other non-cardiovascular	5 (0.9%)	17 (2.4%)

COST-EFFECTIVENESS OF INTEGRATED CARE VERSUS USUAL CARE FOR PATIENTS WITH ATRIAL FIBRILLATION IN PRIMARY CARE

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Submitted

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ABSTRACT

Background: With the increasing prevalence and associated disease burden of atrial fibrillation (AF), ways to cost-effectively organise care for patients with AF are needed. An integrated care strategy for elderly patients with AF in primary care has been shown to reduce mortality by 45% compared to usual care. The current study was performed to assess the cost-effectiveness of this integrated care intervention.

Methods: The ALL-IN trial was a cluster randomised trial in primary care practices in the Netherlands. Practices were randomised to providing integrated care (index) for patients with AF (with a focus on treatment of multimorbidity, anticoagulation monitoring and close collaboration with secondary care), or usual care (control). Data on healthcare resource use and quality of life were collected from primary care electronic medical records and questionnaires. A cost-effectiveness analysis was performed from a societal perspective with a time horizon of 2 years. Multiple imputation and multiple regression were performed to estimate the incremental costs and incremental Quality Adjusted Life Years (QALYs).

Results: 15 practices were allocated to the index intervention and 11 to usual care. Two scenarios were analysed. First, the 522 patients receiving the index intervention were compared to all 704 usual care patients, and second, to a subset of 425 usual care patients of whom detailed information on healthcare related costs and quality of life was available. While, as expected, in the index group, costs spent in primary care were higher, which was outweighed by cost reductions for other resources, notably in home care and assisted living facilities. Consequently, total cost-savings in favour of the index intervention varied between €760 and €3,868 per patient, depending on the scenario. The intervention resulted in a QALY gain between 0.00 and 0.06 over 2 years of follow-up. The probability of the intervention being more effective and less costly varied between 42.1% and 89.3%, depending on the scenario.

Conclusion: Providing integrated care for elderly patients with AF in primary care was more effective *and* less costly compared to usual care. Hence, this poses a possible solution for the expected increase in prevalence of AF and the associated burden on healthcare resources and costs.

INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disorder with a prevalence that increases with age, up to 17.8% in patients aged 85 years and above[1]. Thus, with the ageing population, the population-wide prevalence of AF will increase even further. Indeed, the number of patients with AF is expected to more than double between the years 2010 and 2060.[2] AF is a condition associated with high healthcare expenditures. Hospital admissions occur very frequently and are an important cost-driver, accounting for 50-70% of all AF-related costs.[3,4] In the Netherlands, direct annual costs for patients with AF accounted for €583 million in 2009, reflecting 1.3% of the Netherlands healthcare expenditure.[5] With the expected increasing prevalence of AF, total costs and burden on health care resources will likely increase as well, emphasising the need to investigate other, more cost-effective ways to organise care for patients with AF.

One potential solution could be 'integrated care', i.e. multidisciplinary and coordinated care involving multiple healthcare providers aiming to increase overall quality of care, preferably at lower costs.[6] A meta-analysis of studies investigating such integrated care coordinated by hospitals showed a reduction in all-cause mortality and cardiovascular hospitalisation.[7] Furthermore, providing nurse-led integrated care at specialised and experienced AF clinics likely also saves costs.[8] Nevertheless, these studies were all performed in hospital care settings, whereas many elderly patients with AF are no longer managed in outpatient cardiology clinics, but in the primary care setting. Therefore, primary care is an interesting venue to orchestrate integrated AF care, specifically for the elderly AF population, with the potential also to be more cost-effective.

To quantify the effects of integrated AF care in primary care, we performed the large ALL-IN cluster randomised trial in the Dutch primary healthcare setting. Patients in the index group received an integrated care intervention, consisting of i) quarterly check-ups for AF with a focus on treatment of comorbidities, ii) anticoagulation management in primary care, and iii) close collaboration with secondary care.[9] In patients who received this index intervention, we observed a 45% reduction in all-cause mortality when compared to patients receiving usual care.[10] Analysis of the cost-effectiveness of this intervention was a secondary objective of the ALL-IN trial. This paper describes the potential cost-effectiveness of organising integrated care for patients with AF in primary care. The ALL-IN trial is registered at the Netherlands Trial Register (NTR5532).

METHODS

Study design of the ALL-IN trial

The study design of the ALL-IN trial has been described in detail previously.[9] In short, we performed a cluster randomised, pragmatic, non-inferiority trial in primary care practices in the Netherlands, starting in 2016 with a follow-up period of 2 years. After randomisation of primary care practices, patients with documented AF aged 65 years or older were included. The main exclusion criteria were valvular AF or the presence of an internal cardioverter defibrillator or cardiac resynchronisation therapy device.[9] In practices randomised to the index intervention, patients who provided informed consent for participating in the intervention received integrated care and also a questionnaire on quality of life and resource use at baseline, after 12 months and after 24 months of follow-up. The index intervention consisted of three main aspects: (1) case management of anticoagulation treatment, with International Normalized Ratio (INR) measurements performed in the primary care practice in patients treated with a vitamin K antagonist (VKA) and special attention for drug compliance and monitoring of kidney function in patients with a non-vitamin K oral anticoagulant (NOAC), (2) quarterly check-ups by the practice nurses, supervised by the GP, for AF and its related comorbidities and (3) easy-access consultation with anticoagulation clinics and cardiologists. Practice nurses were trained in anticoagulation treatment and monitoring, and educated in the signs, symptoms and treatment of AF and its comorbidities.

In practices randomised to the control group, patients received usual care, mostly consisting of care provided by cardiologists (generally once a year), anticoagulation clinics, and ad-hoc consultation of the GP. Some patients were also seen by a practice nurse for treatment of diabetes mellitus type 2, cardiovascular risk management, or chronic obstructive pulmonary disease (COPD), yet without special attention for AF. A modified informed consent procedure was carried out, in which a waiver for informed consent to collect data on baseline characteristics and clinical outcomes from the primary care electronic medical records (EMRs) was provided by the Medical Ethics Committee.[9,10] Patients in control practices were asked for informed consent to fill out the questionnaires on quality of life and resource use.

Cost-utility analyses

The outcomes of the cost-utility analysis are the incremental costs and incremental Quality Adjusted Life Years (QALYs). The cost-utility analysis was performed from a societal perspective, so including available costs from different providers and settings,

also outside the hospital. The time horizon used was equal to the study period, i.e. 24 months. Given the short follow-up period, discounting of costs and effects was considered redundant.

Resource use

Empirical study data were collected for six different cost categories: 1) costs made in primary care practices, 2) costs from cardiology outpatient clinic visits, 3) costs from hospital or nursing home admissions and electrocardioversions (ECV), 4) costs from anticoagulant management, 5) other direct costs, and 6) indirect costs (informal care). As all patients were aged 65 years or older, we did not include productivity losses. The methods to obtain data on resource use are described below.

1) Primary care practices

The number of procedures in primary care were derived from the EMRs of the practices in which the ICT system allowed for such data extraction. Procedures consisted of consultations with GPs and practice nurses and diagnostic/therapeutic procedures (for example surgical procedures by the GP and electrocardiography).

2) Outpatient cardiology visits

For cardiology outpatient clinic visits, patients were asked through the resource use questionnaires administered at 12 and 24 months of follow-up how often, on average, they visited their cardiologist per year. If missing, information on follow-up frequency from the available cardiologist letters in the EMR was used.

3) Admissions and ECV

Information on hospital and nursing home admissions and ECV therapy was collected from specialists' letters available in the EMRs of the primary care practices. An admission was defined as an admission with at least one overnight stay. For nursing home admissions, only temporary admissions were included in this category, as patients were censored when permanently admitted to a nursing home. Permanent nursing home admissions were taken into account in an additional analysis (see section on statistical analyses).

4) Anticoagulation management

For patients using a vitamin K antagonist in the intervention group, data on the number of INR measurements in 2017 were derived from the three anticoagulation clinics located in the areas of the participating primary care practices. Patients included in the usual care group could not exactly be identified by the anticoagulation clinics.[9]

Therefore, the number of INR measurements in 2017 from a representative proxy was taken, including all patients with AF aged 65 years and over, without an artificial heart valve, registered with the affiliated control practices of their region. For simplicity, the anticoagulant used at baseline was assumed to remain unchanged throughout the follow-up period. For vitamin K antagonists, we assumed an average number of 2 tablets acenocoumarol per day.

5) Other direct costs
Through the questionnaires at 12 and 24 months of follow-up, self-reported data on use of the following resources were collected: visits to non-cardiology specialists' outpatient clinics; emergency department visits, ambulance rides; day admissions (e.g. for short surgical procedures); paramedical care; and home care (by professional caregivers). The answers from the three month recall periods were extrapolated to the follow-up period of 24 months. Data on which patients were living in an assisted living facility were provided by the practices at the end of follow-up.

6) Indirect costs
Resource use of self-reported informal care, was also derived from the questionnaires at 12 and 24 months, and trimmed at 2 hours a day.

Unit costs
The number of procedures were multiplied by the costs, which were specified in the Dutch Manual for costing research in health care.[11] Costs of anticoagulant drugs were derived from the website www.medicijnkosten.nl. For NOAC treatment, the average price of the four available NOACs was taken and standard doses were assumed. For VKA monitoring, €17,00 per INR measurement was counted.[12]

Quality Adjusted Life Years (QALYs)
QALYs were calculated using an area under the curve approach. Utility scores were derived from the generic health related quality of life EuroQol 5D questionnaires (EQ5D-5L) filled out by the patients at baseline, after 12 months and after 24 months of follow-up.

Statistical analyses
The main analyses consisted of two scenarios. In the first scenario, we included all eligible usual care patients. Because a substantial part of the usual care patients did not provide informed consent to fill out the questionnaires, the proportion of missing data for EQ5D-5L and self-reported resource use (denoted with * in Table 1) was

considerable. In the second scenario we therefore included only the subset of usual care patients who provided informed consent for the questionnaires.

Multiple imputation was performed for missing data from the questionnaires, i.e. other direct costs, indirect costs and EQ5D time points (i.e. at baseline, after 12 months and after 24 months). The multiple imputation had to differ for the two scenario's because of the high proportion of missing data in the first scenario. Therefore, in the first scenario, multiple imputation was not possible for each type of self-reported resource use, but was performed on the total costs of other direct and indirect costs, and the missing EQ5D values at the different time points. The variables age, sex and Frailty Index (FI, a validated frailty indicator [13]), death, total GP costs, total admissions and ECV costs and available EQ5D values were used as predictors. In the second scenario, multiple imputation was performed for each type of self-reported resource use and the missing EQ5D values at the different time points, with the same predictors. Missing data for the number of primary care consultations were not imputed, as the reason for being missing was considered missing completely at random, i.e. depending on the primary care ICT system.

As we could not collect additional follow-up data from nursing homes when patients permanently moved to a nursing home, and because the primary care practice is no longer involved in providing care for these patients, we had to censor patients after a permanent move to a nursing home. Nevertheless, nursing home admission is an important cost-driver and we did collect data on the exact timing of nursing home-admission. Therefore, we performed additional analyses in which we assumed a scenario with the largest impact on costs and QALYs: we assumed these patients survived in the nursing home up to the end of the 2-year follow-up, at a quality of life comparable to a comatose state (utility of 0.1). In this way, together with the two scenarios, the analyses with and without taking permanent nursing home admission into account provide a range that likely covers the 'true' incremental costs and effects.

In all analyses, costs were adjusted for baseline differences in age, sex, FI and clustering (at the practice level) using multiple regression models. QALY contribution was additionally adjusted for baseline EQ5D-5L utility score.

We performed bootstrapping on both scenarios with 100 iterations on each of the 40 imputation sets in order to assess the uncertainty around the incremental costs and effects. The incremental costs and effects of all bootstraps were plotted in cost-effectiveness planes.

Sensitivity analyses

Finally, in a sensitivity analysis, a third party payer (TPP) perspective was applied to both scenarios, disregarding informal care and using unit costs for primary care consultations as specified by the Dutch Health Authority, in which the unit cost per consultation is lower and the residual costs are reimbursed separately through a fixed price per registered patient.[14] In addition, a sensitivity analysis was performed with the unadjusted values.

RESULTS

Descriptive statistics

15 practices were allocated to the intervention and 11 to the control group (see Figure 1). In the intervention practices, 522 (55.0%) of the eligible patients provided informed consent for participation in the intervention (and for the questionnaires). These 522 patients were included in our analyses and compared to *all* 704 usual care patients in scenario 1 and next, in scenario 2, to the subset of 425 usual care patients who were willing to fill out detailed questionnaires on healthcare related costs and quality of life. Baseline characteristics of the intervention group and both usual care groups are shown in the appendix. Most baseline characteristics of the 425 control patients willing to fill out questionnaires were more comparable to the 522 index patients, than all 704 usual care patients.

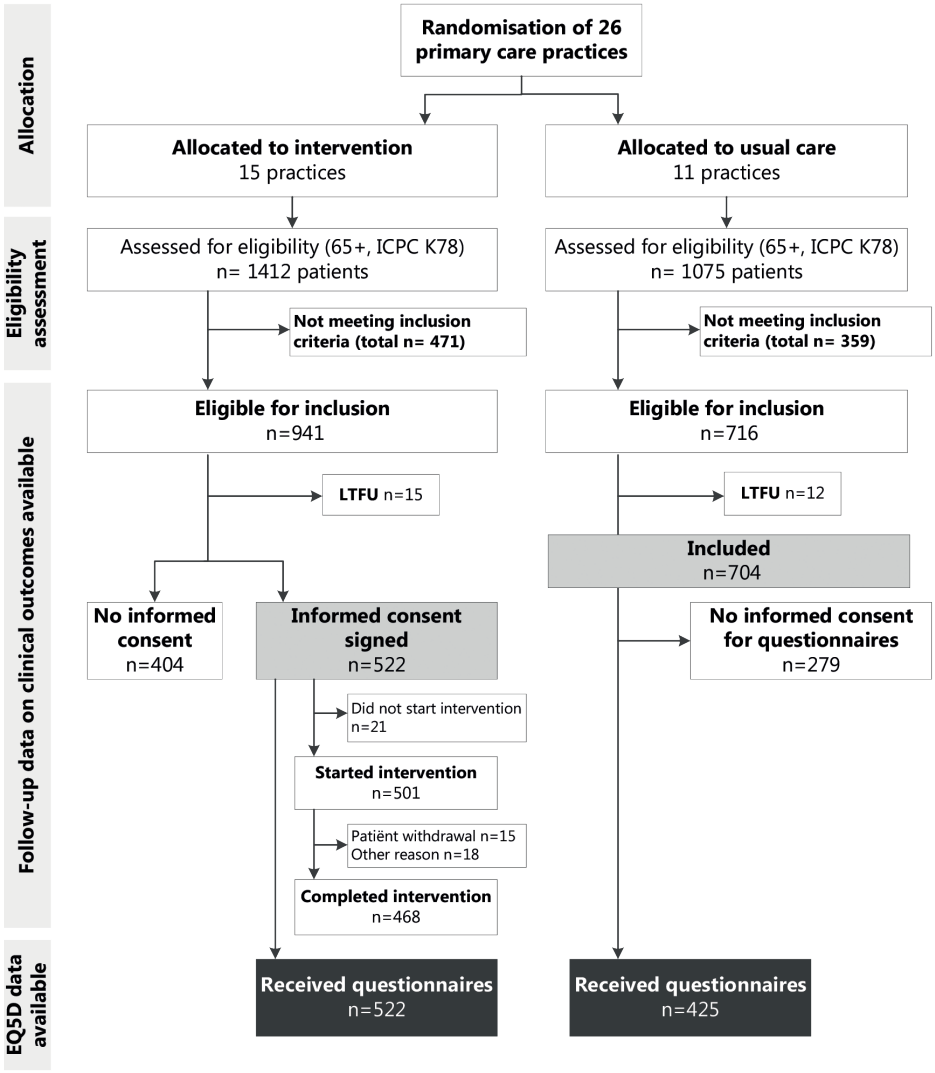
Missing data

In the intervention group, 445 out of 522 patients (85%) filled out the questionnaire at baseline, 345 out of 510 (68%) completed the questionnaire after 1 year and 305 out of 488 (63%) completed the final questionnaire after 2 years. In the usual care group, 279 out of 704 patients (39.6%) did not provide informed consent and did not fill out questionnaires; hence the other direct costs and indirect costs could not be calculated in scenario 1. In scenario 2, 369 out of the 425 patients (87%) who provided informed consent for the questionnaires filled out the questionnaire at baseline, 301 out of 411 (73%) completed the questionnaire after 1 year and 253 out of 397 (64%) after 2 years. Data on consultations and procedures in primary care were available from 19 out of 26 practices.

Costs of health care utilisation

The costs of unadjusted and imputed costs are shown in Table 1. Except for telephone consultations, costs from consultations in primary care were higher in the intervention group compared to usual care.

FIGURE 1. FLOWCHART OF THE ALL-IN TRIAL



LTFU = Lost to follow-up.

For all other cost categories, reductions in costs in the intervention group were observed, except for the number of days admitted to the hospital and day treatment procedures in scenario 2. The largest difference was observed for the other direct costs (adjusted difference up to -€1,648 per patient over 2 years), predominantly caused by more use of assisted living facilities and home care resource use in the usual care group. The number of INR measurements did not differ between the intervention and usual care group.

TABLE 1. IMPUTED, UNADJUSTED COSTS FOR THE INTERVENTION VERSUS USUAL CARE

		Integrated care (n = 522)		Usual care			
				All eligible patients (n = 704, scenario 1)		With informed consent for questionnaires (n=425, scenario 2)	
Type of procedure		**Mean number of procedures**	**Mean costs**	**Mean number of procedures**	**Mean costs**	**Mean number of procedures**	**Mean costs**
PRIMARY CARE COSTS	GP consults						
	Consults	12.73	120.05	8.67	81.79	9.11	86.04
	Double consult	4.11	271.25	2.09	137.87	2.41	158.85
	Visitations	7.17	358.52	4.48	223.81	3.21	160.37
	Telephone consults	6.09	103.54	7.37	125.21	6.45	109.59
	Practice nurse consults (chronic conditions)	4.78	90.53	1.47	58.18	0.74	64.22
	Practice nurse consults (mental health)	0.09	4.78	0.02	1.47	0.01	0.74
	ECG	0.19	8.56	0.10	3.85	0.10	4.04
	Small surgery, injections, ACT	0.52	31.73	0.99	69.15	0.70	46.17
	Other	49.16	50.21	54.47	40.88	44.29	41.88
	Subtotal primary care costs		*1,039.18*		*742.20*		*671.88*
CARDIOLOGY OUTPATIENT CLINIC VISITS			99.05		115.50		119.02
ANTICOAGULANT TREATMENT COSTS			2,185.57		2,239.88		2,284.81

TABLE 1. *CONTINUED*

		Integrated care (n = 522)		Usual care			
				All eligible patients (n = 704, scenario 1)		With informed consent for questionnaires (n=425, scenario 2)	
Type of procedure		**Mean number of procedures**	**Mean costs**	**Mean number of procedures**	**Mean costs**	**Mean number of procedures**	**Mean costs**
ADMISSIONS AND ECV	Hospital admissions	4.16	1,980.60	4.41	2,099.40	3.79	1,804.32
	Temporary nursing home admissions	3.88	652.05	5.06	849.55	4.48	753.04
	ECV	0.09	17.61	0.09	16.66	0.11	21.62
	Subtotal admissions and ECV		*2,650.25*		*2,948.95*		*2,578.98*
OTHER DIRECT COSTS	Other outpatient visits*	7.05	445.13	na	na	6.99	481.17
	Day treatment*	2.07	572.30	na	na	1.98	546.93
	Paramedic consults*	17.83	567.25	na	na	24.48	786.50
	Home care*	141.78	6,133.61	na	na	145.44	6,584.49
	Day care institution*	5.08	1,246.55	na	na	3.44	644.58
	Emergency department visit*	1.07	276.07	na	na	1.07	276.19
	Ambulance ride*	0.78	402.33	na	na	0.70	358.44
	Assisted living facility*	15.94	2,678.34	na	na	24.95	4,191.40
	Subtotal other direct costs		*12,321.59*		na		*13,869.70*
INDIRECT COSTS	Informal care*	238.63	3,042.27	na	na	217.30	3,340.78

Mean number of procedures and costs (in euros) per patient throughout the 2 year follow-up period. For admissions, the mean length of stay in days (summed for all admissions per patient) is shown. Except for the number of INR measurements in the usual care group (for which an assumption was made, see text), all number of procedures were observed or, if indicated with *, derived through questionnaires. ECG = Electrocardiography; ACT=Ambulant compression therapy for crural ulcers; ECV = electrocardioversion.

QALYs

Mean EQ5D-5L utility scores at baseline and after 12 and 24 months of follow-up are shown in Table 2, together with the QALY contributions. Utility scores were slightly higher in the intervention group compared to the usual care groups and, in all groups, decreased during follow-up. The mean QALY contribution over 2 years in the intervention group was 1.42, versus 1.36 in the usual care group, providing a QALY gain of 0.06 in the intervention group in scenario 1 (i.e. 22 extra days alive with perfect quality of life per patient over the 2 years). Due to different coefficients in the different multiple imputation regression models (depending on the scenario and whether censored patients were included), the adjusted QALY contribution for the 522 intervention patients also varied across the analyses.

TABLE 2. IMPUTED EQ5D-5L AT DIFFERENT TIME POINTS AND THE QALY CONTRIBUTION OVER 2 YEARS FOR THE INTERVENTION VERSUS CONTROL GROUP

		Integrated care (n = 522)	Usual care	
			All eligible patients (n = 704)	With informed consent for questionnaires (n=425)
IMPUTED TIMEPOINTS	T0	0.766	0.730	0.754
	T1	0.711	0.639	0.699
	T2	0.668	0.598	0.654
QALY CONTRIBUTION 2 YEARS	**Unadjusted**			
	Scenario 1, censored patients included	1.436	1.307	1.416
	Scenario 2, censored patients excluded	1.450	1.340	1.432
	Adjusted			
	Scenario 1, censored patients included	1.390	1.341	
	Scenario 2, censored patients included	1.430		1.429
	Scenario 1, censored patients excluded	1.422	1.362	
	Scenario 2, censored patients excluded	1.443		1.441

The 522 intervention patients are compared with all 704 eligible usual care patients in scenario 1, and with the 425 usual care patients who provided informed consent for the questionnaires in scenario 2.

TABLE 3. RESULTS OF THE COST-UTILITY ANALYSES OF THE INTEGRATED CARE INTERVENTION COMPARED TO USUAL CARE

	Δ costs in primary care	Δ consults cardiologist	Δ anticoagulant costs	Δ admissions and ECV	Δ other direct costs	Δ indirect costs	Δ permanent nursing home admission	Δ total costs, including permanent nursing home admission	Δ total costs, excluding permanent nursing home admission	Δ effects (QALYs) including permanent nursing home admission	Δ effects (QALYs) excluding permanent nursing home admission
Base case Imputed & adjusted											
Scenario 1: 522 vs 704 patients	€ 375	-€ 17	-€ 54	-€ 337	-€ 1,648	-€ 1,013	-€ 1,175	-€ 3,868	-€ 2,693	0.05	0.06
Scenario 2: 522 vs 425 patients	€ 358	-€ 20	-€ 105	-€ 34	-€ 739	-€ 219	-€ 478	-€ 1,238	-€ 760	0.002	0
Sensitivity analyses											
Unadjusted, scenario 1	€ 321	-€ 14	-€ 81	-€ 315	-€ 2,947	-€ 1,274	-€ 1,296	-€ 5,607	-€ 4,311	0.13	0.11
Unadjusted, scenario 2	€ 331	-€ 17	-€ 115	€ 71	-€ 1,512	-€ 299	-€ 521	-€ 2,062	-€ 1,540	0.02	0.01
Health care perspective, scenario 1	€ 121	-€ 17	-€ 54	-€ 337	-€ 1,648	na	-€ 1,175	-€ 3,110	-€ 1,935	0.05	0.06
Health care perspective, scenario 2	€ 151	-€ 20	-€ 105	-€ 34	-€ 739	na	-€ 478	-€ 1,225	-€ 747	0.002	0

Adjusted = for baseline differences in age, sex, Frailty Index and clustering. QALYs were also adjusted for differences in baseline EQ5D-5L utility score. Δ is the mean difference between intervention - usual care patients of 100 bootstrapped samples. The colours correspond to the different colours in Figure 2, indicating whether patients who were censored due to permanent nursing home admission, and their follow-up time while admitted to the nursing home, were included or not. ECV=electrocardioversion.

Incremental costs and effects

In Table 3, the results of the cost-utility analysis (with the mean differences between the intervention and usual care for the different adjusted and imputed cost categories and QALYs) are presented. The number of consultations provided in the intervention group and, hence, costs in primary care were higher (up to €375 per intervention patient). In all other cost categories, the mean differences indicated lower costs in the intervention group.

Additional analyses permanent nursing home admission

In the control group, 21 out of 704 patients (3.0%) and 8 out of 425 patients (1.9%) permanently moved to a nursing home, compared to 5 out of 522 patients (1.0%) in the intervention group. When including the remaining follow-up time assuming patients stayed alive at very low quality of life, the difference in total costs between the intervention and control group was higher (-€3,868 versus -€2,693 in scenario 1) and the QALY gain slightly smaller (0.05 instead of 0.06).

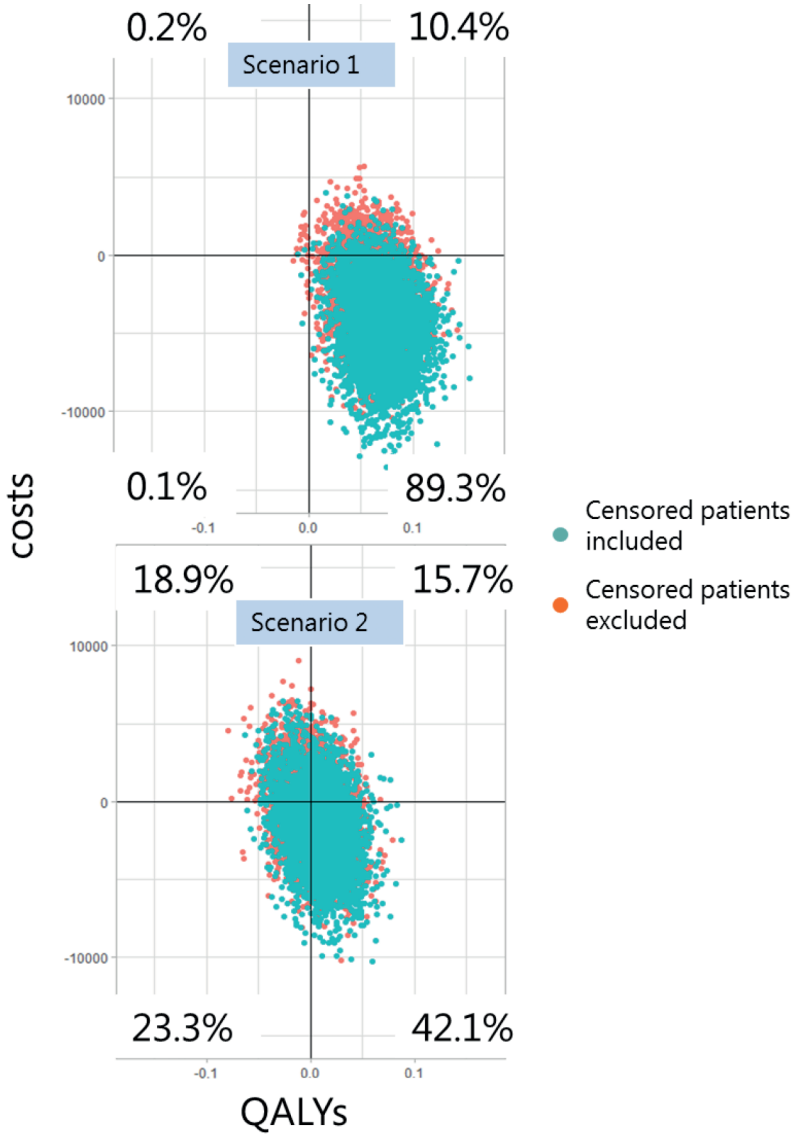
Cost effectiveness planes

The cost-effectiveness planes are shown in Figure 2. In scenario 1, including all eligible usual care patients, 89.3% of the bootstrapped samples were located in the southeast quadrant, demonstrating a probability of 89.3% that the integrated care intervention is dominant, i.e. resulting in lower costs and more effectiveness. In Figure 2B, the scenario including the 425 usual care patients who were willing to fill-out the questionnaires shows a probability of 42.1% of the intervention being dominant. The results of the additional analyses regarding the in- or exclusion of censored patients, and their assumed costs and effects in the remaining follow-up time after permanent nursing home admission, show a large overlap in the incremental costs and effects of the bootstrapped samples (depicted in blue and orange).

Sensitivity analyses

Results of the sensitivity analyses are shown in Table 3. Without adjustment for age, sex, FI and clustering, differences in QALYs and total costs were larger. The health care perspective resulted in smaller differences in costs from primary care consultations (as expected, as lower unit costs were used).

FIGURE 2. COST-EFFECTIVENESS PLANES



Cost effectiveness planes showing the incremental costs (on the Y-axis) and incremental QALYs (on the X-axis) of integrated care compared to usual care of all the bootstrapped samples for both scenarios and, as is shown with the different colours, for the analyses with and without patients who were censored due to permanent nursing home admission. Negative costs (on the Y-axis) indicate cost-savings of integrated care compared to usual care, while positive costs (on the Y-axis) indicate additional spending. Negative QALYs (on the X-axis) indicate loss of QALYs due to integrated care compared to usual care, while positive QALYs (on the X-axis) indicate QALYs gained. The southeast quadrant therefore indicates the intervention to be dominant, i.e. more effective and less costly.

DISCUSSION

We have evaluated the cost-effectiveness of the ALL-IN trial, a cluster randomised trial investigating whether integrated care for patients with atrial fibrillation can be safely, and cost-effectively, organised in primary care. This cost-utility analysis shows that integrated care for elderly patients with AF in primary care reduces costs (ranging between €760 to €3,868 per patient per 2 years, depending on the selection of usual care patients (scenario 1 or 2) and whether or not permanent nursing home admissions were included) and likely gives a, albeit small, QALY gain.

Interpretation of results

While the integrated care intervention, as expected, led to increased costs from consultations in primary care, this was outweighed by lower costs from other resources. The observed cost-reduction was mainly driven by lower use in the intervention group of living in an assisted living facility, home care, and informal care. The lack of data on use of these resources at baseline, unfortunately, makes it difficult to conclude whether this difference was truly caused by the intervention, or due to selection inherent to our cluster randomised design and subsequent informed consent procedure. Nevertheless our various scenario analyses, including different subsets of usual care patients, all yielded similar inferences. Moreover, because patients following the intervention were frequently monitored and treated for comorbidities including heart failure, it is very well possible that these patients experienced less functional decline than patients in the usual care group, requiring less assistance in daily activities. This is supported by the results regarding our main clinical outcomes, especially the reduction in all-cause mortality, and the findings from Bleijenberg and colleagues, who also reported a, rather small, effect on functional decline and reduced costs due to fewer days of nursing home admissions and fewer hours of informal care among frail elderly receiving nurse-led care, compared to usual care.[15,16]

Remarkably, in our data, hospital admissions and cardiology outpatient clinic consultations contributed relatively little to the difference in total costs. This can be partly explained by the observation that also in usual care an already high proportion (52%) of patients had been discharged from routine outpatient cardiology follow-up, decreasing potential substitution of care. Altogether, our data suggest that integrated AF care influences healthcare costs by bringing patients with AF to a more 'stable clinical condition', thereby reducing informal care, home care, the need to admit patients to a nursing home, and in the end a reduction in all-cause mortality.

Strengths and limitations

An important strength of this cost-effectiveness study is that we included data from a broad range of resources, ranging from informal care to secondary care. Furthermore, most of the resources consisted of actually observed data from our trial. Nevertheless, the following limitations need to be noted.

First, data on quality of life and self-reported health care consumption were missing for about 40% of usual care patients who did not provide informed consent for the questionnaires. However, an alternative informed consent procedure, i.e. requiring informed consent for data collection (including, importantly, on hospitalisation) from all eligible patients, would have had a more serious drawback on the study by limiting generalizability, as the older and frailer patients with AF, who form an important part of the study domain, would less likely have provided informed consent. As is reflected in the baseline characteristics (see appendix) and in the smaller QALY gain in scenario 2, the usual care patients who provided informed consent to fill out the questionnaires indeed appeared to be healthier than those who did not. As multiple imputation of all missing data in the first scenario could have raised validity concerns, we transparently presented the 2 scenarios, which both showed a high probability of cost-effectiveness of the integrated care intervention.

Second, as a consequence of our informed consent procedure we did not have the exact number of INR measurements per patient in the usual care group. Third, for the same reason, we had to censor patients after permanent nursing home admission. Because the admission rate might have been affected by the intervention, we decided to make extreme assumptions on the duration of stay to display the potential influence of these censored patients on the outcome. Even though the difference in total costs and QALYs attenuated when follow-up time was censored in case a patient permanently moved to a nursing home, it did not alter the conclusions on the cost-effectiveness of the intervention.

Lastly, in the intervention group, the increase in GP consultations was larger than the increase in practice nurse consultations, likely caused by the difficulty to distinguish between practice nurse and GP consultations in our data. For reimbursement reasons, a practice nurse consultation is sometimes registered as a GP consultation.[17] As a practice nurse consultation (approximately 30 minutes) costs the same as a GP consultation (approximately 10 minutes), a better distinction would not have affected the total costs. However, it does complicate estimating the extra time investment when considering future implementation of integrated AF care.

Comparison to existing literature

The results of this cost-effectiveness study are in line with the results from Hendriks and colleagues, who investigated the cost-effectiveness, of integrated nurse-led care at a specialised atrial fibrillation clinic of a tertiary care hospital in the Netherlands.[8] Although performed from a hospital perspective, in which costs from primary care and informal care were not taken into account, they observed a cost reduction of €1,109 per patient per year and a mean QALY gain of 0.009. We observed a QALY gain between 0.00 and 0.03 and a cost reduction ranging between €380 and €1,934 per patient per year (depending on the selection of usual care patients and whether or not costs of permanent admission to a nursing home were included). Studies evaluating other nurse-led care programs in primary care, regarding for example heart failure, frail elderly, cardiovascular risk management, have also observed cost reductions and QALY maintenance or gains.[16,18,19]

Clinical implications

This cost-effectiveness study, together with the observed reduction in mortality as presented elsewhere[10], provides valuable information for policy makers and health insurance companies to guide further implementation of integrated care for patients with AF. In that matter, the GP perspective is also important to consider. Given the increase in consultations and the extra burden on the practice to perform the extra check-ups, implementing the intervention could be costly for primary care practices. In the Netherlands, the reimbursement per consultation is substantially lower than the estimated unit costs (approximately 1/3). The residual reimbursement is payed to the GP as a fixed amount per registered patient, which becomes relatively lower when the number of consultations increases.

Currently, substitution of care from secondary to primary care is an increasingly popular strategy in managing the increasing disease burden of an ageing society. Regarding patients with AF, however, this might not be desirable, as a considerable number of patients following our intervention received *extra* care, including consultations in secondary care, which likely contributed to the beneficial results. More substitution might therefore reduce the effects (both on clinical outcomes and QALYs), as shared care rather than substitution of care is likely to better meet the complex needs of patients with AF, especially in those who suffer from severe cardiac comorbidity.[19,20] Joint consultations between cardiologists and general practitioners might be a promising alternative to implement truly shared care and reduce referrals to secondary care.[21] While further research into the most suitable setting and frequency of follow-up for certain subgroups of patients is needed, it appears that the extra care and extra

consultations that many patients in the ALL-IN trial received paid off, both from a clinical and economical view.

Conclusion

Integrated care for patients with atrial fibrillation organised in primary care was observed to be more effective and less costly compared to usual care, with an estimated QALY gain between 0.00 and 0.06 and a cost reduction between €760 and €3,868 per patient per 2 years. Widespread implementation of integrated AF care in primary care could therefore possibly be instrumental in managing the increasing disease burden and costs associated with the rising prevalence of AF.

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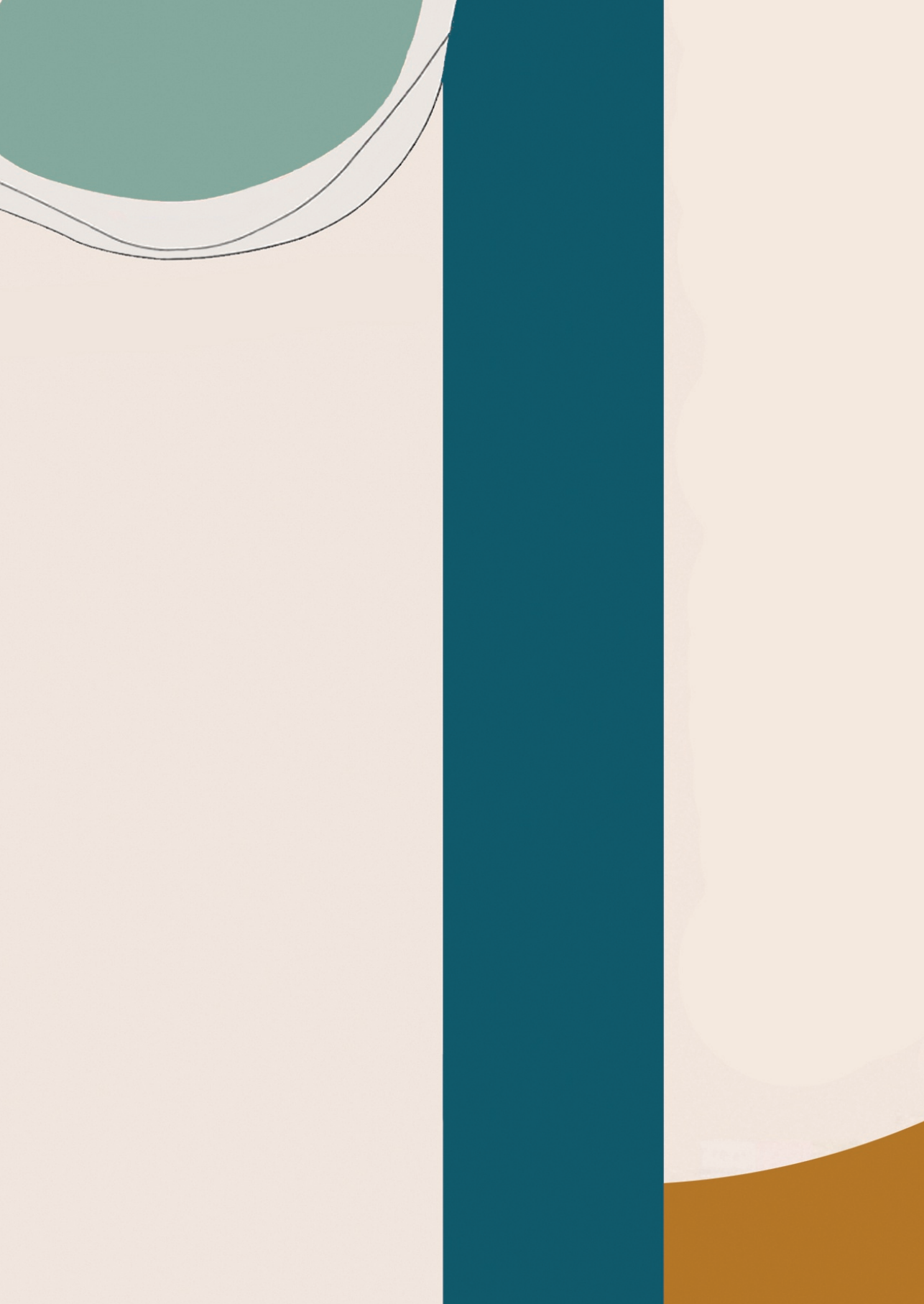
APPENDIX

TABLE 1. BASELINE CHARACTERISTICS OF INCLUDED PATIENTS

	Integrated care (n = 522)	Usual care	
		All eligible patients (n = 704)	*With informed consent for questionnaires (n=425)*
Age (years), median (IQR)	76.0 (71.0-80.0)	78.0 (72.0-83.0)	*77.0 (72.0-82.0)*
Female sex	236 (45.2)	369 (52.4)	*211 (49.6)*
Hypertension	308 (59.0)	386 (54.8)	*230 (54.1)*
Diabetes mellitus	130 (24.9)	182 (25.9)	*110 (25.9)*
Prior stroke/TIA	81 (15.5)	95 (13.5)	*49 (11.5)*
Coronary artery disease	93 (17.8)	119 (16.9)	*73 (17.2)*
Prior myocardial infarction	36 (6.9)	49 (7.0)	*28 (6.6)*
Heart failure	72 (13.8)	132 (18.8)	*66 (15.5)*
Peripheral vascular disease	35 (6.7)	47 (6.7)	*29 (6.8)*
Prior venous thromboembolism	25 (4.8)	30 (4.3)	*10 (2.4)*
Chronic renal impairment	59 (11.3)	108 (15.3)	*61 (14.4)*
COPD	71 (13.6)	97 (13.8)	*62 (14.6)*
History of cancer	94 (18.0)	128 (18.2)	*82 (19.3)*
Pacemaker	34 (6.5)	62 (8.8)	*36 (8.5)*
Frailty index, median (IQR)	0.14 (0.11-0.22)	0.17 (0.11-0.19)	*0.14 (0.11-0.19)*
Polypharmacy (≥5 chronic drugs)	134 (25.7)	139 (19.7)	*86 (20.2)*
Anticoagulant use *VKA*	386 (73.9)	564 (80.1)	*340 (80.0)*
NOAC	83 (15.9)	79 (11.2)	*57 (13.4)*
Antiplatelet therapy	48 (9.2)	50 (7.1)	*22 (5.2)*
Beta-blockers	373 (71.5)	516 (73.3)	*312 (73.4)*
Calcium channel antagonists	149 (28.5)	181 (25.7)	*111 (26.1)*
Digoxin	96 (18.4)	135 (19.2)	*79 (18.6)*
Class I and III antiarrhythmic drugs	32 (6.1)	52 (7.4)	*31 (7.3)*
Diuretics	194 (37.2)	336 (47.7)	*186 (43.8)*
RAAS-inhibitors	278 (53.3)	393 (55.8)	*248 (58.4)*

Numbers are counts (%) unless stated otherwise. The frailty index consists of the presence or absence of 36 health deficit items (scale 0–1, higher value indicating more frailty).
COPD, chronic obstructive pulmonary disease; EQ5D-5L, EuroQol 5D questionnaire; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; RAAS, renin–angiotensin–aldosterone system; TIA, transient ischaemic attack; VKA, vitamin K antagonist.



OFF-LABEL DOSE REDUCTION OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION AND ITS CLINICAL CONSEQUENCES

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ABSTRACT

For stroke prevention in atrial fibrillation (AF), the correct dose of non-vitamin K antagonist oral anticoagulants (NOACs) is essential to achieve optimal prevention of thromboembolism while avoiding excessive bleeding. Concerns have been raised that in everyday practice patients with AF frequently receive a reduced dose of NOAC without a clear indication. In this review, we discuss the indications for reducing the NOAC dose, the occurrence of 'off-label' dose reduction, and associated patient characteristics and clinical consequences. In current literature, around one in six to seven patients seems to receive an off-label reduced NOAC dose, predominantly patients at high age, those with low body weight, and those with a decrease in renal function. Some studies show a tendency of an increased risk of hospitalisation and mortality, and possibly stroke or thromboembolism in patients with off-label dose reduction of NOACs, though many studies are conflicting, not statistically significant due to small numbers and – importantly – confounding by indication may not be completely ruled out. Awaiting more definitive evidence, physicians should base NOAC dosing on current recommendations that are primarily aimed at maintaining the standard bioavailability of NOACs in different patients. To prevent bleeds, therefore, other strategies including addressing modifiable bleeding risk factors should be followed.

1. INTRODUCTION

Oral anticoagulants are of critical value for stroke prevention in atrial fibrillation (AF). For many decades, vitamin K antagonists (VKAs) were the predominant treatment option. They are associated with a two third relative risk reduction in stroke compared to placebo.[1] Yet, despite this effectiveness, historical studies have repeatedly shown that patients with AF often do not receive anticoagulants or antiplatelet therapy instead.[2] Such 'underuse' of anticoagulants in patients with AF at high risk of stroke was in the order of 50%.[2] Concerns about high risk of bleeding, patient compliance, and VKA-related inconvenience of International Normalized Ratio (INR) testing and many potential food- and drug interactions are all contributing factors to underuse of VKAs.[3]

With the introduction of non-VKA oral anticoagulants (NOACs) in 2009 underuse of anticoagulants for AF was expected to decrease 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. Moreover, NOACs do not require INR monitoring; a fixed dose can be used.[4] Currently, four NOACs have been approved for patients with AF,[5-9] and these agents rapidly became recommended as first-line agents for most patients with AF in clinical guidelines.

And indeed, recent studies showed an increase in overall uptake of oral anticoagulants in patients with AF.[3] While this initially alleviated the concerns about 'underuse' of anticoagulants because fewer patients with AF received no treatment or antiplatelet therapy only, a new pitfall has arisen. For each NOAC, besides a standard dose, a reduced dose is available for specified subcategories of patients fulfilling strict criteria for dose-reduction. Accrual of post-marketing evidence, however, showed that many patients receive a reduced NOAC dose *without* any clear indication, likely because of a presumed increased risk of bleeding.[10-13] This so-called 'off-label dose reduction' 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 off-label dose reduction.[14]

In this *Clinical Review* we describe the evidence and recommendations from clinical trials and clinical guidelines for dose reduction of NOACs in patients with AF. Furthermore, we address the occurrence of off-label dose reduction, and associated patient characteristics and clinical consequences.

2. DOSE REDUCTION IN CLINICAL TRIALS

In patients with AF, two out of four randomised clinical trials actually studied the safety and effectiveness of *two* doses of NOAC against VKA-treatment, with both NOAC doses assigned by random allocation. In the RE-LY trial,[6] in total 18,113 patients with AF were randomised to receive either dabigatran 150 mg b.d., 110 mg b.d., or INR-guided warfarin dosages. The study showed that dabigatran 110 mg b.d. was non-inferior to warfarin in preventing stroke (1.69% per year in the warfarin group versus 1.53% per year in the dabigatran 110 mg b.d. group; relative risk [RR] 0.91; 95% confidence interval [CI] 0.74 to 1.11), with a lower risk of major bleeding (3.36% versus 2.71% per year; RR 0.80; 95% CI 0.69 to 0.93). Dabigatran in a dose of 150 mg b.d. was superior to warfarin for prevention of stroke (1.69% per year in the warfarin group versus 1.11% per year in the dabigatran 150 mg b.d. group; RR 0.66; 95% CI 0.53 to 0.82), with a similar risk of bleeding (3.36% per year versus 3.11% per year; RR 0.93; 95% CI 0.81 to 1.07). This led to approval of both dosages in Europe while only dabigatran 150 mg b.d. was approved for in the United States of America (USA).

In the ENGAGE AF-TIMI 48 trial,[9] 21,105 patients with AF were randomly assigned to receive either edoxaban 60 mg o.d., edoxaban 30 mg o.d., or INR-guided warfarin. Both edoxaban doses were non-inferior to warfarin in preventing stroke or systemic embolism: 1.50% per year in the warfarin group versus 1.18% per year in the edoxaban 60 mg o.d. group (hazard ratio [HR] 0.79; 95% CI 0.63 to 0.99); and 1.50% per year in the warfarin group versus 1.61% per year in the edoxaban 30 mg o.d. group (HR 1.07; 95% CI 0.87 to 1.31). Importantly, there was a 41% increase in risk of ischaemic stroke with the 30 mg o.d. dose versus the 60 mg o.d. dose, highlighting the risk when NOACs are underdosed. The risk of major bleeding was lower for both the 60 mg o.d. and 30 mg o.d. edoxaban dose: 3.43% per year in the warfarin group versus 2.75% per year in the edoxaban 60 mg o.d. group (HR 0.80; 95% CI 0.71 to 0.91); and 1.61% per year in the edoxaban 30 mg o.d. group (HR 0.47; 95% CI 0.41 to 0.55).

In each NOAC group of the ENGAGE AF-TIMI 48 trial[9], in the ROCKET-AF trial[7] (comparing rivaroxaban with warfarin), and in the ARISTOTLE trial[8] (comparing apixaban with warfarin), only if patients met pre-defined criteria the edoxaban dose was reduced from 60 mg o.d. to 30 mg o.d. (in the 60 mg o.d. group) and from 30 mg o.d. to 15 mg o.d. (in the 30 mg o.d. group), the rivaroxaban dose was reduced from 20 mg o.d. to 15 mg o.d., and the apixaban dose was reduced from 5 mg b.d. to 2.5 mg b.d. In the RE-LY trial no dose reduction was applied, regardless of the presence or absence of certain conditions that could increase NOAC plasma level. Therefore, RE-LY in fact

was the only trial that *randomly* compared both different NOAC doses – *without* further dose reduction in each NOAC treatment arm – with INR-guided warfarin.

Noteworthy, and adding to complexity, the criteria for dose reduction and the proportion of patients eligible for a reduced dose differed considerably among trials. For instance, in ROCKET-AF and in ENGAGE AF-TIMI 48 over 20% of patients with AF had an indication for a reduced NOAC dose, while this was less than 5% in the ARISTOTLE trial.

3. INDICATIONS FOR DOSE REDUCTION

Multiple bodies have formulated specific conditions that warrant dose reduction of NOACs. Although largely comparable, several differences exist between criteria used in the NOAC-trials,[6-9] the Summary of Product Characteristics (SPC),[15-18] the Food and Drugs Administration (FDA),[19-22] the European Society of Cardiology (ESC)[23] and the European Heart Rhythm Association (EHRA)[24], all of which are listed in Table 1.

Importantly, appropriate NOAC dosing aims to achieve a bioavailability that balances effectiveness (reducing stroke risk) and safety (reducing bleeding risk) in all patients. Some patient characteristics and conditions – e.g. renal impairment, low body weight and high age – result in increased plasma levels and the indications for dose reduction are aimed at restoring the balance between effectiveness and safety. As an illustration, post-hoc analyses of the ROCKET-AF, the ARISTOTLE, and the ENGAGE AF-TIMI 48 trial indeed indicated that compared to VKA both the relative effectiveness and safety of NOACs in patients who had an indication for dose reduction, and thus correctly received the reduced NOAC dose, remained similar to those without an indication for dose reduction, and thus correctly received the full NOAC dose.[8, 25, 26] Likewise, in the ARISTOTLE trial, in patients who had only one of the minimum two required dose reduction criteria, and thus correctly received the full apixaban dose, the comparable relative risk of stroke or thromboembolism and the reduced relative risk of major bleeding compared to warfarin was similar to those without any dose reduction criteria.[27]

It is important to understand that reducing the dose solely because of the presence of bleeding risk factors – either modifiable (e.g. hypertension) or non-modifiable (e.g. previous stroke or bleeding)[23] –would result in suboptimal plasma levels.

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

	NOAC-trials[6-9]	SPC[15-18]	FDA[19-22]	ESC guidelines 2016[23]	EHRA guidelines 2017[41]
Dabigatran	RE-LY: **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/1.73m²* *- Gastritis/esophagitis/ GERD* *- Other increased bleeding risk*	**150 mg b.d. → 75 mg b.d.** - CrCl 15-30 ml/ min/1.73m² - CrCl 30-50 ml/ min/1.73m² + 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/1.73m²* *- Body weight ≤60 kg* *- Quinidine, amiodarone, clarithromycin, or erythromycin use* *- Other reasons for increased bleeding risk*
Rivaroxaban	ROCKET-AF: **20 mg o.d. → 15 mg o.d.** - CrCl 30-49 ml/min/1.73m² J-ROCKET-AF: **15 mg o.d. → 10 mg o.d.** - CrCl 30-49 ml/min/1.73m²	**20 mg o.d. → 15 mg o.d.** - CrCl 15-49 ml/min/1.73m²	**20 mg o.d. → 15 mg o.d.** - CrCl 15-50 ml/ min/1.73m²	**20 mg o.d. → 15 mg o.d.** - CrCl 30-49 ml/min/1.73m²	**20 mg o.d. → 15 mg o.d.** - CrCl 15-49 ml/min/1.73m² *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 <50ml/min/1.73m²* *- Other reasons for increased bleeding risk*

TABLE 1. *CONTINUED*

	NOAC-trials[6-9]	SPC[15-18]	FDA[19-22]	ESC guidelines 2016[23]	EHRA guidelines 2017[41]
Apixaban	ARISTOTLE: **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/1.73m² - ≥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/1.73m² - ≥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*

TABLE 1. *CONTINUED*

	NOAC-trials[6-9]	SPC[15-18]	FDA[19-22]	ESC guidelines 2016[23]	EHRA guidelines 2017[41]
Edoxaban	ENGAGE AF-TIMI 48: **60 mg o.d. → 30 mg o.d.** - CrCl 30-50 ml/min/1.73m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone **30 mg o.d. → 15 mg o.d.** - CrCl 30-50 ml/min/1.73m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone	**60 mg o.d. → 30 mg o.d.** - CrCl 15-50 ml/min/1.73m² - Body weight ≤60 kg - Ciclosporin, ketoconazole, dronedarone, erythromycin	**60 mg o.d. → 30 mg o.d.** - CrCl 15-50 ml/min/1.73m²	**60 mg o.d. → 30 mg o.d.** - CrCl 30-50 ml/min/1.73m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone **30 mg o.d. → 15 mg o.d.** - CrCl 30-50 ml/min/1.73m² - Body weight ≤60 kg - Verapamil, quinidine, dronedarone	**60 mg o.d. → 30 mg o.d.** - CrCl 15-49 ml/min/1.73m² - 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*

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

This could lead to attenuation of the preventive effect of NOACs while the anticipated benefits on bleeding risk may not be substantial, or at least uncertain. More precisely, one could argue that this even ignores dose finding evidence from phase I and II studies.

4. DOSE REDUCTION IN CLINICAL PRACTICE

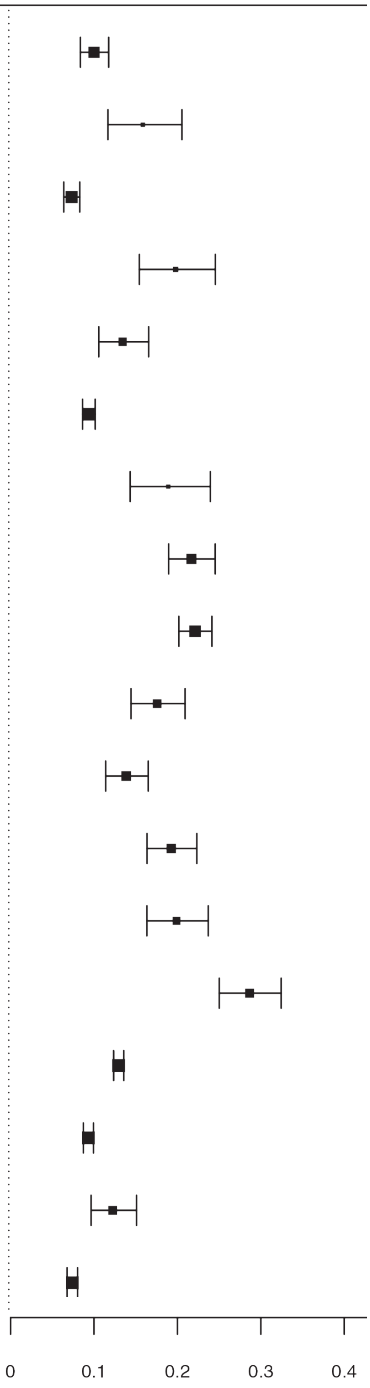
Concerns have been raised that in daily clinical practice patients with AF often receive a NOAC for stroke prevention in a reduced dose *without* a clear indication. In order to review the scope of the occurrence of this off-label dose reduction in clinical practice, we systematically searched and identified large, observational studies with low risk of bias. For full details on methodology, search strategy and study selection, see Supplement.

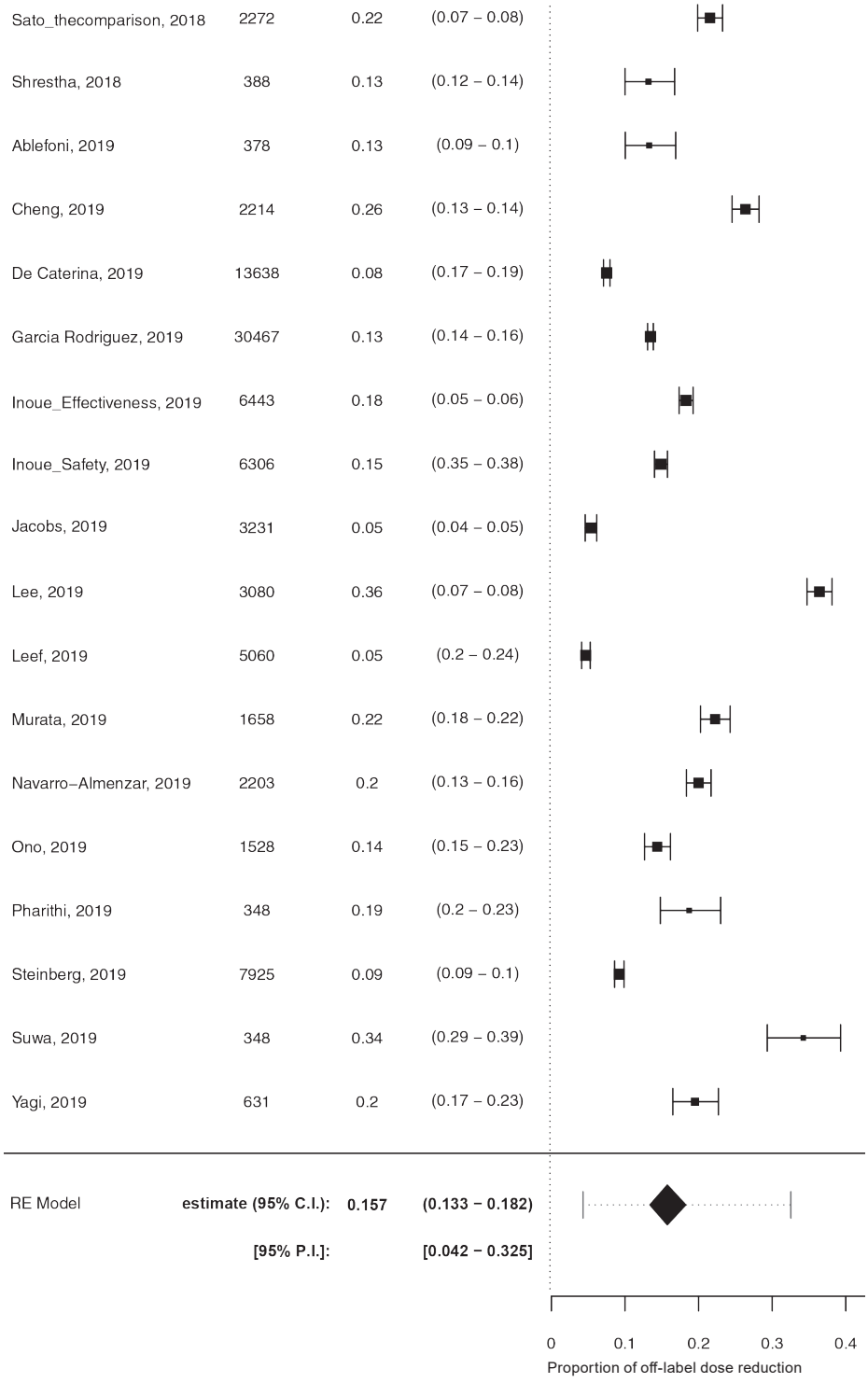
From January 1st 2008 until October 1st 2019, a total of 36 studies meeting our selection criteria were published, encompassing 132,631 patients. Most of these studies were based on electronic health records from Western countries, most notably the USA. The majority of patients were enrolled in hospital care rather than from the general, unselected population. The most commonly prescribed NOAC was rivaroxaban. Edoxaban, being the latest of the NOACs to enter the market, was the least prescribed. The majority of the studies used the FDA criteria or a modification thereof as the reference for adequate dose reduction, followed by the SPC. For a brief overview of all included studies, see Supplement.

Figure 1 shows the forest plot of the selected studies, sorted by year of publication. The median proportion of patients receiving an off-label reduced NOAC dose was 15.4% (interquartile range (IQR) 11.7% to 19.9%). However, there were some considerable outlying studies that reported much lower off-label dose reduction (only 5%)[28, 29] or much higher (over 30%).[30, 31] A random-effects meta-analysis (for details, see Supplement) showed that on average 15.7% (95% CI 13.3% to 18.2%) receives a NOAC in a reduced dose without a clear indication. There is, however, substantial heterogeneity in the current literature. The so-called 95% prediction interval (PI), indicating the range wherein the anticipated results of future studies similar to those included in our meta-analysis will lie, is wide from 4.2% to 32.5%.

FIGURE 1. PROPORTION OF OFF-LABEL DOSE REDUCTION OF NOACS FOR STROKE PREVENTION IN AF

Author, year	Total	Proportion	(95% C.I.)
Steinberg, 2013	1217	0.1	(0.06 – 0.08)
Tellor, 2015	260	0.16	(0.1 – 0.15)
Bell, 2016	2856	0.07	(0.14 – 0.24)
Kilickiran, 2016	294	0.2	(0.15 – 0.25)
Lavoie, 2016	500	0.13	(0.11 – 0.17)
Steinberg, 2016	5738	0.09	(0.19 – 0.25)
Helmert, 2017	255	0.19	(0.2 – 0.24)
Lee, 2017	844	0.22	(0.14 – 0.21)
Okumura, 2017	1689	0.22	(0.1 – 0.17)
Ruiz, 2017	530	0.18	(0.08 – 0.12)
Tellor, 2017	707	0.14	(0.09 – 0.1)
Umei, 2017	670	0.19	(0.12 – 0.21)
Bando, 2018	453	0.2	(0.11 – 0.17)
Buchholz, 2018	569	0.29	(0.16 – 0.22)
Ellis, 2018	11926	0.13	(0.1 – 0.17)
Essien, 2018	8791	0.09	(0.16 – 0.24)
Gibson, 2018	556	0.12	(0.25 – 0.32)
McAlister, 2018	6658	0.07	(0.25 – 0.28)





RE, random effects; P.I. prediction interval.

While the occurrence of off-label dose reduction seems to be higher in studies performed in the hospital setting (19%, 95% PI 7.3% to 34.7%) as compared to the general population (10.4%, 95% PI 3.7% to 19.7%), other characteristics such as type of NOAC or year of publication could not further explain this. Likely, clinical factors such as comorbidity, as well as methodological factors such as differences in patient selection (e.g. new or prevalent NOAC users) and differences in reporting (e.g. completeness of health records), contribute to this heterogeneity.

Our systematic search identified 12 studies that analysed whether patient characteristics were associated with off-label NOAC dose reduction. Detailed findings from these studies are depicted in the Supplement. Despite the variation in the definitions, an increase in age, a decrease in body weight and a decrease in renal function were generally associated with an off-label reduced NOAC dose. For sex, findings were more ambiguous: four studies reported that females were more likely to receive an off-label reduced NOAC dose (statistically significant in two studies), whereas in two others, both studying rivaroxaban, the reverse was observed.

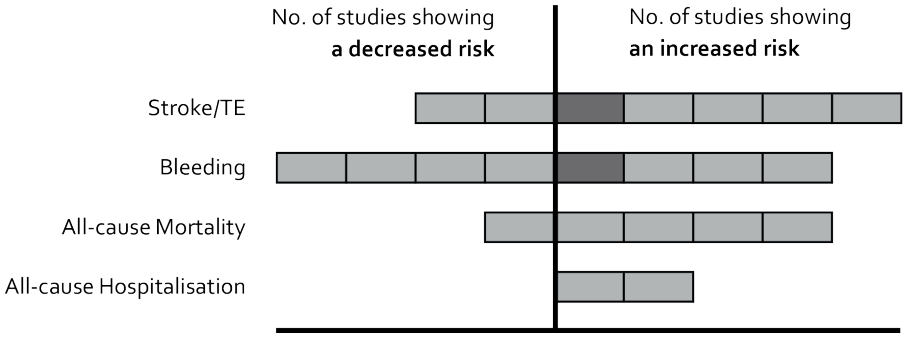
5. CONSEQUENCES OF OFF-LABEL DOSE REDUCTION

Finally, and most importantly, in recent years, several studies compared adverse clinical outcomes in patients with AF receiving an off-label reduced NOAC dose. A narrative overview by Santos et al. found an association with increased cardiovascular hospitalisation and, particularly for apixaban, with a nearly 5-fold increased risk of stroke.[32]

More specifically, our systematic search identified 10 studies on clinical outcomes related to off-label NOAC dose reduction (see Figure 2, for details see Supplement). Most of these used adjusted survival analyses, [33-35] or propensity scoring methods (either matching,[36-38], adjustment[39] or weighting[40]) to adjust for confounding. Five studies found a positive association between off-label NOAC dose reduction and increased occurrence of stroke or thromboembolism (of which one study was statistically significant), while two studies found a non-significant negative association. Two studies looked into different NOACs separately. One of these found an increased stroke risk in patients using an off-label reduced apixaban dose, but a non-significant decreased risk in off-label reduced dabigatran and rivaroxaban users. In the other study no significant associations were found. The observations for the outcome bleeding are even more conflicting: increased risk in four studies (one of which was statistically

significant), decreased risk in three (all non-significant), and no significant differences between NOACs in two studies. Perhaps most consistent is the risk of hospitalisation and mortality in patients receiving an off-label reduced NOAC dose. Overall, available data suggest there is a tendency of an increased risk of hospitalisation and mortality: two studies reported an increased risk for all-cause hospitalisation, and five studies reported an increased risk and one study a neutral effect for all-cause mortality. Statistical significance, though, was not reached in any of the studies.

FIGURE 2. STUDIES INVESTIGATING THE CLINICAL OUTCOMES OF OFF-LABEL DOSE REDUCTION.



Light shaded areas are studies with statistically non-significant results. Dark shaded areas are studies with statistically significant results. TE = thromboembolism.

With such conflicting study results, possible relations between off-label NOAC dose reduction and clinical outcomes should be interpreted with caution. Numbers of events, furthermore, were small and thus often not statistically significant. Most importantly, in these observational studies off-label dose reduction is not randomly allocated, but based on physician judgment and/or patient preference and adjustment for such confounding by indication is notoriously difficult.

6. CONSIDERATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

In this *Clinical Review*, we described the evidence and recommendations from clinical trials and clinical guidelines for dose reduction of NOACs. In current observational studies, one in every six to seven patients with AF receives a reduced NOAC dose without a clear indication. Off-label NOAC dose reduction appears to be related to an increased risk of all-cause hospitalisation and all-cause mortality and possibly an

increased risk of stroke or thromboembolism, though strong evidence is still lacking. This warrants several considerations for clinical practice and future research.

First, reducing the NOAC dose in patients with a high perceived bleeding risk in the absence of pharmacokinetic criteria is for sure currently not recommended. As we have illustrated in this *Clinical Review*, indications for dose reduction should be based on pharmacokinetic principles associated with certain clinical conditions leading to increased plasma levels, rather than on bleeding risk. It may result in a subtherapeutic NOAC plasma level and thus in suboptimal prevention of thromboembolism, without any clear (or at least highly uncertain) benefit on bleeding risk.

Future research should focus on off-label NOAC dose reduction and close important gaps in the current evidence. Effort may be needed to educate physicians to identify groups of patients, conditions or clinical settings where optimisation of NOAC dosing is most needed. For instance, the current literature suggests that females, elderly and patients with low body weight are at highest risk of receiving NOAC treatment with an off-label reduced dose. It could by hypothesised that these patient groups, due to differences in body composition, indeed may already benefit a lower NOAC dose. However, the effects of off-label dose reduction are only scarcely studied and as of yet there is no evidence that an off-label reduced NOAC dose results in excess stroke or a lower risk of bleeding. Foremost, this implicates that in preventing bleeding in patients with AF, measures *other* than off-label reducing a NOAC doses, most notably addressing the so-called modifiable bleeding risk factors as recommended by the ESC,[23] seem the preferred strategy. Furthermore, awaiting further data, observational studies comparing different NOACs or NOACs versus VKA should describe the proportion of patients receiving an off-label NOAC dose. If this proportion is substantial, the observed effectiveness (and safety) of NOAC may be hampered and affect such comparisons.

CONCLUSIONS

This *Clinical Review* discusses off-label dose reduction of NOACs. While indications for dose reduction of NOACs are well-defined, around one in six to seven patients appear to receive an off-label reduced NOAC dose without a clear indication. A lack of strong evidence that this influences stroke or bleeding risk calls for bleeding risk reduction by means of addressing modifiable bleeding risk factors, and future efforts to study the consequences of off-label dose reduction.

CONTRIBUTORS

LPTJ, RM, CD, GJG and SD had the original idea for the study and participated in study concept and design. LTPJ, RM and SD screened and selected the articles for inclusion. LPTJ, RM, CD and SD performed the data-extraction and risk of bias assessment. SD performed statistical analysis. LPTJ and RM drafted the first version of the manuscript, which was subsequently critically reviewed for intellectual input by GJG, SD, FHR, AWH, and CBG. All authors participated in finalisation of the manuscript.

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POTENTIAL CONFLICTS OF INTEREST

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SUPPLEMENTAL FILES

1. Full methodology of the systematic review and meta-analysis
2. Search syntax
3. Supplemental Figure 1: Flowchart with the results of the systematic search
4. Overview of included studies
5. Overview of excluded studies
6. Risk of bias assessment tool
7. Supplemental references

SUPPLEMENT 1. FULL METHODOLOGY OF THE SYSTEMATIC REVIEW AND META-ANALYSIS

Search strategy

We performed a systematic search to identify all observational studies reporting on off-label non-vitamin K antagonist (NOAC) dose reduction from January 1st 2009 until October 1st 2019. We searched PubMed and EMBASE using search terms for 'dose reduction' and 'NOAC' including MeSH headings where appropriate, and synonyms. No language restrictions were applied. For the full search syntax, see Supplement 2. Cross-reference checks were performed of each selected article. For a flowchart with the results of the systematic search, see Supplemental Figure 1.

Definitions and study selection

We selected all studies fulfilling the following inclusion criteria:

- Original observational studies on stroke prevention in patients with atrial fibrillation (AF) without a mechanical heart valve and/or severe mitral valve stenosis;
- Describing the use of any of the registered NOACs: dabigatran, rivaroxaban, apixaban and/or edoxaban;
- Presenting data on the proportion of off-label NOAC dose reduction relative to the total number of NOAC users, irrespective of whether or not clinical characteristics and/or outcomes associated with off-label NOAC dose reduction were mentioned.

Furthermore, we used the following quality criteria for inclusion:

- Inclusion of at least 200 patients;
- A low risk of bias on the items on patient selection of the Newcastle-Ottawa quality assessment Scale for cohort studies (NOS) (item 1-3);[1]

- The use of appropriate guidelines (SPC, FDA, ESC, EHRA or other guidelines if well-defined) to determine whether a standard or reduced NOAC dose is indicated.

Any disagreements were resolved by discussion.

Studies including patients with venous thromboembolism (VTE) patients were excluded unless it was possible to analyse patients with AF separately. Studies in highly selected patient populations (i.e. those after major surgery or arrhythmia surgery) and studies on prophylaxis of thromboembolism (i.e. after orthopaedic surgery) were excluded.

Off-label NOAC dose reduction was defined as the use of a NOAC dose *lower* than the standard recommended NOAC dose in absence of a clear indication for dose reduction as formulated by the Summary of Product Characteristics (SPC), the Food and Drug administration (FDA), the European Society of Cardiology (ESC) or the European Heart Rhythm Association (EHRA) (See Main manuscripts Table 1). Modification of the standard indications for dose reduction (i.e. different from SPC, FDA, ESC or EHRA) were allowed for if well-defined.'

Three reviewers (LPTJ, RM, SD) independently screened the total of selected articles based on title and abstract in duplicate. Any uncertainties were resolved by discussion. Of all potential studies and studies without an abstract the full text was independently evaluated for eligibility in duplicate by two out of three reviewers (LPTJ, RM, SD). Full-text versions not initially available were requested from the authors. Any disagreements were resolved by discussion, or consultation of a fourth reviewer (GJG). For an overview of the excluded studies based on full-text screening, see Supplement 3.

Data extraction

From each included study, the following data were extracted in duplicate by four reviewers (LPTJ, RM, CD or SD):

- Study characteristics: data source; country; setting (general population or hospital care); time frame; number of included NOAC-users; duration of follow-up.
- Patient characteristics: age (mean or median); proportion of patients aged > 75 years; weight, proportion of patients with a history of hypertension, stroke, thromboembolism, cardiovascular disease, coronary heart disease, and diabetes, proportion of patients with impaired renal function, including the definition used; proportion of patients on concomitant medication relevant for NOAC

dosage (i.e. those interacting with platelet function or the cytochrome P450 and P-glycoprotein system).
- The guidelines used to determine whether a standard or reduced NOAC dose is indicated, defined as SPC, FDA, ESC, EHRA, landmark NOAC trials, other guidelines or not reported.
- The absolute number of patients receiving off-label NOAC dose reduction and the absolute number of all NOAC users stratified by dabigatran, rivaroxaban, apixaban, and edoxaban if applicable.
- If reported, we extracted data on clinical characteristics associated with off-label NOAC dose reduction, presented as relative risks, e.g. risk ratio (RR) or odds ratio (OR).
- If reported, we extracted data on clinical outcomes associated with off-label reduced NOAC dosage, presented as hazard ratios (HR).

Disagreements were resolved by discussion.

Data analysis

We calculated the proportion of patients receiving off-label dose reduction of NOACs as the number of off-label reduced NOAC dose users relative to the total number of NOAC users in each study. As the proportions of off-label dose reduction of NOACs were anticipated to be relatively low (i.e. not centred around 0.5), a double arcsine transformation was applied.[2] We performed random effects meta-analysis where appropriate to obtain a summarised proportion of off-label NOAC dose reduction. Therefore, we used restricted maximum likelihood estimation and 95% confidence intervals (95% CI) were calculated using the Hartung–Knapp–Sidik–Jonkman method.[3] Between-study heterogeneity was expressed by the 95% prediction interval (95% P.I.). These intervals indicate the range of proportions of 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. Analyses were performed in *R* version 3.3.2,[4] with the package *metaphor* version 1.9-9.[5]

During the planning and conduct of this systematic review with meta-analysis, we followed the reporting guideline for the Meta-analyses Of Observational Studies in Epidemiology (MOOSE).[6]

SUPPLEMENT 2. SEARCH SYNTAX

Search until October 1st 2019

(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 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 NOAC*[Title/Abstract] OR non-vitamin-K-antagonist*[Title/Abstract] OR non-VKA*[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 ((*vitami*[Title/Abstract] AND *antagonist*[Title/Abstract]) OR *VKA*[Title/Abstract])))

(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 inappropria*:ti,ab OR appropria*:ti,ab OR incorrec*:ti,ab OR correc*: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 drug use'/exp) AND

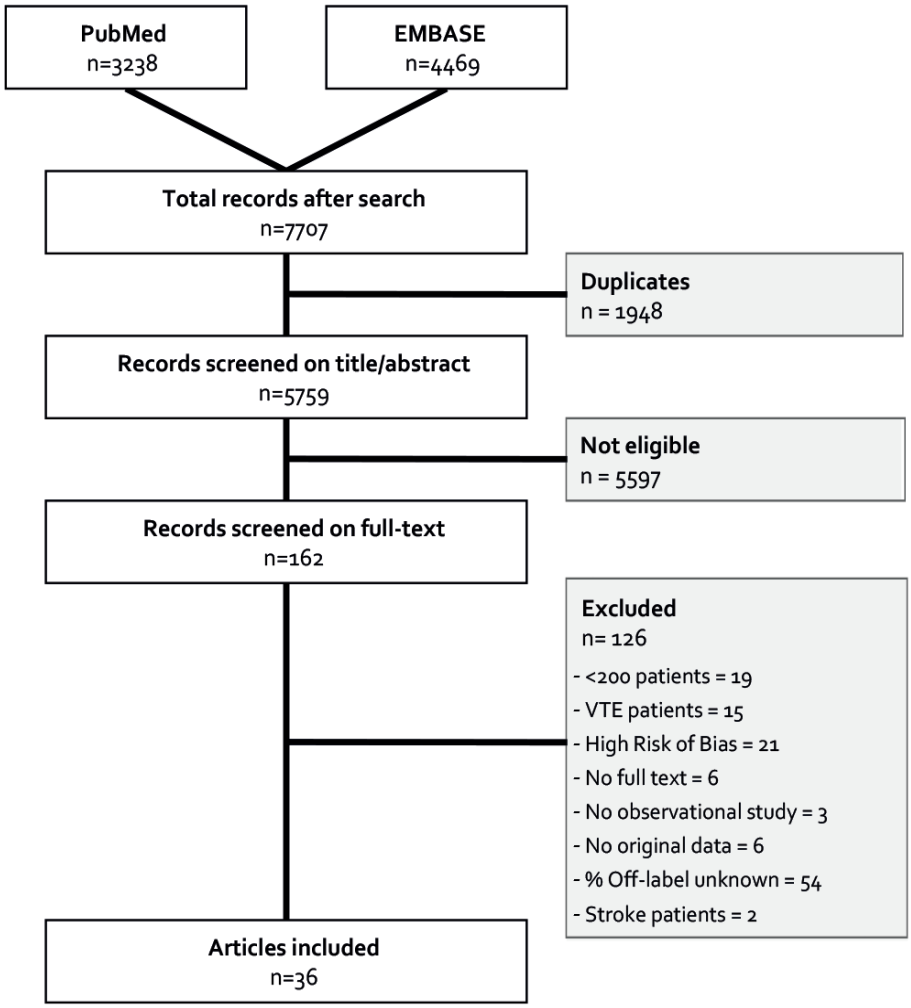
(dabigatran:ti,ab OR 'dabigatran'/exp OR 'dabigatran etexilate'/exp OR pradaxa:ti,ab OR rivaroxaban:ti,ab OR 'rivaroxaban'/exp OR xarelto:ti,ab OR apixaban:ti,ab OR 'apixaban'/exp OR eliquis:ti,ab OR edoxaban:ti,ab OR 'edoxaban'/exp OR lixiana:ti,ab OR noac*:ti,ab OR doac*:ti,ab OR

((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 [1-1-2008]/sd NOT [30-09-2019]/sd

SUPPLEMENT 3: SUPPLEMENTAL FIGURE 1

Flowchart with the results of the systematic search



SUPPLEMENT 4. OVERVIEW OF INCLUDED STUDIES

Study characteristics						Patient characteristics associated with off-label dose reduction				Clinical consequences of off-label dose reduction			
Author	*Year*	*n*	*%*	*Setting*	*NOAC*	*Female Sex*	*High Age*	*Low Weight*	*Low renal function*	*Stroke/TE*	*Bleeding*	*Hospitalisation*	*Mortality*
Steinberg	2013	1217	10.0	Both	Dabigatran								
Tellor	2015	260	15.8	Hospital	Rivaroxaban								
Bell	2016	2856	7.4	General pop.	Mix								
Kilickiran	2016	294	19.7	Hospital	Mix								
Lavoie	2016	500	13.4	Hospital	Mix								
Steinberg	2016	5738	9.4	Both	Mix					↑	↓	↑	
Helmert	2017	255	18.8	Both	Apixaban								
Lee	2017	844	21.7	Hospital	Dabigatran					↑	↓	↑	↓
Okumura	2017	1689	22.1	Hospital	Mix	↑	↑*	↑	↑*				
Ruiz	2017	530	17.6	Hospital	Mix		↓	↑					
Tellor	2017	707	13.9	Hospital	Apixaban								
Umei	2017	670	19.3	Hospital	Mix								
Yao	2017	5399	15.1	Both	Rivaroxaban					+/-	+/-		

Study characteristics						Patient characteristics associated with off-label dose reduction				Clinical consequences of off-label dose reduction			
Author	*Year*	*n*	*%*	*Setting*	*NOAC*	*Female Sex*	*High Age*	*Low Weight*	*Low renal function*	*Stroke/TE*	*Bleeding*	*Hospitalisation*	*Mortality*
Bando	2018	453	19.9	Hospital	Rivaroxaban				↓*				
Buchholz	2018	569	28.7	Hospital	Apixaban		↓*	↑*					
Ellis	2018	11926	13.0	Both	Mix		↑*	↑*	↑*				
Essien	2018	8791	9.4	Both	Mix								
Gibson	2018	556	12.2	Hospital	Apixaban		↑*	↑*	↑		↓		
McAlister	2018	6658	7.5	General pop.	Mix	↑	↑						
Sato	2018	2272	21.6	Hospital	Mix	+/-	+/-	↑	+/-	+/-	+/-	+/-	
Shrestha	2018	388	13.1	Both	Mix					↓	↑*		↑
Steinberg	2018	7925	9.3	Both	Mix					↑	↑		↑
Ablefoni	2019	378	13.2	Hospital	Rivaroxaban				↓*				
Cheng	2019	2214	26.4	Hospital	Rivaroxaban					↑*	↑		
De Caterina	2019	13638	7.6	Both	Edoxaban								
Garcia Rodriguez	2019	30467	13.5	General pop.	Mix								
Inoue_a	2019	6443	18.3	n.r.	Dabigatran								

Study characteristics						Patient characteristics associated with off-label dose reduction				Clinical consequences of off-label dose reduction			
Author	*Year*	*n*	*%*	*Setting*	*NOAC*	*Female Sex*	*High Age*	*Low Weight*	*Low renal function*	*Stroke/TE*	*Bleeding*	*Hospitalisation*	*Mortality*
Inoue_b	2019	6306	14.9	Hospital	Apixaban								
Jacobs	2019	3231	5.4	Hospital	Mix								
Lee	2019	3080	36.4	Hospital	Mix	↑*	↑*	↑*	↑*				
Leef	2019	5060	4.7	Both	Mix								
Murata	2019	1658	22.3	Hospital	Mix					↓	↓		↑
Navarro-Almenzar	2019	2203	20.0	Hospital	Mix					↑	↑		↑
Ono	2019	1528	14.4	Hospital	Mix	↑	↑*	↓	↑*				
Pharithi	2019	348	18.7	Hospital	Mix								
Suwa	2019	348	34.2	Hospital	Mix		↑*	↑*	↑*				
Yagi	2019	631	19.5	Hospital	Rivaroxaban	↓*	↑*	↑*	↑*				

n.r. = not reported
↑ = increased risk
↓ = decreased risk
+/- = differences between NOACs
* = statistically significant

SUPPLEMENT 5. OVERVIEW OF EXCLUDED STUDIES

Author	Year	Category for exclusion
Akagi	2019	OLDR not obtainable
Akao	2014	OLDR not obtainable
Alali	2019	<200
Alcusky	2018	Stroke patients
Alghadeer	2017	OLDR not obtainable
Alnsasra	2018	OLDR not obtainable
Altay	2017	OLDR not obtainable
Amarenco	2018	RoB
Andreu Cayuelas	2018	OLDR not obtainable
Antoniazzi	2019	RoB
Arbel	2019	RoB
Armbruster	2014	OLDR not obtainable
Ashjian	2017	Both AF/VTE
Ashrafi	2017	OLDR not obtainable
Bando	2018	RoB
Barra	2016	Both AF/VTE
Basaran	2016	RoB
Bastida	2017	OLDR not obtainable
Belen	2015	<200
Berod	2014	OLDR not obtainable
Blin	2019	OLDR not obtainable
Bochatay	2016	<200
Brabant	2017	No original data
Bruneau	2019	<200
Carley	2014	OLDR not obtainable
Carlin	2016	<200
Chin	2013	<200
Cho	2019	OLDR not obtainable
Chopard	2018a	VTE only
Chopard	2018b	VTE only
Chowdhry	2016	RoB
de la Figuera	2018	OLDR not obtainable
Dentali	2017	No original data

Author	Year	Category for exclusion
Diaz	2018	OLDR not obtainable
Dillinger	2018	No original data
Draper	2017	OLDR not obtainable
Du		No full text available
Ebrahimi	2017	OLDR not obtainable
Elewa	2018	OLDR not obtainable
Falissard	2019	>50% missing and excluded
Fava	2018	<200
Forslund	2018	OLDR not obtainable
Franchi	2018	OLDR not obtainable
Giustozzi	2016	OLDR not obtainable
Gomez-Lumbreras	2018	RoB
Haastrup	2018	OLDR not obtainable
Han	2019	OLDR not obtainable
Hecker	2016	OLDR not obtainable
Hirsh Raccah	2019	<200
Howard	2018	<200
Howerton		No full text available
Hussain	2012	OLDR not obtainable
Ikeda	2019	RoB
Isaacs	2013	OLDR not obtainable
Jang	2019	RoB
Jara-Palomares	2014	OLDR not obtainable
Jelonek	2018	RoB
Kartas	2019	RoB
Keller	2018	VTE only
Khan	2016	RoB
Kim	2019	RoB
Komen	2017	OLDR not obtainable
Kreutz	2019	VTE only
Kwon	2016	OLDR not obtainable
Lafon	2017	<200
Lafon	2018	No full-text available
Larock	2014	RoB
Larsen	2013	OLDR not obtainable
Ledroit	2016	<200

Author	Year	Category for exclusion
Lee	2015	OLDR not obtainable
Li	2017	OLDR not obtainable
Lin	2015	<200
Martin	2014	<200
Maura	2019	OLDR not obtainable
Maura	2018	OLDR not obtainable
Mayet	2018	OLDR not obtainable
Miele	2017	VTE profylaxis
Mitrovic	2017	<200
Moudallel	2018	Both AF/VTE
Mumoli	2017	No original data
Muniz Lobato	2018	<200
Nguyen	2016	OLDR not obtainable
Nielsen	2017	OLDR not obtainable
Nissan	2019	No observational study
Ogawa	2014	RoB
Paciaroni	2019	Case control study
Pattullo	2016	<200
Perlman	2019	Both AF/VTE
Pesavento	2017	OLDR not obtainable
Piran	2017	RoB
Pisters	2017	OLDR not obtainable
Pogge		No full text available
Rieser	2017	OLDR not obtainable
Russo	2015	OLDR not obtainable
Sato	2018	OLDR not obtainable
Schwartz	2017	RoB
Schwartz	2016	OLDR not obtainable
Sharma	2017	OLDR not obtainable
Sheikh-Taha	2019	Both AF/VTE
Shimizu	2017	Criteria unclear
Shinoda	2018	<200
Shinohara	2019	RoB
Sidman	2014	VTE profylaxis
Sieg	2015	OLDR not obtainable
Simon	2015	Both AF/VTE

Author	Year	Category for exclusion
Sorigue	2018	No observational study
Staerk	2018	OLDR not obtainable
Suarez Fernandez	2018	OLDR not obtainable
Suárez Fernandez	2018	No full-text available
Sukumar	2019	OLDR not obtainable
Suzuki	2018	ICH patients
Tedders	2013	<200
Thomas	2019	Only VTE
Tran	2014	OLDR not obtainable
Tran	2014	No full-text available
Tran	2014	VTE patients
Trujillo-Santos	2017	VTE patients
Vedovati	2017	OLDR not obtainable
Viprey	2017	RoB
Weitz	2016	No original data
Whitworth	2017	OLDR not obtainable
Witt	2016	No original data
Wu	2013	OLDR not obtainable
Xing	2019	OLDR not obtainable
Xu	2013	OLDR not obtainable
Yiginer	2017	<200

SUPPLEMENT 6: RISK OF BIAS ASSESSMENT TOOL

Risk of bias items on patient selection of the Newcastle-Ottawa quality assessment Scale for cohort studies (NOS) (item 1-3).[1]

Selection

1) *Representativeness of the exposed cohort*
   a. truly representative of the average _____(describe) in the community *
   b. somewhat representative of the average _____ 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

SUPPLEMENT 7. SUPPLEMENTAL REFERENCES

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2. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013; 67: 974-978.
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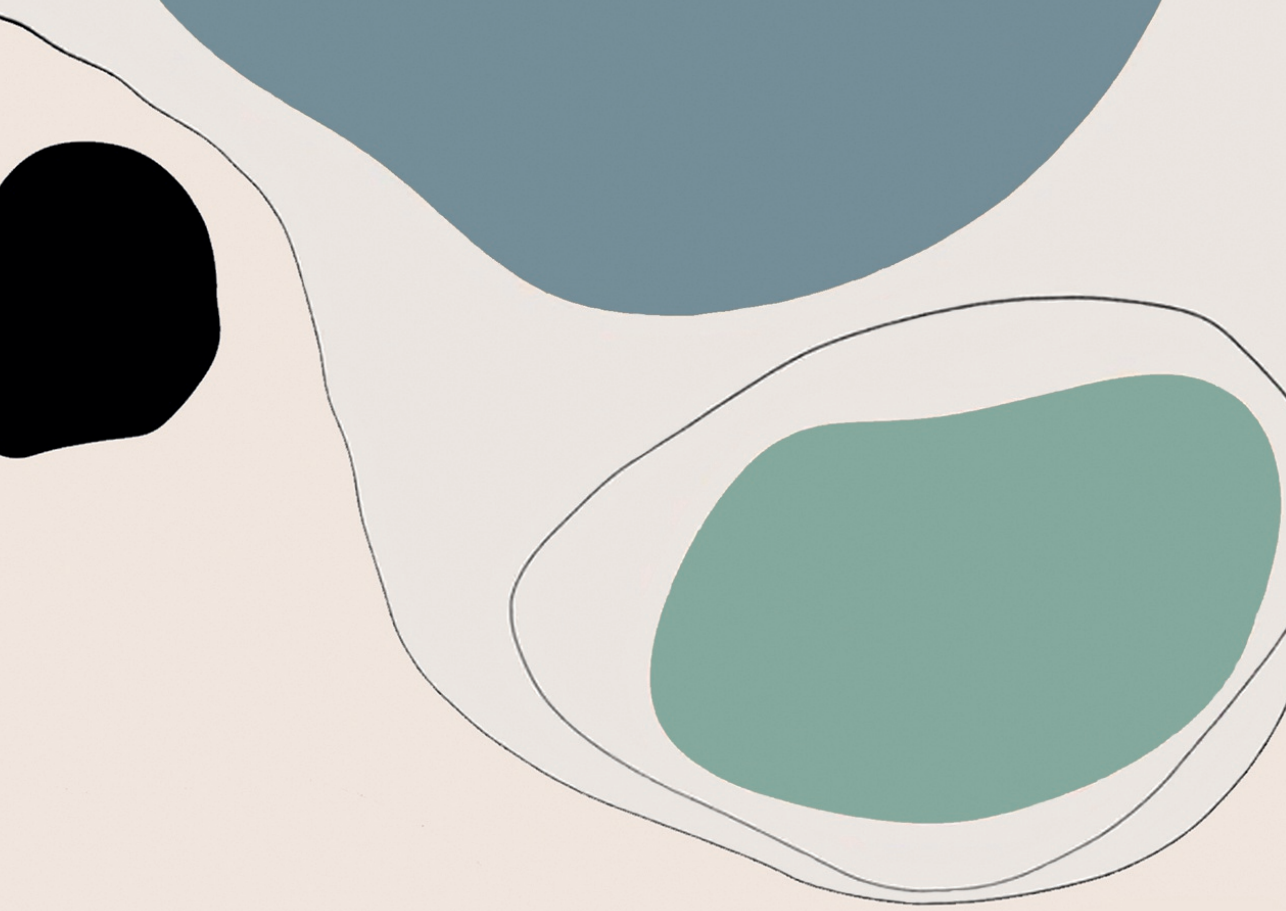

SAFETY OF OFF-LABEL DOSE REDUCTION OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION

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Submitted

ABSTRACT

Objectives: To investigate the effects of off-label NOAC dose reduction on thromboembolic and bleeding risk, compared to on-label standard dosing in patients with AF in routine care.

Design: Population-based cohort study.

Setting: General practitioner (GP) practices contributing to the United Kingdom Clinical Practice Research Datalink.

Participants: Adults with non-valvular AF and a first NOAC prescription between January 1st 2010 and July 1st 2018 were included if they received an off-label reduced dose or an on-label standard dose.

Main outcome measures: Outcomes were ischaemic stroke, major bleeding and non-major bleeding. Cox proportional hazard analyses were used to estimate the effects of off-label dose reduction compared to standard dosing. Inverse probability of treatment weighting (IPTW) on the propensity score was applied to adjust for confounding.

Results: 30,933 AF-patients initiated a NOAC during the study period. Off-label dose reduction occurred in 2,466 patients (8.0%). These patients were compared to 18,108 patients (58.5%) with an on-label standard dose. Patients receiving an on-label reduced dose or an off-label non-reduced dose were excluded. Median age was 80 years (interquartile range (IQR) 73.0-86.0) for patients with an off-label reduced dose and 72 years (IQR 66-78) for on-label standard dose users. Incidence rates were higher among patients with an off-label reduced dose compared to patients with an on-label standard dose for ischaemic stroke (0.94 vs. 0.70 per 100 person years), major bleeding (1.48 vs. 0.83) and non-major bleetding (6.78 vs 6.16). IPTW resulted in an adjusted hazard ratio (HR) of 1.07 (95% CI 0.65 to 1.74) for ischaemic stroke. For major bleeding, the adjusted HR was 0.98 (95%CI 0.65 to 1.48), and for non-major bleeding the adjusted HR was 0.89 (95%CI 0.74 to 1.08).

Conclusion: In this large population-based study, no major differences were observed among patients with AF receiving an off-label NOAC dose reduction compared to on-label standard dose users, for the risk of ischaemic stroke, non-major bleeding and, importantly, neither for major bleeding. This suggests that off-label NOAC dose reduction is unlikely to be a fruitful strategy when aiming to reduce the, indeed elevated, major bleeding risk in certain older patients with AF and multimorbidity.

What is already known on this topic

- Prevalence of off-label NOAC dose reduction in patients with AF, i.e. receiving a reduced NOAC dose without a clear indication, is estimated between 8.7% and 39.3% and likely occurs in an attempt to reduce bleeding risk.
- It is not yet known whether off-label NOAC dose reduction in patients with AF indeed prevents bleeding complications, or whether this puts patients at an unnecessary risk of ischaemic stroke.

What this study adds

- Physicians appeared to opt for off-label dose-reduction in older patients with more comorbidity, indicating that this is indeed a high-risk population for both thromboembolic events and bleeding risk.
- However, no major differences were observed among patients with AF receiving an off-label reduced NOAC dose compared to on-label standard dose users, for the risk of ischaemic stroke, non-major bleeding and, importantly, neither for major bleeding.
- Therefore, off-label NOAC dose reduction is unlikely to be a fruitful strategy when aiming to reduce bleeding risk.

INTRODUCTION

Non-vitamin K oral anticoagulants (NOACs, or direct acting oral anticoagulant, DOACs) play a central role in anticoagulant treatment for stroke prevention in patients with non-valvular atrial fibrillation (AF). The lower risk of intracranial bleeding, as well as the practical advantages of NOACs over vitamin K antagonists (VKA), including a fixed dose, no need for INR monitoring and fewer food and drug interactions, likely explain the observed increase in the proportion of patients receiving anticoagulant therapy.[1–3] Although this partially reduces the concerns for 'undertreatment' (i.e. receiving no anticoagulant therapy at all)[4], new concerns have emerged about 'underdosing' or off-label dose reduction: patients receiving a NOAC dose lower than recommended in the guidelines.[5,6] While the understandable desire to avoid bleeding events might motivate physicians and their patients to choose for an off-label reduced dose, a lower than recommended dosage might in fact increase the risk of ischaemic stroke.

Previous studies reporting on the prevalence of off-label NOAC dose reduction have shown variable results, with estimates between 8.7% and 39.3%.[7] There is limited high-quality data on the effects on health outcomes in AF patients with an off-label reduced dose compared to AF patients with an on-label standard dose. To the best

of our knowledge, ten studies have reported on this, showing conflicting results and often suffering from small number of events and methodological shortcomings.[8–17] Therefore, it is not yet known whether off-label reducing a NOAC dose in patients with AF indeed prevents bleeding complications and whether or not this affects the effectiveness of preventing stroke.

Our aim was therefore to investigate the patient's health outcomes, in terms of the occurrence of ischaemic stroke, major bleeding and non-major bleeding, of off-label NOAC dose reduction compared to on-label standard dosing, in patients with AF treated in routine care.

METHODS

Study design and data source

We performed a large population based cohort study using routine care data from the United Kingdom Clinical Practice Research Datalink (CPRD). The CPRD contains data from electronic health care records of over 11.3 million patients (6.9% of the UK population) treated in primary care practices in the United Kingdom.[18] CPRD has been widely used for epidemiological research and its validity and its representativeness of the general UK population is well-established.[19,20] Data recorded in CPRD include demographics, symptoms and diagnoses, prescriptions, results of diagnostic investigations, referrals to specialists and secondary care settings, and lifestyle, such as body mass index and smoking status. The study protocol was approved by the CPRD ISAC Committee (ISAC protocol number 18_241R).

Study population

We first selected all adult patients (≥18 years) registered in a CPRD practice with a first prescription of a NOAC during the study period between January 1st 2010 and July 1st 2018. The date of the first NOAC prescription during the study period was set as the index date. Only NOAC users with a record of AF ever before the index date or within 3 months after the index date, were then included in our study. Patients did not have to be OAC naïve, as patients who previously used a VKA (i.e. switchers) before starting the NOAC were also included. Patients needed to be enrolled in the database at least twelve months prior to the index date to ensure that valid baseline data were available. Patients who started an on-label reduced dose (i.e. a reduced dose in the presence of a clear indication, according to the Summary of Product Characteristics (SmPC)) or an off-label standard dose (a standard dose where the dose should have been reduced)

were excluded from the analyses. We excluded patients with a prosthetic heart valve or a history of rheumatic mitral valve stenosis to study patients with non-valvular AF only. Also, we excluded patients with a CHA_2DS_2-VASc score of 0 or 1 who either had a diagnosis of a deep vein thrombosis or pulmonary embolism in the three months around the index date, or a hip or knee replacement together with a reduced NOAC dose in the three months around the index date, as these patients likely used the NOAC (and a non-standard dose accordingly) for a different indication than stroke prevention in atrial fibrillation. Patients with an estimated eGFR below 15 were also excluded, as NOACs are contra-indicated in these patients. Patients were followed up until they reached the outcome of interest, died, switched to a different NOAC or dosage, discontinued the NOAC, moved out of the CPRD practice, or until the last day of valid, available data (whichever occurred first).

Exposure

The criteria of the SmPC of the four different NOACs were used to define which patients used an off-label reduced dose and are shown in table 1.[21–24] For example, when a patient used a reduced dose of rivaroxaban but had a creatinine clearance of 55 ml/min/1.73m^2 this was regarded as an off-label reduced dose. For dabigatran, dose reduction in the presence of one or more of the subjective criteria (shown in italics in Table 1) was considered as on-label dose reduction except for 'other increased bleeding risk', which could not be determined in our dataset. The number of tablets per day was disregarded in determining whether prescriptions were off-label reduced or not, as this information was often missing and we deemed it unlikely that a patient would use, for example, two tablets of apixaban 2,5 mg twice a day, instead of one tablet of 5 mg twice a day.

Treatment episodes were constructed according to the method of Gardarsdottir *et al*, to define current use and past use of NOACs.[25] A so-called permissible gap time, or grace period, of 60 days between the theoretical end date of a prescription and the next prescription was allowed for, as patients may have had tablets left due to non-adherence or temporary discontinuation around invasive medical procedures. The grace period only accounted for gaps *between* subsequent prescriptions and was not applied at the end of a current use period. In case an off-label reduced first prescription was changed to an on-label standard dose within 7 days after the index date, we reclassified the exposure of the first prescription to on-label standard dose, to disregard incorrect prescriptions that were timely corrected (for example by pharmacists) as in these cases the physician did not mean to prescribe a reduced dose.

TABLE 1. CRITERIA FOR DOSE REDUCTION PER NOAC ACCORDING TO THE SMPC, FOR THE INDICATION OF STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION [21–24]

Type of NOAC	Standard dose	Reduced dose	Criteria for dose reduction
Dabigatran	150 mg bd	110 mg bd	Age ≥80 years Verapamil *Consider dose reduction in case of:* *- Age 75-80 years* *- CrCl 30-50 ml/min/1.73m²* *- Gastritis/esophagitis/GERD* *- Other increased bleeding risk*
Rivaroxaban	20 mg od	15 mg od	CrCl 15-49 ml/min/1.73m²
Apixaban	5 mg bd	2.5 mg bd	CrCl 15-29 ml/min/1.73m², *or* ≥2 of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL (133 µmol/L) - Body weight ≤60 kg
Edoxaban	60 mg od	30 mg od	CrCl 15-50 ml/min/1.73m² Body weight ≤60 kg Ciclosporin, ketoconazole, dronedarone or erythromycin

SmPC, summary of product characteristics; CrCl, creatinine clearance; GERD, gastro-oesophageal reflux disease; bd, twice a day; od, once daily.

The exposure to an on-label standard dose or off-label reduced dose was treated as fixed by censoring follow-up time when the NOAC dose changed, when a patient switched to a different NOAC or warfarin, or when NOAC treatment was discontinued. However, follow-up data after such treatment discontinuation or changes were available and when we examined the data after NOAC discontinuation, it appeared that a considerable number of major bleeding events occurred shortly after the presumed end of a current use period. In fact, the incidence rate for major bleeding was higher in the period immediately following apparent discontinuation than during exposure to NOAC, which is highly improbable and is most likely explained by exposure misclassification at the time of the recorded outcome. Therefore, we post-hoc decided to reclassify the first 30 days after apparent discontinuation to the last NOAC used for all analyses (i.e. a 'last measurement carried forward' approach).

The available serum creatinine levels were used to calculate the estimated glomerular filtration rate (eGFR) based on the CKD-EPI equation.[26] After disregarding values of

outdated creatinine levels and body weight measured more than 5 years before the index date, missing creatinine values were assumed to be normal, as the fact that it was missing in these patients likely indicates no suspicion of renal insufficiency and hence, no indication for dose reduction. For the same reason, we assumed the body weight to be over 60 kg in case of missing data for body weight.

Outcomes

Outcomes of interest were ischaemic stroke, major bleeding, and non-major bleeding. In line with previous research in this field, ischaemic strokes registered during the *first month* of NOAC use were excluded, (i.e. a so-called blanking or quarantine period) [27], because in those cases an ischaemic stroke is probably the first presentation of atrial fibrillation, when the anticoagulant had not yet been initiated. Hence, due to the possibility of late registration of the stroke in the GP registry, counting these strokes as an outcome event during anticoagulation treatment would likely induce misclassification.[27]

Major bleeding was defined as a symptomatic bleeding in one of the following critical areas or organs: intracranial, intraspinal, retroperitoneal, intraocular, gastrointesttinal, intra-articular or intrathoracic. This definition was chosen, as the definition of major bleeding recommended by the International Society on Thrombosis and Haemostasis (ISTH)[28] is difficult to use because of missing information about haemoglobin levels or blood transfusions in CPRD data. Non-major bleeding was defined according to the remaining Read codes on bleeding events that were not included in the definition of major bleeding. Lists of the Read codes defining each outcome are provided in the Supplementary material, *Appendix Section A*.

Statistical analysis

Incidence rates of the endpoints with 95% confidence intervals (CI) were calculated as the number of events per 100 person years. When comparing stroke and bleeding outcomes in patients with an off-label reduced NOAC dose to patients with an on-label standard dose, we used inverse probability of treatment weighting (IPTW) to adjust for confounding. We calculated propensity scores (PS) for the probability of being treated with an off-label reduced NOAC dose conditional on 39 predefined potential confounders and used the PS to calculate the weights used in IPTW (in which patients with higher propensity scores received larger weights).[29] For an overview of the 39 potential confounders that were included in the PS model, see Supplementary material, *Appendix Section B*.

Two IPTW approaches were used. Usually, observational studies use IPTW to obtain marginal effect estimates, or the *average treatment effect in the population* (ATE). The ATE analysis answers the question what, on average, would have happened if *all* patients with an indication for an on-label standard dose received an off-label reduced dose (i.e. targeting the counterfactual scenario in which *all patients* eligible for a standard dose were randomised towards either the reduced dose, or the standard dose). However, we were primarily interested in the estimates of the treatment effect among patients for whom a clinician ultimately decides to prescribe an off-label reduced dose, the so-called *average treatment effect in the treated* (ATT).[29,30] The ATT-analysis answers the question what, on average, would have happened if patients who were treated with an off-label reduced dose had been given the standard dose (i.e. targeting the theoretical scenario in which patients in whom the clinician reduced the dose were randomised towards either the reduced dose, or the standard dose). For all our analyses, both the IPTW-ATE and IPTW-ATT estimates were provided, but from a clinical perspective we considered the IPTW-ATT-analyses as our main analyses.

Propensity score weights were truncated at the 99th percentile, to prevent extreme weights. Standardised mean differences and boxplots for continuous covariates were used to assess covariate balance after IPTW.[29] We used IPTW-weighted Cox proportional hazards regression with robust sandwich variance estimation to calculated hazard ratios (HRs) and 95% CIs for the comparative treatment effect, using each set of IPTW weights (ATT and ATE). Unadjusted HRs were estimated using unweighted Cox regression. The proportional hazards assumption was assessed visually by plotting the scaled Schoenfeld residuals.[31] All analyses were performed using *R* version 3.6.0.[32]

RESULTS

Descriptives

We identified 30,933 AF-patients who initiated a NOAC during the study period. We included the 2,466 patients (8.0%) who received an off-label reduced dose and 18,108 patients (58.5%) who received an on-label standard dose in our analyses. Off-label dose reduction occurred in 5.8% of dabigatran users (n=206), 6.2% of apixaban users (n=774), 9.9% of rivaroxaban users (n=1,417) and 11.9% of edoxaban users (n=69). Patients receiving an on-label reduced dose (6,496 patients, 21.0%) and patients receiving an off-label non-reduced dose (3,863 patients, 12.5%) were excluded from the current analyses. Baseline characteristics of the off-label reduced dose patients and the on-label standard dose patients are shown in Table 2. Patients in the off-label

reduced dose group were older than patients in the on-label standard dose group (median age 80 vs 72) and almost all comorbidities were more prevalent among the off-label reduced dose patients, in particular history of major bleeding, non-major bleeding, ischaemic stroke or TIA, venous thromboembolism and hypertension. Renal function was lower among off-label reduced dose patients compared to the on-label standard dose group (eGFR 61.5 vs. 76.3 mL/min per 1.73m^2, respectively). Information on recent creatinine level was missing for 645 patients (3.1%) and recent body weight was missing for 3,427 patients (16.7%).

TABLE 2. BASELINE CHARACTERISTICS

	Off-label reduced dose (n=2,466)	**On-label standard dose (n=18,108)**
Age in years, median (IQR)	80 (73.0-86.0)	72.0 (66.0-78.0)
Female sex	1134 (46.0)	6857 (37.9)
Dabigatran	206 (8.4)	926 (5.1)
Apixaban	774 (31.4)	6237 (34.4)
Rivaroxaban	1417 (57.5)	10578 (58.4)
Edoxaban	69 (2.8)	367 (2.0)
Previous VKA use	952 (38.6)	6181 (34.1)
eGFR in mL/min per 1.73 m2, median (IQR)	61.5 (51.3-76.6)	76.3 (64.7-87.4)
Creatinin in umol/L, median (IQR)	88.0 (74.0-109.0)	81.0 (70.0-93.0)
Weight in kg, median (IQR)	76.8 (65.0-90.0)	85.0 (73.0-99.0)
Comorbidities/risk factors		
History of major bleeding	196 (7.9)	847 (4.7)
History of non-major bleeding	910 (36.9)	5563 (30.7)
History of ischaemic stroke or TIA	597 (24.2)	3213 (17.7)
History of VTE	109 (4.4)	671 (3.7)
Hypertension	1653 (67.0)	10590 (58.5)
Heart failure	451 (18.3)	2292 (12.7)
Ischaemic heart disease	768 (31.1)	3921 (21.7)
History of chronic kidney disease	852 (34.5)	2319 (12.8)
Diabetes	567 (23.0)	3434 (19.0)
Presence of malignancy	100 (4.1)	691 (3.8)
Anaemia	2 (0.1)	14 (0.1)
Peptic ulcer disease	190 (7.7)	1068 (5.9)
Liver disease	42 (1.7)	391 (2.2)

TABLE 2. *CONTINUED*

	Off-label reduced dose (n=2,466)	On-label standard dose (n=18,108)
Medication use		
Concomitant antiplatelet therapy	366 (14.8)	1740 (9.6)
Non-steroidal anti-inflammatory drugs	68 (2.8)	735 (4.1)
Corticosteroids	292 (11.8)	1778 (9.8)
SSRI	224 (9.1)	1642 (9.1)
CYP3A4/P-gp inhibitors	294 (11.9)	1785 (9.9)
CYP3A4/P-gp inducers	19 (0.8)	80 (0.4)
Diuretics	1139 (46.2)	5818 (32.1)
ACE inhibitors/ARB	1307 (53.0)	8919 (49.3)
Calcium channel blockers	823 (33.4)	5725 (31.6)
Digoxin	358 (14.5)	1669 (9.2)
Statins	1330 (53.9)	9276 (51.2)
Proton pump inhibitors	1047 (42.5)	6898 (38.1)

All values are expressed as n (%), unless otherwise specified. IQR, interquartile range; VKA, vitamin K antagonist; eGFR, estimated glomerular filtration rate; TIA, transient ischaemic attack; VTE, venous thromboembolism; SSRI, selective serotonin reuptake inhibitor; CYP, cytochrome P450; P-gp, P-glycoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers.

Outcomes

During follow-up 6,717 patients (33%) were censored because of discontinuation of the NOAC, switching from one NOAC to another, or changing NOAC dose (i.e. changing exposure). During a median follow-up time of 285 days (10.2 months), 21 ischaemic stroke events occurred in the off-label reduced dose group and 159 ischaemic stroke events in the on-label standard dose group (IR 1.04 and 0.74 per 100 person-years of follow-up, respectively). The unadjusted HR of off-label dose reduction compared to on-label standard dose for ischaemic stroke was 1.32 (95% CI 0.84 to 2.09). In the analysis using the IPTW-ATT weights, the adjusted HR for ischaemic stroke was 1.07 (95% CI 0.65 to 1.74). In the IPTW-ATE analysis, the adjusted HR was 1.25 (95% CI 0.75 to 2.08).

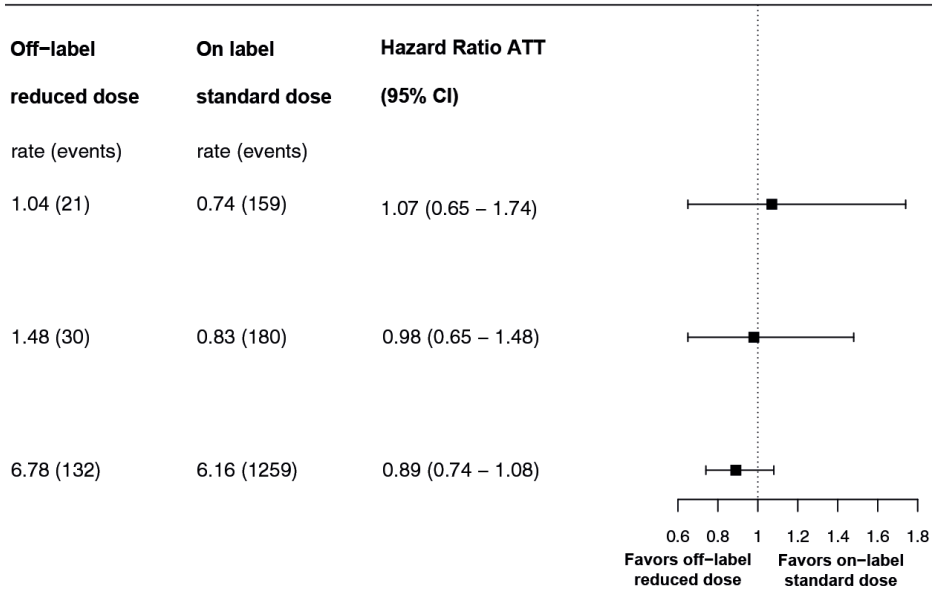
For major bleeding, we observed 30 events in the off-label reduced dose group and 180 events in the on-label standard dose group. The incidence rate for major bleeding was higher in the off-label dose reduced group compared to the on-label standard dose group (IR 1.48 and 0.83 per 100 person-years, respectively). The unadjusted HR for major bleeding was 1.63 (95% CI 1.11 to 2.41). After applying IPTW-ATT, the adjusted

HR for major bleeding was not different for the off-label dose reduced group compared to the on-label standard dose group (adjusted HR-ATT 0.98; 95% CI 0.65 to 1.48), nor did the IPTW-ATE analysis (adjusted HR-ATE 1.12; 95% CI 0.70 to 1.78).

Non-major bleeding occurred in 132 patients (5.3%) in the off-label reduced dose group, compared to 1259 patients (7.0%) in the on-label standard dose group (IR 6.78 and 6.16 per 100 person-years, respectively). The IPTW-ATT and IPTW-ATE analyses both showed a non-statistically significant trend towards a small reduction in non-major bleeding risk among patients receiving an off-label reduced dose (HR-ATT 0.89; 95% CI 0.74 to 1.08 and HR-ATE 0.87; 95% CI 0.69 to 1.10).

Unadjusted and adjusted hazard ratio's are presented in Table 3 and Figure 1, including also the results of the ATE analyses. After IPTW, all potential confounders among the weighted samples appeared to be well balanced, with standardised mean differences ≤ 0.099 (see Supplementary material, *Appendix Section C*).

FIGURE 1. FOREST PLOT SHOWING THE MAIN RESULTS, COMPARING OFF-LABEL DOSE REDUCTION TO ON-LABEL STANDARD DOSING



Event rates are incidence rates per 100 person years. ATT= average treatment effect among the treated.

TABLE 3. PRIMARY AND SECONDARY OUTCOMES FOR OFF-LABEL REDUCED DOSE VS. ON-LABEL STANDARD DOSE

	Off-label reduced dose (n=2,466)			On-label standard dose (n=18,108)			Off-label reduced dose vs. on-label standard dose		
	n events	Total follow-up (py)	Event rate per 100 py	n events	Total follow-up (py)	Event rate per 100 py	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI) ATT	Adjusted HR[b] (95% CI) ATE
Ischaemic stroke	21	2016.6	1.04 (0.66-1.57)	159	21499.8	0.74 (0.63-0.86)	1.32 (0.84-2.09)	1.07 (0.65-1.74)	1.25 (0.75-2.08)
Major bleeding	30	2027.2	1.48 (1.02-2.09)	180	21579.6	0.83 (0.72-0.96)	1.63 (1.11-2.41)	0.98 (0.65-1.48)	1.12 (0.70-1.78)
Non-major bleeding	132	1947.8	6.78 (5.69-8.01)	1259	20452.3	6.16 (5.82-6.50)	1.02 (0.86-1.23)	0.89 (0.74-1.08)	0.87 (0.69-1.10)

[a] Adjusted hazard ratios after IPTW using the propensity score with the IPTW-ATT weights, yielding the average treatment effect among the treated (ATT). [b] Adjusted hazard ratios after IPTW using the propensity score with the IPTW-ATE weights, yielding the average treatment effect (ATE) for the whole study population. Py, person-years.

DISCUSSION

This large population based cohort study showed that off-label dose reduction occurred in 8.0% of patients with AF treated with a NOAC and was most prevalent among edoxaban and rivaroxaban users. Physicians appeared to opt for off-label dose-reduction in older patients with more comorbidity, indicating that this is indeed a high-risk population for both thromboembolic events and bleeding risk, which is exemplified by the higher crude incidence rate for these outcomes in these patients. The adjusted hazard ratios of off-label dose reduction compared to on-label standard dose for ischaemic stroke, major bleeding and non-major bleeding were 1.07, 0.98 and 0.89, respectively, not reaching statistical significance.

Strengths and limitations

When putting these results into perspective, several strengths and limitations should first be considered. The main strength of this study is the large size and richness of the data in the UK CPRD. The availability of clinical and laboratory measurements like weight and renal function creates the possibility to determine the prevalence of off-label dose reduction *and* its health effects on relevant patient outcomes for a large number of patients with AF, in contrast to studies using claims databases, for example. The routine care general practice setting of the data source also ensures that results are generalizable to the general non-valvular AF population. We included only incident NOAC users, identified important signs of exposure misclassification and dealt with this through reclassification of the first 30 days after apparent discontinuation (i.e. we carried the last exposure status forward), and applied robust modelling techniques like IPTW to adjust for a large number of measured confounders. We added clinical relevance to this study by calculating the ATT, as a clinician would probably not consider off-label dose reduction in *all* patients, but more likely in old or frail patients who are suspected of a higher bleeding risk. Our study is also the first to compare the occurrence of the outcome *non*-major bleeding in patients with an off-label reduced dose to patients with an on-label standard dose. This is a particularly relevant outcome as clinicians might prescribe an off-label reduced NOAC dose to patients with an anticipated high risk or previous occurrence of a more frequently occurring non-major bleeding.

Nevertheless, for full appreciation, a few issues deserve further attention. First, a limitation of our study is the possibility of so-called *informative censoring*, especially in the one third of patients in whom follow-up time was censored because of NOAC discontinuation or switching to a different NOAC or dose. For instance, if a suspicion

of high bleeding risk arose during follow-up, a patient may have been switched to an off-label reduced dose and been subsequently censored. Any anticipated bleeding events in the future then would not have been captured in our data.

Second, and possibly in part due to censoring, the median length of follow-up (10.2 months) was relatively short. Previous studies in patients treated with warfarin showed risk of bleeding to be highest shortly after initiation of the anticoagulant.[33] The residual risk of ischaemic stroke, conversely, persists and may unfold only later on during anticoagulant treatment. Therefore, while possibly long enough for bleeding events our follow-up might have been too short to pick up a significant number of ischaemic strokes. Short follow-up, however, appears to be a common phenomenon in observational studies on oral anticoagulant use, especially in non-registry studies, as the median length of follow-up was only 12 months (range 4.0 to 39.3 months) in the other studies reporting on clinical impact of off-label dose reduction.[8–17]

Third, inherent to observational studies, is that exposure misclassification and confounding bias (especially unmeasured confounding) can never be completely eliminated. For example, bias due to misclassification of prescriptions classified as off-label reduced by assuming missing renal function and body weight to be normal could have occurred. However, the proportion of patients with missing data on renal function and body weight was small (3.1% and 16.7%, respectively). In addition, ethnicity was likely to be underreported, which might have caused the eGFR to be less precise. For dabigatran, the subjective criterion 'other increased bleeding risk' in which dose reduction can be considered, could not be identified in our data. Therefore, it is possible that we considered patients as off-label reduced while, albeit still quite subjectively, the dose was in fact on-label reduced. As this was a criterion only for dabigatran and on-label dose reduced patients were excluded, we expect the impact of this limitation to be minimal.

Fourth, in spite of the large size of UK CPRD, our study still suffered from small numbers of events for ischaemic stroke and major bleeding, also because of the relatively low prevalence of off-label dose reduction. This is reflected in the relatively wide 95% confidence intervals of the effect estimates. As CPRD is one of the largest routine clinical datasets with laboratory results available worldwide, combining multiple large routine care datasets would be necessary to draw definite conclusions, especially regarding the impact of dose reduction for the different NOACs. As the relative amount of dose reduction varies among the different NOACs, the clinical impact of off-label dose reduction could also vary between NOACs. For example, the reduced

dose of apixaban and edoxaban contains 50% of the standard dose, whereas the reduced dose of dabigatran and rivaroxaban still comprise about 75% of the standard dose. This hypothesis is supported by the study of Yao and colleagues, showing an increased risk of ischaemic stroke and systemic embolism only in patients receiving an off-label reduced dose of apixaban (adjusted HR 4.87; 95% CI 1.3 to 18.3), which was not observed for dabigatran and rivaroxaban.[12] Lastly, we did not have data on hospital admissions, drug adherence and reasons why physicians decided to prescribe an off-label reduced dose.

Comparison with existing literature

In our study, off-label dose reduction occurred in 8.0% of all NOAC prescriptions, which is somewhat lower compared to previous literature although prevalence numbers in other studies are highly variable. Garcia Rodriguez and colleagues also used CPRD data (in combination with data from The Heath Improvement Network (THIN)) to evaluate the occurrence of off-label dose reduction of NOACs, albeit without investigating clinical outcomes.[34] They observed an overall prevalence of 13.5% underdosing. To see if these differences were due to better guideline adherence over time (since Garcia Rodriguez only included patients up to 2016), we explored the proportion off-label dose reduction per entry-year, but did not observe any decrease in prevalence off-label dose reduction in the more recent years (data not shown). It is therefore likely that other differences in methodological choices made between studies as well as the addition of THIN data in the study of Garcia Rodriguez *et al,* could explain the observed differences in prevalence of off-label dose reduction. Most studies evaluating off-label dose reduction for the different NOACs have reported off-label dose reduction to occur most frequently for apixaban.[9,12,34–36] In our study, the prevalence of off-label dose reduction among apixaban users was only 6.2%, and highest for edoxaban (11.8%). More complex dose reduction criteria for apixaban have been suggested to be responsible for the higher prevalence of underdosing with apixaban, although our data might attenuate this concern.[35]

When looking at observational studies, nine have investigated the occurrence of ischaemic stroke events among patients receiving an off-label reduced dose.[9–17] Results are inconsistent and most studies reported small numbers of events (the median number of ischaemic strokes among the off-label reduced dose patients in these studies was 11, range 4 to 29). Only one of these studies, by Cheng and colleagues, reported a statistically significant increased risk of ischaemic stroke (adjusted HR 2.75; 95% CI 1.62 to 4.69), although they compared patients receiving

an off-label reduced dose to *all* patients receiving an on-label dose, including on-label reduced dosages.

For major bleeding, the observation that off-label dose reduction does not decrease major bleeding risk is further strengthened by our study. In line with our findings, nine out of ten studies that have evaluated occurrence of major bleeding among patients receiving an off-label reduced dose showed no statistically significant difference when comparing patients with an off-label reduced dose to patients receiving an (on-label) standard dose.[8–17] Four of these studies reported a trend towards an increased risk of major bleeding among off-label reduced dose patients, of which Shrestha and colleagues show a statistically significant increase (adjusted HR 3.1; 95% CI 1.15 to 8.39). [8,11,16,17] To the best of our knowledge, our study is the first to compare the occurrence of non-major bleeding between off-label reduced dose and on-label standard dose users, a relevant outcome especially from a patient perspective.

The ATE analysis in our study allows for a direct comparison with the randomised trial RELY, which compared two different dosages of dabigatran with each other. In the RELY-trial, patients randomised to the 150 mg dose had a significantly lower risk of ischaemic stroke or systemic embolism than patients using the 110 mg dose, a higher risk of major bleeding (especially gastro-intestinal bleeding), and a comparable risk of minor bleeding and intracranial bleeding.[37] While we did observe a trend towards an increased risk of ischaemic stroke in our data, we did not observe similar patterns for bleeding risk (although the small numbers of events were small and did not allow for the analyses to be stratified per NOAC). This emphasises the challenge to generalise findings from randomised trials to clinical practice, and the importance of observational studies using routine care data.

Clinical implications and future considerations

The observed differences in baseline characteristics suggest that physicians may indeed weigh for instance patient age, history of stroke/TIA and history of bleeding in deciding between an off-label reduced NOAC dose and an on-label standard dose. Our data indeed indicate that they intuitively correctly identify a group with a high risk of bleeding, as the crude incidence rates of bleeding were highest in the group with off-label dose-reduction. Fear of bleeding in frail elderly patients, therefore, may be an important driver for off-label dose reduction.

However, our results suggest that by reducing the NOAC dose without a clear indication to do so, risk of major bleeding is *not* attenuated at all. The ATT HR of 0.98 (95% CI

0.65 to 1.48) indicates that patients who are given an off-label dose reduction do not benefit in terms of a reduction in bleeding risk. Perhaps different interventions, such as managing so-called modifiable risk factors as described by the ESC in the 2016 guidelines for the management of AF (e.g. hypertension control and preventing use of NSAIDs or platelet inhibitors), and carefully monitoring kidney function are more effective strategies to prevent bleeds.[38] Indeed, the proportion of patients with hypertension, NSAID-use or concurrent antiplatelet therapy was highest in the group of patients where physicians opted for off-label dose-reduction.

Future research may not only serve to confirm our findings on clinical outcomes of off-label dose reduction, but also to support the hypothesis that different strategies are needed to prevent bleeding complications in the often frail, elderly patients with AF treated with NOACs. In addition, given the observational nature of our data and small number of events, our results emphasise that further research in even larger or combined routine care datasets is warranted to confirm whether off-label dose reduction indeed does not reduce bleeding risk.

Conclusion

In this large study in routine clinical practice, off-label NOAC dose reduction occurred in 8% of patients with AF receiving a NOAC, predominantly those at high risk of bleeding. This dose reduction, however, did not appear to influence the risk of stroke and, importantly, the risk of major bleeding. Therefore, our data suggest that off-label NOAC dose reduction is unlikely to be a fruitful strategy when aiming to reduce the, indeed elevated, major bleeding risk in certain older patients with AF and multimorbidity.

CONTRIBUTORS

CD, SD, GJG, PS and HH wrote the ISAC study protocol. PS, CD and RP prepared the dataset. CD, RP and SD performed the analyses. KM, GJG, AH and HH advised in interpreting the results. CD wrote the first version of the manuscript. All authors participated in revising the manuscript. SD is the guarantor.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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SUPPLEMENTARY MATERIAL

APPENDIX, SECTION A. READ CODES DEFINING OUTCOMES

Ischaemic stroke

readcode	readterm
G63..11	Infarction - precerebral
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs

Gyu6400	[X]Other cerebral infarction
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
G654.00	Multiple and bilateral precerebral artery syndromes
G64z400	Infarction of basal ganglia

Major bleeding (including intracerebral and gastro-intestinal bleeding)

readcode	**readterm**
S62..00	Cerebral haemorrhage following injury
S62..11	Extradural haemorrhage following injury
S62..12	Subarachnoid haemorrhage following injury
S62..13	Subdural haemorrhage following injury
S62..14	Traumatic cerebral haemorrhage
S620.00	Closed traumatic subarachnoid haemorrhage
S620100	Subarachnoid h'ge inj no open intracran wnd+no loss consc
S620600	Subarach h'ge inj no open intracran wnd+LOC unspec duration
S620z00	Subarach h'ge inj no open intracran wnd + concussion unspec
S621.00	Open traumatic subarachnoid haemorrhage
S621z00	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
S622.00	Closed traumatic subdural haemorrhage
S622000	Subdural h'ge inj no open intracranial wnd + unspec consc
S622300	Subdural h'ge inj no open intracran wnd+1-24hr loss consc
S622600	Subdural h'ge inj no open intracran wnd+LOC unspec duration
S622z00	Subdural h'ge inj no open intracran wound+concussion unspec
S623.00	Open traumatic subdural haemorrhage
S624.00	Closed traumatic extradural haemorrhage
S624000	Extradural h'ge inj no open intracranial wnd + unspec consc
S624100	Extradural h'ge inj no open intracranial wnd + no loss consc
S624z00	Extradural h'ge inj no open intracran wnd+concussion unspec
S625.00	Open traumatic extradural haemorrhage
S626.00	Epidural haemorrhage
S627.00	Traumatic subarachnoid haemorrhage
S628.00	Traumatic subdural haemorrhage
S62z.00	Cerebral haemorrhage following injury NOS
S63..00	Other cerebral haemorrhage following injury
S630.00	Other cerebral h'ge after injury no open intracranial wound
S630.12	Intracranial haematoma following injury
S630000	Oth cerebral h'ge inj no open intracran wnd+unspec consc
S630100	Oth cerebral h'ge inj no open intracranial wnd+no loss consc
S630200	Oth cerebral h'ge inj no open intracran wnd+<1hr loss consc
S630300	Oth cerebral h'ge inj no open intracran wnd+1-24hr LOC
S630400	Oth cereb h'ge inj no open intracran wnd+>24hr LOC +recovery
S631300	Oth cerebral h'ge inj + open intracran wnd+1-24hr loss consc
S63z.00	Other cerebral haemorrhage following injury NOS
G60..00	Subarachnoid haemorrhage

G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
G62z.00	Intracranial haemorrhage NOS
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
G621.00	Subdural haemorrhage - nontraumatic
1720.00	Massive haemoptysis
D211.00	Acute posthaemorrhagic anaemia
D211.11	Normocytic anaemia following acute bleed
F212.00	Acute and subacute haemorrhagic leukoencephalitis [Hurst]
F404300	Haemophthalmos (excluding current injury)
F404500	Intra-ocular haemorrhage
F42y.11	Haemorrhage - retinal
F42y000	Preretinal heamorrhage
F42y100	Superficial retinal haemorrhage

F42y300	Deep retinal haemorrhage
F42y400	Subretinal haemorrhage
F42y500	Retinal haemorrhage NOS
F436.00	Choroidal haemorrhage and rupture
F436000	Unspecified choroidal haemorrhage
F436100	Expulsive choroidal haemorrhage
F436z00	Choroidal haemorrhage or rupture NOS
F437200	Haemorrhagic choroidal detachment
F4K2800	Vitreous haemorrhage
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere
G8y0.00	Haemorrhage NOS
H51y200	Haemothorax
N091.00	Haemarthrosis
N091000	Haemarthrosis of unspecified site
G850.00	Oesophageal varices with bleeding
J10y000	Haemorrhage of oesophagus
J68..00	Gastrointestinal haemorrhage
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z200	Upper gastrointestinal haemorrhage
J68zz00	Gastrointestinal tract haemorrhage NOS
J68z000	Gastric haemorrhage NOS
J68z100	Intestinal haemorrhage NOS
J681.00	Melaena
J680.00	Haematemesis
J680.11	Vomiting of blood
J110100	Acute gastric ulcer with haemorrhage
J110300	Acute gastric ulcer with haemorrhage and perforation
J111100	Chronic gastric ulcer with haemorrhage
J111300	Chronic gastric ulcer with haemorrhage and perforation
J11y100	Unspecified gastric ulcer with haemorrhage
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J120100	Acute duodenal ulcer with haemorrhage
J120300	Acute duodenal ulcer with haemorrhage and perforation
J121100	Chronic duodenal ulcer with haemorrhage
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J130100	Acute peptic ulcer with haemorrhage
J13y100	Unspecified peptic ulcer with haemorrhage
J131100	Chronic peptic ulcer with haemorrhage
J130300	Acute peptic ulcer with haemorrhage and perforation
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J140100	Acute gastrojejunal ulcer with haemorrhage

J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J150000	Acute haemorrhagic gastritis
J56y000	Haemoperitoneum - nontraumatic
J121111	Bleeding chronic duodenal ulcer
J111111	Bleeding chronic gastric ulcer
J110111	Bleeding acute gastric ulcer
G852000	Oesophageal varices with bleeding in diseases EC

Non-major bleeding

readcode	**readterm**
172..00	Blood in sputum - haemoptysis
172..12	Haemoptysis - symptom
1A45.00	Blood in urine - haematuria
1A45.12	Haematuria - symptom
1C6..11	Epistaxis symptom
1C62.00	Has nose bleeds - epistaxis
2D25.00	O/E - epistaxis
F4C7100	Subconjunctival haemorrhage
F4C7200	Conjunctival haemorrhage NOS
F4G3200	Exophthalmos due to orbital haemorrhage
F4K7.00	Retrobulbar haemorrhage
K0A2.00	Recurrent and persistent haematuria
K0A2000	Recurrent+persistnt haematuria minor glomerular abnormality
K0A2100	Recur+persist haematuria, focal+segmental glomerular lesions
K0A2200	Recur+persist haematuria difus membranous glomerulonephritis
K0A2600	Recurrent and persistent haematuria, dense deposit disease
K197.00	Haematuria
K197.12	Essential haematuria
K197000	Painless haematuria
K197100	Painful haematuria
K197300	Frank haematuria
K197400	Clot haematuria
K5A1.00	Postmenopausal bleeding
R047.00	[D]Epistaxis
R048.00	[D]Throat haemorrhage
R063.00	[D]Haemoptysis
R063z00	[D]Haemoptysis NOS
K167.00	Haemorrhage into bladder wall
J681.11	Blood in stool
J681.13	Blood in stools altered
J681.12	Altered blood in stools
J573.00	Haemorrhage of rectum and anus

J573000	Rectal haemorrhage
J573100	Anal haemorrhage
J573z00	Haemorrhage of rectum and anus NOS
J573011	Rectal bleeding
J573.11	Bleeding PR
J510900	Bleeding diverticulosis
J573012	PRB - Rectal bleeding

APPENDIX, SECTION B. VARIABLES INCLUDED IN THE PROPENSITY SCORE*

Sex, history of gastrointestinal bleeding, history of intracranial bleeding, alcohol abuse, hypertension, hypercholesterolemia, ischaemic heart disease, peripheral artery disease, history of stroke/TIA, history of deep vein thrombosis, history of venous thromboembolism, history of cancer, history of gastric ulcer, history of gastritis, history of gastro-oesophageal reflux disease, history of esophagitis, mild liver disease, severe liver disease, heart failure, diabetes mellitus, anaemia, thrombocytopenia, use of non-steroidal anti-inflammatory drugs (NSAIDs), use of selective serotonin reuptake inhibitor (SSRI), use of oral corticosteroids, use of antiplatelet therapy, statin use, calcium channel blocker use, use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), use of diuretics, use of digoxin, use of proton pump inhibitors (PPI), use of CYP3A4/P-gp inhibitors, use of CYP3A4/P-gp inducers, use of beta blocking agents, age, creatinine level, body weight and estimated glomerular filtration rate (eGFR).

*Variables (39 in total) were included in the propensity score when they were presumed (expert-based) to be associated with the outcome, not necessarily with the exposure. Variables that were associated with the outcome *only through the exposure* (i.e. instrumental variables) were not included in the propensity score.

APPENDIX, SECTION C. BALANCE STATISTICS (BEFORE AND AFTER APPLYING IPTW-ATT WEIGHTS)

	Mean on-label standard dose	Mean off-label reduced dose	Weighted mean on-label standard dose	Weighted mean off-label reduced dose	**Standardised mean difference**
Sex	0.379	0.460	0.473	0.460	**-0.026**
History of gastrointestinal bleeding	0.026	0.042	0.044	0.042	**-0.010**
History of intracranial bleeding	0.009	0.018	0.018	0.018	**0.000**
Alcohol abuse	0.125	0.084	0.086	0.084	**-0.007**
Hypertension	0.585	0.670	0.664	0.670	**0.013**
Hypercholesterolemia	0.143	0.155	0.154	0.155	**0.003**
Ischemic heart disease	0.217	0.311	0.308	0.311	**0.006**
Peripheral artery disease	0.035	0.062	0.060	0.062	**0.008**
History of stroke/TIA	0.177	0.242	0.240	0.242	**0.005**
History of deep venous thrombosis	0.009	0.010	0.010	0.010	**0.000**
History of cancer	0.038	0.041	0.041	0.041	**0.000**
History of gastric ulcer	0.059	0.077	0.074	0.077	**0.011**
Mild liver disease	0.021	0.015	0.016	0.015	**-0.008**
Severe liver disease	0.001	0.002	0.004	0.002	**-0.037**
Thrombocytopenia	0.000	0.000	0.000	0.000	**0.000**
Heart failure	0.127	0.183	0.178	0.183	**0.013**
Diabetes mellitus	0.190	0.230	0.223	0.230	**0.017**
Anemia	0.001	0.001	0.001	0.001	**0.000**
NSAIDs	0.041	0.028	0.030	0.028	**-0.012**
SSRIs	0.091	0.091	0.091	0.091	**0.000**
Oral corticosteroids	0.098	0.118	0.122	0.118	**-0.012**
Antiplatelet therapy	0.371	0.431	0.430	0.431	**0.002**
Statins	0.512	0.539	0.529	0.539	**0.020**
Calcium channel blockers	0.316	0.334	0.332	0.334	**0.004**
ACE/ARB	0.493	0.530	0.521	0.530	**0.018**
Diuretics	0.321	0.462	0.456	0.462	**0.012**
Digoxin	0.092	0.145	0.151	0.145	**-0.017**
Proton pump inhibitors	0.381	0.425	0.422	0.425	**0.006**
CYP3A4/P-gp inhibitors	0.099	0.119	0.123	0.119	**-0.012**
CYP3A4/P-gp inducers	0.004	0.008	0.008	0.008	**0.000**
Beta blocking agents	0.503	0.511	0.510	0.511	**0.002**
History of VTE	0.037	0.044	0.048	0.044	**-0.019**
History of gastritis	0.092	0.103	0.100	0.103	**0.010**

CONTINUED

	Mean on-label standard dose	Mean off-label reduced dose	Weighted mean on-label standard dose	Weighted mean off-label reduced dose	**Standardised mean difference**
History of GERD	0.213	0.234	0.227	0.234	**0.017**
History of oesophagitis	0.098	0.109	0.105	0.109	**0.013**
Age	71.367	78.634	77.998	78.634	**0.068**
Creatinine level	81.515	94.516	91.799	94.516	**0.099**
Body weight	86.209	78.779	78.976	78.779	**-0.012**
eGFR	76.293	63.276	63.994	63.276	**-0.042**

TIA, transient ischaemic attack; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CYP, cytochrome P450; P-gp, P-glycoprotein; VTE, venous thromboembolism; GERD, gastro-oesophageal reflux disease; eGFR, estimated glomerular filtration rate.

THE NUMBER OF CONCOMITANT DRUGS AND THE SAFETY OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN ROUTINE CARE PATIENTS WITH ATRIAL FIBRILLATION

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Submitted

ABSTRACT

Background: The benefit of non-vitamin K antagonist oral anticoagulants (NOACs) versus vitamin K antagonists (VKAs) on major bleeding appeared less prominent among atrial fibrillation (AF) patients with polypharmacy in post-hoc analyses of trials. If this phenomenon also exists in routine care is unknown.

Objectives: To investigate whether the number of concomitant drugs prescribed modifies major bleeding risk of NOACs compared to VKAs in patients with AF treated in general practice.

Patients/Methods: Adult, non-valvular AF patients with a first NOAC or VKA prescription between January 2010 and July 2018 were included, using data from the United Kingdom Clinical Practice Research Datalink. The primary outcome was major bleeding. Effect modification was assessed by stratification of the number of concomitant drugs into three strata (0-5, 6-8, ≥9 drugs), and by including the continuous variable in an interaction term with the exposure (NOAC vs. VKA).

Results: 63,600 patients with 146,059 person-years of follow-up were analysed (39,840 person-years of NOAC follow-up). Median number of concomitant drugs prescribed was 7. Incidence rates for major bleeding were generally low, and highest in the stratum of 0-5 concomitant drugs (1.39 per 100 person-years for VKA; 1.29 per 100 person-years for NOAC). The adjusted hazard ratio of major bleeding with NOAC versus VKA was 0.98 (95% confidence interval 0.87 to 1.11), with no apparent differences across the 3 strata (interaction p-value 0.65).

Conclusion: In this large study of patients with AF treated in general practice, the number of concomitant drugs did not modify the risk of major bleeding under NOACs versus VKA.

What is known on this topic?

- In clinical trials, non-vitamin K antagonist oral anticoagulants (NOACs) were associated with a lower risk of bleeding complications compared to vitamin K antagonists (VKA) in patients with atrial fibrillation (AF)
- However, in post-hoc analyses this benefit appeared less prominent among AF patients with polypharmacy

What does this paper add?

- In this study using data from routine general practice, the number of concomitant drugs did not modify the risk of major bleeding under NOACs versus VKA

INTRODUCTION

In atrial fibrillation (AF) management, stroke prevention with anticoagulation is pivotal, as the risk of stroke is increased 5-fold in patients with AF if left untreated.[1] For many years, vitamin K antagonists (VKAs) have been the cornerstone therapy in anticoagulation management. Recently, non-VKA oral anticoagulants (NOACs), also known as direct oral anticoagulants (DOACs), became the preferred alternative.[2,3] The original randomised trials on dabigatran, apixaban, rivaroxaban and edoxaban all demonstrate that these drugs are as effective in reducing stroke risk compared to VKAs, while their risk of gastro-intestinal bleeding is increased (except for apixaban) and their risk of major bleeding and especially intracranial haemorrhage decreased.[4]

Patients with AF often use multiple drugs, as most patients with AF are of high age and suffer from multiple comorbidities.[5,6] In two trials, post-hoc analyses examined the impact of polypharmacy (defined as ≥5 concomitant drugs) on the relative risk estimates of the NOACs rivaroxaban and apixaban versus warfarin on major bleeding, respectively. For both NOACs the risk of bleeding increased when the number of concomitant drugs prescribed increased. For apixaban versus warfarin, the benefits of bleeding risk reduction decreased when the number of drugs increased. [7] For rivaroxaban, the reduced risk of major bleeding as compared to warfarin even completely disappeared in patients using 5 or more drugs, which was also shown in a systematic review of these NOAC trials.[8,9] Whether these trial results are generalizable to patients with AF treated in routine care is debatable. The proportion of eligible patients that actually participates in randomised trials is often low (or unknown, as in the NOAC trials) and more importantly, characteristics of patients included in the trials often differ from the characteristics of patients treated in routine

care.[10,11] This makes the generalizability of trial data particularly questionable in elderly patients, to whom NOACs nowadays are increasingly prescribed. As the use of multiple concomitant drugs is generally the rule rather than the exception in the elderly[12] and because the number of concomitant drugs is easy to assess by clinicians, it would be valuable to know whether the number of concomitant drugs affects the safety and efficacy of NOACs compared to VKA in routine care, and, thus, whether this should be taken into account when choosing either treatment strategy.

With this study, we aim to investigate whether the relative safety and efficacy of NOACs compared to VKAs are influenced by the number of concomitant drugs prescribed to patients with AF treated in routine practice. The UK Clinical Practice Research Datalink (CPRD) offers a unique opportunity to quantify the influence of the number of concomitant drugs prescribed on safety and efficacy outcomes in a large number of patients with AF in daily practice, followed over a long period of time.

METHODS

Study design and data source

This retrospective cohort study was performed using data from the UK Clinical Practice Research Datalink (CPRD). This large, widely used, and nationally representative dataset includes electronic health care records from over 11.3 million patients (covering 6.9% of the UK population) treated in general practice in the United Kingdom.[13] Available data from routine clinical practice include demographic characteristics, medical history, drug prescriptions, clinical events and hospital referrals. Drug prescriptions are coded using the British National Formulary (BNF) and clinical symptoms and diagnoses are recorded with Read codes. The validity of the diagnoses recorded in CPRD was demonstrated in previous studies.[14,15] The study protocol was approved by the CPRD ISAC Committee (ISAC protocol number 18_241R). This manuscript was written in accordance with the STROBE guideline for reporting observational studies.[16]

Study population

Adult patients with a first prescription of a NOAC or VKA during the period of January 1st 2010 to July 1st 2018 were included. To ensure that only new users were included, patients could not have a prescription of the same oral anticoagulant (OAC) in the 12 months prior to the date of the first prescription (index date). However, patients were

not necessarily OAC naive: the group of patients with a first NOAC prescription could also include patients with previous VKA use (i.e. switchers), and vice versa.

Only patients with a diagnosis of AF, recorded ever before the index date, were included. To study patients with non-valvular AF only, we excluded patients with a prosthetic heart valve or a history of rheumatic mitral valve stenosis. Patients needed to be enrolled in the database at least twelve months prior to the index date to ensure that valid baseline data were available. Follow-up ended when a patient had the outcome of interest or when a patient was censored (in case of death, moving out of the CPRD practice, end of data collection of the CPRD practice, or end of study period), or on the last day valid data were available (whichever occurred first). A separate dataset was created for each outcome.

Exposure

Treatment episodes, defined as series of subsequent OAC prescriptions independent of dose changes, were constructed according to the method of Gardarsdottir *et al*, in order to define current use and past use of oral anticoagulants.[17] A permissible gap time, or grace period, of 60 days between the theoretical end date of a prescription and the next prescription was allowed for, as patients may have had tablets left due to non-adherence or temporary discontinuation around invasive medical procedures or, in VKA users, in case of too high International Normalized Ratio (INR) values.

During the analysis phase, it appeared that a considerable number of major bleeding events occurred shortly after the end of a current use period. In fact, the incidence rate for major bleeding was higher in the period immediately following apparent discontinuation than during exposure to VKA or NOAC, which is highly improbable and is most likely explained by exposure misclassification at the time of the recorded outcome. If this follow-up time would indeed be classified as non-exposed, a third of all bleeding events would have been ignored. Moreover, this would have introduced a major source of bias, as for almost all 'unexposed' periods the last anticoagulant used was a VKA, which seems reasonable given that VKAs are more prone to stockpiling than NOACs due to the varying dosage regimen. Therefore, we post-hoc reclassified the first treatment period (max. 91 days) after apparent discontinuation to the last anticoagulant used for all analyses (i.e. a 'last measurement carried forward' approach).

Outcome

The primary outcome was major bleeding, defined as a symptomatic bleeding in one of the following critical areas or organs: intracranial, intraspinal, retroperitoneal,

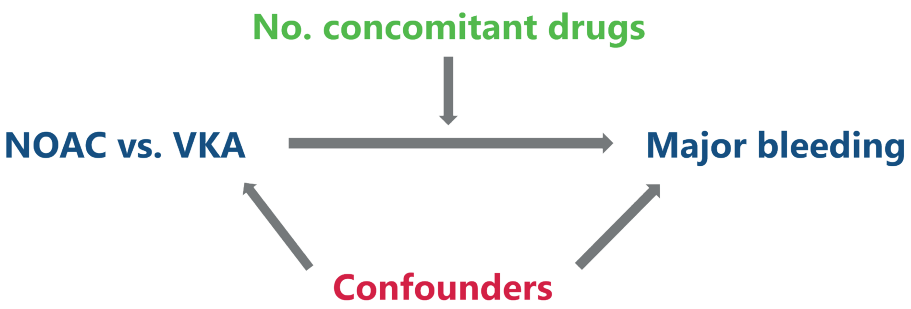
intraocular, gastrointestinal, intra-articular or intrathoracic. This definition was chosen, as the definition of major bleeding recommended by the International Society on Thrombosis and Haemostasis (ISTH)[18] is difficult to use because of missing information about haemoglobin levels or blood transfusions in CPRD data.

Secondary outcomes were ischaemic stroke, gastrointestinal bleeding, non-major bleeding and all-cause mortality. Ischaemic strokes registered during the first month of NOAC or VKA use were excluded, (i.e. a so called blanking or quarantine period), because in those cases an ischaemic stroke is probably the first presentation of atrial fibrillation, when the anticoagulant had not yet been started.[19] Thus, in those cases the OAC is initiated because of the ischaemic stroke and subsequent detection of AF, rather than the occurrence of an ischaemic stroke during follow-up. Due to the possibility of late registration of the stroke in the GP registry, counting these strokes as outcome events during anticoagulation treatment would induce misclassification.[19] Lists of the Read codes defining each outcome are provided in the appendix, section 1.

Effect modification

Figure 1 shows a graphical display of the relations between the different variables in this study. The primary interest of this study was to quantify the influence of the number of concomitant drugs prescribed on the safety and efficacy of NOACs versus VKAs; thus to quantify effect modification by the number of concomitant drugs. This variable was constructed by counting the total number of unique BNF codes prescribed to each patient during each treatment period, excluding all non-pharmacological prescriptions (for instance wound care bandages, stockings, stoma/incontinence materials).

FIGURE 1. THE RELATION BETWEEN THE EXPOSURE, PRIMARY OUTCOME, EFFECT MODIFIER (THE NUMBER OF CONCOMITANT DRUGS, PRIMARILY OF INTEREST IN THIS STUDY), AND CONFOUNDERS



Confounding

A priori, we identified a separate set of possible confounders for each outcome based on prior evidence. For the primary outcome major bleeding, the following 17 patient characteristics were included as possible confounders in the analyses: age, sex, previous use of a different anticoagulant, alcohol abuse, liver disease, chronic kidney disease, hypertension (treated or untreated), history of gastrointestinal bleeding, history of intracranial bleeding, cardiovascular disease (defined as a history of ischaemic heart disease, peripheral artery disease, stroke or transient ischaemic attack (TIA)), active cancer, peptic ulcer disease, concomitant use of platelet inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, proton pump inhibitors (PPIs) or selective serotonin reuptake inhibitors (SSRIs). The confounders for the secondary outcomes are listed in the appendix, section 2. None of the confounding variables were possible intermediate variables in the relation between the exposure and outcome.

Statistical analysis

All variables regarding exposure, confounding (except for sex and alcohol abuse) and the number of concomitant drugs prescribed were treated as time-varying variables and updated either when the exposure status changed, or every 90 days if the exposure remained unchanged. Incidence rates were reported as the number of events per 100 person years. Cox proportional hazard regression models were used to estimate hazard ratios and their 95% confidence intervals when comparing NOACs with VKA. The proportional hazards assumption was assessed visually by plotting the scaled Schoenfeld residuals.[20] We used multivariable Cox regression to adjust for potential confounders mentioned above. To address the effect of the total number of concomitant drugs prescribed and answer our primary research question, we created three strata of the number of concomitant drugs prescribed: 0-5, 6-8, and 9 or more drugs. These cut-offs were chosen as they provided the most equal distribution of the number of patients across the strata. Next, to test for statistically significant effect modification, we included the continuous variable 'number of concomitant drugs*OAC treatment' as an interaction term in the multivariate Cox regression model to derive the p-value for interaction. In case of few events compared to the number of confounding variables adjusted for, Firths correction (a penalised regression technique), with Wald confidence intervals and p-values, was applied to mitigate possible small sample bias.[21] Additionally, we investigated whether the results for major bleeding differed when separately comparing apixaban, rivaroxaban and dabigatran to warfarin.

We performed three sensitivity analyses for the primary outcome (major bleeding). First, we analysed the data without reclassifying any unexposed periods, so without our

post-hoc defined 'last measurement carried forward' approach. Second, we excluded patients who had other indications for OAC (for instance pulmonary embolism or knee/hip replacement surgery) registered within 3 months before and after the index date to ensure that AF was indeed the reason the anticoagulant was started. Finally, we excluded prescriptions from the variable 'number of concomitant drugs prescribed' which we regarded to be less relevant (first all topical drugs and second all incidental prescriptions, see appendix section 3 for an overview of the BNF chapters that were excluded in the sensitivity analyses).

A p-value of 0.05 or lower (or a 95% confidence interval not including a hazard ratio of 1) was considered statistically significant. All analyses were performed using *R* version 3.4.4 and *R* Studio version 1.1.442.[22] The package "survival" (version 2.38) was used for all Cox models, and the package "coxphf" (version 1.13) for Firths correction.[23,24]

RESULTS

Baseline characteristics

In total, 63,600 patients with AF were included (67% of patients using a VKA and 33% using a NOAC at cohort entry), contributing to a total of 146,059 person years of follow-up for the primary outcome major bleeding. Median follow-up time was 2.0 years for VKA patients and 1.1 years for NOAC patients. Patients were exposed to a VKA during 106,219 person years of follow-up (73%) and to a NOAC during 39,840 person years of follow-up (27%). Rivaroxaban accounted for 48% of follow-up time exposed to NOAC, apixaban for 38%, dabigatran for 13% and edoxaban for 4%. Baseline characteristics per stratum are shown in Table 1. At baseline, 19,479 patients (31%) used 0-5 concomitant drugs, 19,012 patients (30%) used 6-8 concomitant drugs and 25,019 patients (39%) used 9 or more concomitant drugs.

In both NOAC and VKA users, median age was 76 years (interquartile range (IQR) 68-82) and the median number of concomitant drugs prescribed was 7 (IQR 5 to 10). The prevalence of comorbidities increased among patients using more concomitant drugs and was similar for VKA and NOAC patients, although heart failure and coronary artery disease were more prevalent in patients using a VKA than in NOAC-users at baseline (unstratified proportions 13.5% versus 11.7% and 26.3% versus 23.6%, respectively). Consequently, beta blocking agents, diuretics, ACE inhibitors/ARBs and digoxin were more often used in the VKA group. In the six months prior to the index date, more VKA patients used antiplatelet therapy than NOAC patients.

TABLE 1. BASELINE CHARACTERISTICS PER STRATUM OF THE NUMBER OF CONCOMITANT DRUGS PRESCRIBED

	Stratum 1 (0-5 drugs)		Stratum 2 (6-8 drugs)		Stratum 3 (≥9 drugs)	
	VKA (n=12,607)	NOAC (n=6,872)	VKA (n=12,798)	NOAC (n=6,214)	VKA (n=17,019)	NOAC (n=8,090)
Female	4,715 (37.4)	2,639 (38.4)	5,654 (44.2)	2,700 (43.5)	8,204 (48.2)	4,099 (50.7)
Age, median (IQR)	73 (65-80)	72 (65-80)	76 (69-82)	76 (69-84)	77 (71-83)	79 (72-85)
N. conc. drugs, median (IQR)	4 (3-5)	4 (3-5)	7 (6-8)	7 (6-8)	11 (10-14)	11 (10-14)
Previous use of different OAC	1 (0.0)	312 (4.5)	2 (0.0)	315 (5.1)	2 (0.0)	495 (6.1)
Comorbidities/risk factors						
Hypertension	5,806 (46.1)	3,102 (45.1)	8,604 (67.2)	4,166 (67.0)	1,2585 (73.9)	5,890 (72.8)
Heart failure	813 (6.4)	365 (5.3)	1,591 (12.4)	661 (10.6)	3,322 (19.5)	1,462 (18.1)
Diabetes	804 (6.4)	475 (6.9)	1,833 (14.3)	1,038 (16.7)	5,152 (30.3)	2,449 (30.3)
Prior TIA or ischaemic stroke	1,661 (13.2)	957 (13.9)	2,413 (18.9)	1,224 (19.7)	3,547 (20.8)	1,889 (23.3)
Prior VTE	509 (4.0)	145 (2.1)	534 (4.2)	163 (2.6)	953 (5.6)	323 (4.0)
Coronary artery disease	1,408 (11.2)	733 (10.7)	3,012 (23.5)	1,415 (22.8)	6,744 (39.6)	2,854 (35.3)
Presence of malignancy	403 (3.2)	217 (3.2)	426 (3.3)	244 (3.9)	730 (4.3)	334 (4.1)
Chronic kidney disease	1,662 (13.2)	826 (12.0)	2,914 (22.8)	1,320 (21.2)	5,416 (31.8)	2,478 (30.6)
Prior major bleeding	344 (2.7)	226 (3.3)	548 (4.3)	302 (4.9)	1,083 (6.4)	545 (6.7)
Peptic ulcer disease	534 (4.2)	289 (4.2)	807 (6.3)	409 (6.6)	1,432 (8.4)	712 (8.8)
Alcohol abuse	847 (6.7)	667 (9.7)	942 (7.4)	663 (10.7)	1,387 (8.1)	921 (11.4)
Active smoking	1,070 (8.5)	605 (8.8)	1,040 (8.1)	550 (8.9)	1,475 (8.7)	814 (10.1)

TABLE 1. ***CONTINUED***

	Stratum 1 (0-5 drugs)		Stratum 2 (6-8 drugs)		Stratum 3 (≥9 drugs)	
	VKA (n=12,607)	NOAC (n=6,872)	VKA (n=12,798)	NOAC (n=6,214)	VKA (n=17,019)	NOAC (n=8,090)
Prior use of drugs increasing bleeding risk						
Antiplatelet therapy	5,937 (47.1)	2,341 (34.1)	7,745 (60.5)	3,159 (50.8)	1,2045 (70.8)	4,979 (61.5)
NSAIDs	625 (5.0)	212 (3.1)	838 (6.5)	252 (4.1)	1,435 (8.4)	486 (6.0)
Corticosteroids	420 (3.3)	241 (3.5)	866 (6.8)	422 (6.8)	3,081 (18.1)	1,474 (18.2)
SSRI	424 (3.4)	263 (3.8)	720 (5.6)	409 (6.6)	1,971 (11.6)	1,121 (13.9)
CYP3A4/P-gp inhibitors	884 (7.0)	368 (5.4)	1,260 (9.8)	463 (7.5)	2,806 (16.5)	1,063 (13.1)
CYP3A4/P-gp inducers	32 (0.3)	14 (0.2)	47 (0.4)	21 (0.3)	159 (0.9)	65 (0.8)
Other drugs						
Beta blocking agents	5,798 (46.0)	2,596 (37.8)	6,946 (54.3)	2,963 (47.7)	9,270 (54.5)	4,001 (49.5)
Diuretics	2,873 (22.8)	1,240 (18.0)	5,434 (42.5)	2,168 (34.9)	10,025 (58.9)	4,090 (50.6)
ACE inhibitors/ARB	4,096 (32.5)	2,021 (29.4)	7,155 (55.9)	3,247 (52.3)	11,437 (67.2)	4,857 (60.0)
Calcium channel blockers	2,864 (22.7)	1,582 (23.0)	4,764 (37.2)	2,197 (35.4)	7,404 (43.5)	3,278 (40.5)
Digoxin	772 (6.1)	192 (2.8)	1,241 (9.7)	345 (5.6)	2,463 (14.5)	755 (9.3)
Statins	3,858 (30.6)	2,160 (31.4)	6,754 (52.8)	3,315 (53.3)	11,367 (66.8)	5,164 (63.8
Proton pump inhibitors	2,521 (20.0)	1,478 (21.5)	4,392 (34.3)	2,370 (38.1)	9,376 (55.1)	4,715 (58.3)

All values are expressed as n (%), unless otherwise specified. IQR, interquartile range; OAC, oral anticoagulant; TIA, transient ischaemic attack; VTE, venous thromboembolism; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors; CYP, cytochrome P450; P-gp, P-glycoprotein

In the first treatment period after the index date however, most antiplatelet drugs had been discontinued but still more VKA patients used concomitant antiplatelet therapy compared to NOAC patients (23.4% versus 12.7%). The unstratified baseline characteristics for NOAC and VKA users are shown in the appendix, Section 4 (Table A1).

Primary outcome

Incidence rates and adjusted hazard ratios are shown in Figure 2. For both NOAC and VKA users, the incidence rate for major bleeding was highest in the stratum of 0-5 concomitant drugs. The adjusted HRs differed slightly among the strata, but did not show a clear trend towards a benefit or harm of NOACs versus VKA with an increasing (or decreasing) number of concomitant drugs prescribed. Likewise, the p for interaction was not statistically significant (p= 0.65), indicating no effect modification by the number of concomitant drugs prescribed. When comparing NOAC use to VKA use in the unstratified analysis, the crude HR for major bleeding was 1.02 (95% CI 0.91 to 1.15). After adjustment for all confounders, the HR changed only marginally and indicated no difference in major bleeding risk between NOACs and VKA (adjusted HR 0.98; 95% CI 0.87 to 1.11).

Secondary outcomes

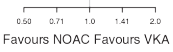
Of the secondary outcomes, effect modification by the number of concomitant drugs prescribed was observed only for the outcome all-cause mortality, with an adjusted HR of 1.52 (95% CI 1.41 to 1.64) with NOAC use versus VKA use in the highest stratum, compared to an adjusted HR of 1.10 (95% CI 1.02 to 1.18) in the lowest stratum (p for interaction <0.01). Overall, the mortality rate was almost 30% higher among NOAC users compared to VKA users (unstratified adjusted HR 1.29; 95% CI 1.23 to 1.35).

For the other outcomes, the number of concomitant drugs prescribed did not modify the effect of NOACs versus VKA (p-values for interaction varied between 0.28 and 0.93). However, in addition to the increased mortality risk, the unstratified analyses also showed an increased risk of gastrointestinal bleeding (adjusted HR 1.20; 95% CI 1.01 to 1.42) with NOAC use versus VKA use. Interestingly, no reduction with NOAC use compared to VKA use was observed for intracranial bleeding (adjusted HR 0.88; 95% CI 0.70 to 1.10). Also for ischaemic stroke and non-major bleeding, no major differences were seen when comparing NOAC and VKA use (see Figure 2 for details).

The stratified and unstratified results comparing rivaroxaban, apixaban and dabigatran to VKA separately for the primary outcome major bleeding, are shown in Table 2.

FIGURE 2. INCIDENCE RATES PER 100 PERSON YEARS, INTERACTION P VALUES AND ADJUSTED HAZARD RATIOS WITH 95% CONFIDENCE INTERVALS FOR PRIMARY AND SECONDARY OUTCOMES

	VKA Incidence rate (n. events)	NOAC Incidence rate (n. events)	Interaction p value	Adjusted HR (95% CI)
Primary outcome				
Major bleeding				
0–5 drugs	1.39 (440)	1.29 (154)		0.87 (0.72 to 1.05)
6–8 drugs	0.69 (230)	0.85 (102)		1.10 (0.86 to 1.40)
9 or more drugs	0.76 (312)	0.84 (133)		1.07 (0.86 to 1.32)
Unstratified	***0.92 (982)***	***0.98 (389)***	**0.65**	***0.98 (0.87 to 1.11)***
Secondary outcomes				
Ischemic stroke				
0–5 drugs	0.78 (247)	0.84 (99)		1.10 (0.86 to 1.40)
6–8 drugs	0.63 (211)	0.82 (97)		1.21 (0.94 to 1.55)
9 or more drugs	0.87 (356)	0.95 (149)		0.98 (0.80 to 1.20)
Unstratified	***0.77 (814)***	***0.88 (345)***	**0.75**	***1.06 (0.93 to 1.21)***
Intracranial bleeding				
0–5 drugs	0.46 (146)	0.40 (48)		0.86 (0.61 to 1.20)
6–8 drugs	0.22 (74)	0.26 (31)		1.04 (0.67 to 1.61)
9 or more drugs	0.21 (89)	0.19 (31)		0.86 (0.57 to 1.32)
Unstratified	***0.29 (309)***	***0.27 (110)***	**0.78**	***0.88 (0.70 to 1.10)***
Gastrointestinal bleeding				
0–5 drugs	0.63 (201)	0.71 (85)		1.01 (0.78 to 1.32)
6–8 drugs	0.29 (98)	0.45 (55)		1.40 (1.00 to 1.97)
9 or more drugs	0.35 (143)	0.49 (78)		1.33 (1.00 to 1.77)
Unstratified	***0.41 (442)***	***0.54 (218)***	**0.28**	***1.20 (1.01 to 1.42)***
Non-major bleeding				
0–5 drugs	4.43 (1285)	4.40 (490)		0.92 (0.83 to 1.02)
6–8 drugs	5.76 (1738)	5.45 (598)		0.89 (0.81 to 0.98)
9 or more drugs	7.34 (2669)	7.29 (1044)		0.96 (0.89 to 1.03)
Unstratified	***5.96 (5692)***	***5.85 (2132)***	**0.93**	***0.92 (0.88 to 0.97)***
Mortality				
0–5 drugs	8.17 (2611)	9.61 (1157)		1.10 (1.02 to 1.18)
6–8 drugs	2.38 (806)	3.57 (435)		1.42 (1.26 to 1.60)
9 or more drugs	4.43 (1843)	7.45 (1203)		1.52 (1.41 to 1.64)
Unstratified	***4.90 (5260)***	***6.92 (2795)***	**<0.01**	***1.29 (1.23 to 1.35)***



Results for edoxaban are not shown, as the exposure time and the numbers of events were too small to provide reliable results. For all three NOACs, no effect modification by the number of concomitant drugs prescribed was observed for the primary outcome (p for interaction 0.67 for apixaban, 0.89 for rivaroxaban and 0.13 for dabigatran). The unstratified results revealed a statistically significant reduction of major bleeding risk with apixaban only. When comparing the three different NOACs separately to VKA for the outcome mortality, statistically significant effect modification was observed for all three NOACs. The observed overall increased mortality risk with NOACs was not driven by one of the NOACs in particular, as we observed similar increased mortality risks for the three different NOACs when compared to VKA (data not shown).

TABLE 2. RESULTS OF THE PRIMARY OUTCOME MAJOR BLEEDING FOR THE DIFFERENT NOACS COMPARED TO VKA, STRATIFIED BY NUMBER OF CONCOMITANT DRUGS

	VKA		Apixaban			Rivaroxaban			Dabigatran		
	Incidence rate per 100 py (n events)	Adjusted HR (95% CI)	Incidence rate per 100 py (n events)	Adjusted HR (95% CI)	Interaction p value	Incidence rate per 100 py (n events)	Adjusted HR (95% CI)	Interaction p value	Incidence rate per 100 py (n events)	Adjusted HR (95% CI)	Interaction p value
Unstratified	0.92 (982)	Ref	0.84 (128)	0.81 (0.68-0.98)	0.67	1.12(212)	1.15 (0.99-1.34)	0.89	0.83 (44)	0.89 (0.66-1.21)	0.13
0-5	1.39 (440)	Ref	1.01 (43)	0.67 (0.49-0.92)	n.a.	1.59 (93)	1.09 (0.87-1.37)	n.a.	0.94 (16)	0.68 (0.42-1.13)	n.a.
6-8	0.69 (230)	Ref	0.78 (35)	0.96 (0.67-1.38)	n.a.	0.93 (54)	1.26 (0.93-1.70)	n.a.	0.67 (11)	0.99 (0.54-1.80)	n.a.
9 or more	0.76 (312)	Ref	0.78 (50)	0.97 (0.72-1.32)	n.a.	0.89 (65)	1.15 (0.88-1.51)	n.a.	0.86 (17)	1.18 (0.72-1.91)	n.a.

Py, person years; HR, hazard ratio; CI, confidence interval; Ref, reference; n.a., not applicable.

Sensitivity analyses

Results of the first sensitivity analysis, in which the first period after apparent discontinuation of the anticoagulant was not reclassified to being exposed to the last anticoagulant used, are shown in the appendix, section 5 (Table A2). In agreement with the main analysis, no significant effect modification by the number of concomitant drugs prescribed was observed. The unstratified adjusted HR of 1.14 (95% CI 1.01 to 1.30) showed an increased risk of major bleeding with NOACs compared to VKA, whereas no difference was observed in our main analysis.

Absolute and relative effects in the second and third sensitivity analyses were very similar to our main analyses and again did not show signs of effect modification by the number of concomitant drugs on major bleeding (data not shown).

DISCUSSION

This large, population based cohort study yielded four principal findings. First and foremost, no effect modification by the number of concomitant drugs was observed for the primary outcome major bleeding when comparing NOACs to VKAs, suggesting that major bleeding risk is comparable between NOACs and VKAs irrespective of the number of concomitant drugs prescribed. Second, the number of concomitant drugs did modify the mortality rate, with an adjusted relative 52% increased rate of all-cause mortality among NOAC use versus VKA use in the stratum with the highest number of concomitant drugs, compared to a relative 10% increased risk in the stratum with the lowest number of concomitant drugs (p for interaction <0.01). Third, in this dataset we did not observe a reduction of intracranial bleeding risk with NOACs compared to VKA, while the risk of gastrointestinal bleeding and all-cause mortality was increased. Finally, of the individual NOACs, only apixaban significantly reduced major bleeding risk (adjusted HR 0.81; 95% CI 0.68 to 0.98) compared to VKA.

Strengths and limitations

The main strength of this study is the large size and richness of the data in the UK CPRD, allowing for thorough adjustment for multiple confounders and stratified analyses. The routine care general practice setting of the data source ensures that our results are generalizable to the general non-valvular AF population. We included only incident OAC users and applied robust modelling techniques. Another important strength is that we assessed the data in a time-varying manner, which better reflects the real life situation in which patients discontinue, start or switch drugs, or develop

important comorbidities during follow-up, instead of assuming all variables to remain unchanged throughout follow-up. In this way, we identified important signs of exposure misclassification and we dealt with this through reclassification of the first period after apparent discontinuation (i.e. we carried the last exposure to VKA or NOAC forward). It is unknown if this phenomenon of higher bleeding rates after discontinuation of OAC (mostly VKAs) is also present in other routine care databases, but it warrants attention and emphasizes the importance of time-varying assessment of exposure.

Despite our thorough assessment of exposure misclassification, misclassification can still be present, including outcome misclassification due to a delayed registration of bleeding events in CPRD after the anticoagulant was stopped *because* of the bleeding. However, McDonald *et al* compared hospital records of major bleeding events in AF patients with corresponding records in CPRD, and found only a 7% increase in corresponding bleeding records in the 12 weeks after the event.[25] McDonald *et al* also showed that only 20% of bleeding events leading to hospitalisation had a corresponding bleeding record in CPRD.[25] This could explain the smaller incidence rates we observed compared to the incidence rates from a large Danish database and from a previous study in UK general practice.[26–28] Fortunately, in the study of McDonald *et al,* the under-recording did not lead to bias, although the degree of under-recording was not investigated separately for NOACs and VKAs. Second, while unmeasured confounding is a known limitation of observational research, extensive adjustment for measured confounders did not have a great impact on the hazard ratios in our study, which suggests that our conclusions would not radically change had we been able to adjust for all sources of confounding. Finally, we did not have data on causes of death, hospital admissions, blood transfusion, or haemoglobin levels, so the definition of major bleeding was hard to match with definitions used in other studies, notably randomised trials.[18] In addition, data on adherence, INR levels and dosage of drugs were unfortunately unavailable.

Comparison with existing literature

Few studies have investigated whether the number of concomitant drugs modifies the safety and effectiveness of NOACs compared to VKAs. One previous study using routine care data from the United States did not find signs of effect modification for major bleeding comparing rivaroxaban to warfarin. In patients using 5 or more concomitant drugs and in patients using 10 or more concomitant drugs, hazard ratios for major bleeding in the two polypharmacy cohorts were similar to our study (HR 1.08; 95% CI 0.92 to 1.28 for ≥5 drugs and HR 1.07; 95% CI 0.73 to 1.58 for ≥10 drugs).[29]

Further research solely consists of post-hoc analyses of the ARISTOTLE trial (comparing apixaban with VKA in strata of 0-5, 6-8 and ≥9 concomitant drugs) and the ROCKET-AF trial (comparing rivaroxaban with VKA in strata of 0-4, 5-9 and ≥10 concomitant drugs).[7,8] In the ARISTOTLE trial, relative risk reductions for major bleeding decreased among the strata, from 50% (0-5 drugs), to 28% (6-8 drugs) and 16% (≥9 drugs), showing statistically significant effect modification (p for interaction 0.017). In the ROCKET-AF trial, a reduction in major bleeding risk was only observed in the stratum of 0-4 drugs (HR 0.71; 95% CI 0.52 to 0.95), whereas major bleeding risk was increased or inconclusive in the higher strata (HR 1.23; 95% CI 1.01 to 1.49 in stratum 5-9 drugs; HR 1.17; 95% CI 0.87 to 1.56 in stratum ≥10 drugs, p for interaction 0.007). While in the latter study the authors state that this might have been a false-positive association (type 1 error) due to multiple testing and small sample size, the results of these two studies were pooled in a systematic review to show significant effect modification by polypharmacy, in which the benefit of NOACs versus VKA on major bleeding disappeared in patients with polypharmacy (pooled RR 0.59; 95% CI 0.45 to 0.76 with <5 drugs, versus 0.95; 95% CI 0.65 to1.39 with ≥5 drugs).[9] This review did not find signs of effect modification by polypharmacy for the outcomes stroke or systemic thromboembolism, intracranial bleeding and, in discordance with our results, neither for mortality.

Furthermore, contrary to a meta-analysis of the four pivotal NOAC trials as well as in a meta-analysis of observational studies, we found no reduction of intracranial bleeding risk with NOAC use compared to VKA use.[4,30] Although we applied Firths correction to mitigate small sample bias, our results on intracranial bleeding should still be interpreted with caution in respect of the large amount of existing literature. For all-cause mortality, our results are also in contrast with the two meta-analyses, that both showed a consistent decreased mortality risk with NOACs compared to VKA, except for apixaban in the meta-analysis of observational studies. The finding that apixaban has a more positive effect on major bleeding compared to VKA than dabigatran and especially rivaroxaban has also been previously observed.[4,27,28,30–32].

To summarize, while the absence of effect modification by the number of concomitant drugs on major bleeding risk between NOACs and VKAs is consistent with one observational study, clear differences exist compared to post-hoc analyses of NOAC trials. Results for the outcome all-cause mortality are also remarkably different compared to these post-hoc analyses, with higher mortality rates among NOAC users as the number of concomitant drugs prescribed increases.

Several considerations can be made in explaining these discrepancies. Differences in outcome definitions and, more importantly, patient selection likely account for the fact that the number of concomitant drugs modified the effect of NOACs versus VKAs on major bleeding in trial data, but not in our observational study. Nowadays, both the relatively fit and the frail patients with AF in primary and secondary care receive NOAC treatment, whereas patients included in the NOAC trials were likely to be more homogeneous and less frail. Studies show that less than 50% of routine care patients with AF would have met the strict inclusion criteria of the NOAC trials. [33,34] Furthermore, patients included in trials receive a more intensive follow-up. Those patients in the highest stratum of the number of concomitant drugs prescribed are therefore more likely to be optimally treated for their many comorbidities, whereas the highest stratum in our study could also include patients who receive too many drugs, including contra-indicated or interacting drugs. Likewise, patients in the lowest stratum in the trials probably have little comorbidity and do not need more medication, whereas patients in the lowest stratum in our study can very well be undertreated. Thus, the way in which effect modification by the number of concomitant drugs prescribed is captured might differ between trial data and routine care data. While we can only speculate, factors such as drug interactions, underlying indications, and side-effects may be important.

The finding that the number of concomitant drugs modified mortality risk is more difficult to clarify as we did not have information on the causes of death. Definite conclusions on any potential causal relation between NOAC use and increased mortality risk, especially in patients using many concomitant drugs, can therefore not be drawn. A possible explanation could be confounding by indication, in which clinicians prefer a NOAC over a VKA especially in patients with many concomitant drugs (and multiple possible interactions that would enhance fluctuating INR levels with VKA use) and that these patients have the highest mortality risk. However, the baseline characteristics per stratum do not show signs supporting this possible explanation and, as explained above, adjustments for potential confounding in our analyses did not materially change the effect estimates. Second, it could be hypothesised that, contrary to the results of (mostly) non-fatal stroke and major bleeding, the number of concomitant drugs does influence the safety of NOACs for fatal events. Our observation then may be attributable to sudden death caused by for instance acute stroke or major bleeding, that were not reported as such as the cause of sudden death often remains unknown. This, of course, is highly speculative and should be confirmed in future studies that investigate also the occurrence of myocardial infarction for example. In addition, our observation of higher incidence rates among patients receiving fewer concomitant

drugs requires further exploration. One explanation may involve issues like end-of-life discontinuation, though this was considered beyond the scope of the current study.

Clinical implications and suggestions for further research

In our routine care study population, we did not observe effect modification by the number of concomitant drugs prescribed. Although one could regard the number of concomitant drugs prescribed as a proxy for frailty, it remains uncertain whether NOACs are completely safe in frail elderly patients with AF. A high number of concomitant drugs could also indicate that someone is adequately treated and not necessarily frail. Therefore, studies comparing NOACs to VKA in frail patients, like the FRAIL-AF trial, will have to be awaited before this question can be answered.[35] Nevertheless, from this study it appears that clinicians would not need to use the number of concomitant drugs as a tool in deciding which anticoagulant to prescribe in view of major bleeding risk. Future research in different routine care datasets or pragmatic trials is required to confirm our findings. This should also include an assessment of the causes of death, before conclusions on the possible excess mortality risk with NOAC use, especially in patients using many concomitant drugs, can be drawn. Also, it would be interesting to take a closer look into the different types of concomitant drugs prescribed, including pharmacokinetic and -dynamic interactions, which was beyond the scope of the current study.

Conclusion

Major bleeding risk was comparable between NOACs and VKAs, irrespective of the number of concomitant drugs prescribed. Further research including an assessment of the causes of death is required before drawing conclusions on possible increased mortality risk with NOACs and effect modification with the number of concomitant drugs concerning mortality.

CONTRIBUTORS

CD, SD, GJG, PS and HH wrote the ISAC study protocol. PS and RP prepared the dataset. CD, RP and SD performed the analyses. KM, GJG and AH advised in interpreting the results. CD wrote the first version of the manuscript. All authors participated in revising the manuscript. HH is the guarantor.

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APPENDIX

SECTION 1. READ CODES DEFINING OUTCOMES

Major bleeding (including intracerebral and gastro-intestinal bleeding)
All codes up to G621.00 were used for the outcome intracranial bleeding
All codes from G850.00 up to G852000 were used for the outcome gastrointestinal bleeding

readcode	readterm
S62..00	Cerebral haemorrhage following injury
S62..11	Extradural haemorrhage following injury
S62..12	Subarachnoid haemorrhage following injury
S62..13	Subdural haemorrhage following injury
S62..14	Traumatic cerebral haemorrhage
S620.00	Closed traumatic subarachnoid haemorrhage
S620100	Subarachnoid h'ge inj no open intracran wnd+no loss consc
S620600	Subarach h'ge inj no open intracran wnd+LOC unspec duration
S620z00	Subarach h'ge inj no open intracran wnd + concussion unspec
S621.00	Open traumatic subarachnoid haemorrhage
S621z00	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
S622.00	Closed traumatic subdural haemorrhage
S622000	Subdural h'ge inj no open intracranial wnd + unspec consc
S622300	Subdural h'ge inj no open intracran wnd+1-24hr loss consc
S622600	Subdural h'ge inj no open intracran wnd+LOC unspec duration
S622z00	Subdural h'ge inj no open intracran wound+concussion unspec
S623.00	Open traumatic subdural haemorrhage
S624.00	Closed traumatic extradural haemorrhage
S624000	Extradural h'ge inj no open intracranial wnd + unspec consc
S624100	Extradural h'ge inj no open intracranial wnd + no loss consc
S624z00	Extradural h'ge inj no open intracran wnd+concussion unspec
S625.00	Open traumatic extradural haemorrhage
S626.00	Epidural haemorrhage
S627.00	Traumatic subarachnoid haemorrhage
S628.00	Traumatic subdural haemorrhage
S62z.00	Cerebral haemorrhage following injury NOS
S63..00	Other cerebral haemorrhage following injury
S630.00	Other cerebral h'ge after injury no open intracranial wound
S630.12	Intracranial haematoma following injury
S630000	Oth cerebral h'ge inj no open intracran wnd+unspec consc
S630100	Oth cerebral h'ge inj no open intracranial wnd+no loss consc
S630200	Oth cerebral h'ge inj no open intracran wnd+<1hr loss consc
S630300	Oth cerebral h'ge inj no open intracran wnd+1-24hr LOC
S630400	Oth cereb h'ge inj no open intracran wnd+>24hr LOC +recovery

S631300	Oth cerebral h'ge inj + open intracran wnd+1-24hr loss consc
S63z.00	Other cerebral haemorrhage following injury NOS
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
G62z.00	Intracranial haemorrhage NOS
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
G621.00	Subdural haemorrhage - nontraumatic
1720.00	Massive haemoptysis
D211.00	Acute posthaemorrhagic anaemia
D211.11	Normocytic anaemia following acute bleed
F212.00	Acute and subacute haemorrhagic leukoencephalitis [Hurst]
F404300	Haemophthalmos (excluding current injury)

F404500	Intra-ocular haemorrhage
F42y.11	Haemorrhage - retinal
F42y000	Preretinal heamorrhage
F42y100	Superficial retinal haemorrhage
F42y300	Deep retinal haemorrhage
F42y400	Subretinal haemorrhage
F42y500	Retinal haemorrhage NOS
F436.00	Choroidal haemorrhage and rupture
F436000	Unspecified choroidal haemorrhage
F436100	Expulsive choroidal haemorrhage
F436z00	Choroidal haemorrhage or rupture NOS
F437200	Haemorrhagic choroidal detachment
F4K2800	Vitreous haemorrhage
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere
G8y0.00	Haemorrhage NOS
H51y200	Haemothorax
N091.00	Haemarthrosis
N091000	Haemarthrosis of unspecified site
G850.00	Oesophageal varices with bleeding
J10y000	Haemorrhage of oesophagus
J68..00	Gastrointestinal haemorrhage
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z200	Upper gastrointestinal haemorrhage
J68zz00	Gastrointestinal tract haemorrhage NOS
J68z000	Gastric haemorrhage NOS
J68z100	Intestinal haemorrhage NOS
J681.00	Melaena
J680.00	Haematemesis
J680.11	Vomiting of blood
J110100	Acute gastric ulcer with haemorrhage
J110300	Acute gastric ulcer with haemorrhage and perforation
J111100	Chronic gastric ulcer with haemorrhage
J111300	Chronic gastric ulcer with haemorrhage and perforation
J11y100	Unspecified gastric ulcer with haemorrhage
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J120100	Acute duodenal ulcer with haemorrhage
J120300	Acute duodenal ulcer with haemorrhage and perforation
J121100	Chronic duodenal ulcer with haemorrhage
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J130100	Acute peptic ulcer with haemorrhage

J13y100	Unspecified peptic ulcer with haemorrhage
J131100	Chronic peptic ulcer with haemorrhage
J130300	Acute peptic ulcer with haemorrhage and perforation
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J140100	Acute gastrojejunal ulcer with haemorrhage
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J150000	Acute haemorrhagic gastritis
J56y000	Haemoperitoneum - nontraumatic
J121111	Bleeding chronic duodenal ulcer
J111111	Bleeding chronic gastric ulcer
J110111	Bleeding acute gastric ulcer
G852000	Oesophageal varices with bleeding in diseases EC

Ischaemic stroke

G63..11	Infarction - precerebral
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome

G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
G654.00	Multiple and bilateral precerebral artery syndromes
G64z400	Infarction of basal ganglia

Non-major bleeding

172..00	Blood in sputum - haemoptysis
172..12	Haemoptysis - symptom
1A45.00	Blood in urine - haematuria
1A45.12	Haematuria - symptom
1C6..11	Epistaxis symptom
1C62.00	Has nose bleeds - epistaxis
2D25.00	O/E - epistaxis
F4C7100	Subconjunctival haemorrhage
F4C7200	Conjunctival haemorrhage NOS
F4G3200	Exophthalmos due to orbital haemorrhage
F4K7.00	Retrobulbar haemorrhage
K0A2.00	Recurrent and persistent haematuria
K0A2000	Recurrent+persistnt haematuria minor glomerular abnormality
K0A2100	Recur+persist haematuria, focal+segmental glomerular lesions
K0A2200	Recur+persist haematuria difus membranous glomerulonephritis
K0A2600	Recurrent and persistent haematuria, dense deposit disease
K197.00	Haematuria
K197.12	Essential haematuria
K197000	Painless haematuria
K197100	Painful haematuria
K197300	Frank haematuria
K197400	Clot haematuria
K5A1.00	Postmenopausal bleeding
R047.00	[D]Epistaxis
R048.00	[D]Throat haemorrhage
R063.00	[D]Haemoptysis
R063z00	[D]Haemoptysis NOS

K167.00	Haemorrhage into bladder wall
J681.11	Blood in stool
J681.13	Blood in stools altered
J681.12	Altered blood in stools
J573.00	Haemorrhage of rectum and anus
J573000	Rectal haemorrhage
J573100	Anal haemorrhage
J573z00	Haemorrhage of rectum and anus NOS
J573011	Rectal bleeding
J573.11	Bleeding PR
J510900	Bleeding diverticulosis
J573012	PRB - Rectal bleeding

SECTION 2. CONFOUNDERS PER OUTCOME

Ischaemic stroke (16 confounders):
Age, sex, previous use of a different anticoagulant, alcohol abuse, liver disease, chronic kidney disease, hypertension, hypercholesterolemia (including statin use), ischaemic heart disease or peripheral artery disease, history of stroke or TIA, history of venous thromboembolism, active cancer, congestive heart failure, chronic kidney disease, diabetes, concomitant use of platelet inhibitors.

Intracranial bleeding (11 confounders):
Age, sex, previous use of a different anticoagulant, alcohol abuse, liver disease, chronic kidney disease, hypertension, history of intracranial bleeding, history of gastrointestinal bleeding, cardiovascular disease (defined as a history of ischaemic heart disease, peripheral artery disease, stroke or transient ischaemic attack (TIA)), concomitant use of platelet inhibitors.

Gastrointestinal bleeding (17 confounders, same as for major bleeding):
Age, sex, previous use of a different anticoagulant, alcohol abuse, liver disease, chronic kidney disease, hypertension, history of gastrointestinal bleeding, history of intracranial bleeding, cardiovascular disease (defined as a history of ischaemic heart disease, peripheral artery disease, stroke or transient ischaemic attack (TIA)), active cancer, peptic ulcer disease, concomitant use of platelet inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, proton pump inhibitors (PPIs) or selective serotonin reuptake inhibitors (SSRIs).

Non-major bleeding (18 confounders, including history of non-major bleeding):
Age, sex, previous use of a different anticoagulant, alcohol abuse, liver disease, chronic kidney disease, hypertension, history of non-major bleeding, history of gastrointestinal bleeding, history of intracranial bleeding, cardiovascular disease (defined as a history of ischaemic heart disease, peripheral artery disease, stroke or transient ischaemic attack (TIA)), active cancer, peptic ulcer disease, concomitant use of platelet inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, proton pump inhibitors (PPIs) or selective serotonin reuptake inhibitors (SSRIs).

Death (21 confounders):
Age, sex, previous use of a different anticoagulant, alcohol abuse, liver disease, chronic kidney disease, hypertension, hypercholesterolemia (including statin use), congestive heart failure, history of gastrointestinal bleeding, history of intracranial bleeding, cardiovascular disease (defined as a history of ischaemic heart disease, peripheral artery disease, stroke or transient ischaemic attack (TIA)), history of venous thromboembolism, active cancer, peptic ulcer disease, diabetes, concomitant use of platelet inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, proton pump inhibitors (PPIs) or selective serotonin reuptake inhibitors (SSRIs).

SECTION 3. BNF CODES LEFT OUT OF NUMBER OF CONCOMITANT DRUGS VARIABLE FOR THIRD SENSITIVITY ANALYSES

List of BNF chapters of topical drugs
- 1.7.4: Management of Anal Fissures

11: Eye
- 11.3: Anti-Infective Eye Preparations
  - 11.3.1: Antibacterials
  - 11.3.2: Antifungals
  - 11.3.3: Antivirals
- 11.4: Corti'roids & Other Anti-Inflamm.Preps.
  - 11.4.1: Corticosteroids
  - 11.4.2: Other Anti-Inflammatory Preparations
- 11.5: Mydriatics And Cycloplegics
- 11.6: Treatment Of Glaucoma
- 11.7: Local Anaesthetics
- 11.8: Miscellaneous Ophthalmic Preparations
  - 11.8.1: Tear Deficiency,Eye Lubricant/Astringent
  - 11.8.2: Ocular Diagnos/Peri-op Prepn&Photodyn Tt
  - 11.8.3: Other Eye Preparations

12: Ear, Nose And Oropharynx
- 12.1: Drugs Acting On The Ear
  - 12.1.1: Otitis Externa
  - 12.1.3: Removal of Ear Wax & other Substances
- 12.2: Drugs Acting On The Nose
  - 12.2.1: Drugs Used In Nasal Allergy
  - 12.2.2: Topical Nasal Decongestants
  - 12.2.3: Nasal Prepn for Infection
- 12.3: Drugs Acting On The Oropharynx
  - 12.3.1: Drugs For Oral Ulceration & Inflammation
  - 12.3.2: Oropharyngeal Anti-Infective Drugs
  - 12.3.3: Lozenges & Sprays
  - 12.3.4: Mouth-Washes, Gargles, And Dentifrices
  - 12.3.5: Treatment Of Dry Mouth

13: Skin
- 13.1: Management of Skin Conditions
- 13.2: Emollient & Barrier Preparations
- 13.3: Top Local Anaesthetics & Antipruritics
- 13.4: Topical Corticosteroids
- 13.5: Preparations For Eczema And Psoriasis
- 13.6: Acne and Rosacea
- 13.7: Preparations For Warts And Calluses
- 13.10: Anti-Infective Skin Preparations
- 13.14: Topical Circulatory Preparations
- 13.15: Miscellaneous Topical Preparations

21: Appliances
- 21.14: Lubricant Gels
- 21.16: Irrigation Solutions
- 21.21: Dry Mouth Products
- 21.22: Emollients
- 21.23: Vaginal Moisturisers
- 21.24: Nasal Products
- 21.34: Vaginal PH Correction Products

List of BNF chapters of incidental drugs
- 2.8.1: Parenteral Anticoagulants
- 4.8.2: Drugs Used In Status Epilepticus
- 7.3.3: Spermicidal Contraceptives
- 7.3.5: Emergency Contraception
- 9.2.2: Parent Prepn for Fluid & Electrolyte Imb
- 9.3: Intravenous Nutrition
- 14.3: Diagnostic Vaccines
- 14.4: Vaccines And Antisera
- 15.1: General Anaesthesia
  - 19.2.7: Poisoning Antidotes
- 21.43: Micro-Enema - Sodium Citrate

SECTION 4. UNSTRATIFIED BASELINE CHARACTERISTICS

TABLE A1. BASELINE CHARACTERISTICS, UNSTRATIFIED

	VKA (n=42,424)	NOAC (n=21,176)
Female	18,573 (43.8)	9,438 (44.6)
Age, median (IQR)	76 (68-82)	76 (68-83)
Number of concomitant drugs prescribed, median (IQR)	7 (5-10)	7 (5-10)
Previous use of different OAC	5 (0.0)	1,122 (5.3)
Comorbidities/risk factors		
Hypertension	26,995 (63.6)	13,158 (62.1)
Congestive heart failure	5,726 (13.5)	2,488 (11.7)
Diabetes	7,789 (18.4)	3,962 (18.7)
Prior TIA or ischaemic stroke	7,621 (18.0)	4,070 (19.2)
Prior venous thromboembolism	1,996 (4.7)	631 (3.0)
Coronary artery disease	11,164 (26.3)	5,002 (23.6)
Presence of malignancy	1,559 (3.7)	795 (3.8)
Chronic kidney disease	9,992 (23.6)	4,624 (21.8)
Prior major bleeding	1,975 (4.7)	1,073 (5.1)
Peptic ulcer disease	2,773 (6.5)	1,410 (6.7)
Alcohol abuse	3,176 (7.5)	2,251 (10.6)
Active smoking	3585 (8.5)	1969 (9.3)
Prior use of drugs increasing bleeding risk		
Antiplatelet therapy	25,727 (60.6)	10,479 (49.5)
NSAID	2,898 (6.8)	950 (4.5)
Corticosteroids	4,367 (10.3)	2,137 (10.1)
SSRI	3,115 (7.3)	1,793 (8.5)
CYP3A4 or P-gp inhibitors	4,950 (11.7)	1,894 (8.9)
CYP3A4 or P-gp inducers	238 (0.6)	100 (0.5)
Other drugs		
Beta blocking agents	22,014 (51.9)	9,560 (45.1)
Diuretics	18,332 (43.2)	7,498 (35.4)
ACE inhibitors/ARB	22,688 (53.5)	10,125 (47.8)
Calcium channel blockers	15,032 (35.4)	7,057 (33.3)
Digoxin	4,476 (10.6)	1,292 (6.1)

TABLE A1. *CONTINUED*

	VKA (n=42,424)	NOAC (n=21,176)
Statins	21,979 (51.8)	10,639 (50.2)
Proton pump inhibitors	16,289 (38.4)	8,563 (40.4)

All values are expressed as n (%), unless otherwise specified. Active cancer at baseline was defined as having a Read code for any type of cancer in the 6 months preceding the index date. All other comorbidities/ risk factors were considered present when a Read code was registered ever/before the index date. Drugs prescribed in the 6 months prior to the index date were regarded as used at baseline. OAC, oral anticoagulant; TIA, transient ischaemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors; CYP, cytochrome P450; P-gp, P-glycoprotein

SECTION 5. SENSITIVITY ANALYSIS EXPOSURE MISCLASSIFICATION

TABLE A2. UNSTRATIFIED AND STRATIFIED RESULTS (PER STRATUM OF THE NUMBER OF CONCOMITANT DRUGS PRESCRIBED) FOR PRIMARY OUTCOME WITHOUT RECLASSIFICATION OF FIRST UNEXPOSED PERIOD.

	VKA (n=42,424)	NOAC (n=21,176)	NOAC vs VKA	
	Incidence rate per 100 py (n events)	Incidence rate per 100 py (n events)	Crude HR (95% CI, p)	Adjusted HR* (95% CI, p)
Major bleeding				
0-5	1.10 (290)	1.19 (131)	1.04 (0.84-1.28, 0.74)	1.06 (0.86-1.31, 0.57)
6-8	0.63 (192)	0.82 (96)	1.23 (0.96-1.57, 0.11)	1.19 (0.92-1.52, 0.18)
9 or more	0.69 (262)	0.82 (128)	1.17 (0.95-1.45, 0.14)	1.18 (0.95-1.46, 0.13)
Unstratified	0.78 (744)	0.93 (355)	1.14 (1.01-1.30, 0.04)	1.14 (1.01-1.30, 0.04)

*Multivariate adjusted HR (for the list of confounders, see text).

GENERAL DISCUSSION

THE CASE OF MS. WILLEMS, TWO YEARS LATER

Luckily, Ms. Willems recovered from her pneumonia and the gastrointestinal bleeding. Two years later, she receives a letter from her general practitioner (GP) and the anticoagulation clinic, to inform her that the anticoagulation clinic location in her village soon has to close due to a decreasing number of patients treated with a vitamin K antagonist. Fortunately, she does not need to go to the nearest location in the city 15 kilometres away, because the primary care practice will take over the INR-measurements from the anticoagulation clinic. Moreover, the GP and the practice nurse also invited her for a quarterly check-up that combines the diabetes care she already received, with care for her other conditions, including her atrial fibrillation and heart failure.

A few months later, Ms. Willems again feels unwell. She recognises her symptoms from 2 years ago and calls the GP, who again diagnoses pneumonia and prescribes an antibiotic. This time however, the GP asks her assistant to cycle by Ms. Willems' house that same afternoon, for an extra INR measurement. The INR level appears to be elevated, so the assistant calls the anticoagulation clinic and asks what to do. The anticoagulation clinic advises to give vitamin K, temporarily discontinue the anticoagulant and to check the INR again in two days.

MAIN FINDINGS OF THE STUDIES INCLUDED IN THIS THESIS

As described in the introduction of this thesis, the current atrial fibrillation (AF) epidemic and the shift in anticoagulation treatment from vitamin K antagonists (VKA) to non-VKA oral anticoagulants (NOACs) have led to important clinical and organisational questions and challenges. The increasing prevalence of AF contributes to the challenge of managing the increasing number of elderly patients with multimorbidity in general. [1] Managing care for elderly patients with AF is complex. Given the multiple caregivers that are often involved and the inherent risk of fragmentation of care, it can be unclear who is 'in the lead' and lines of communication can be confusing at times, certainly for patients. This could lead to situations where the risk of avoidable complications suddenly increases, as described in the case of Ms. Willems in the introduction chapter. Moreover, with the shift to NOAC treatment, the number of anticoagulation clinics is expected to decline. Solutions to preserve accessibility to anticoagulation monitoring for patients who require VKA treatment are therefore warranted.

Integrated care has been suggested to be a promising and key feature in the future of AF management.[2] The first three chapters of this thesis described the ALL-IN trial, which aimed to evaluate if integrated care for patients with AF could be safely and (cost)effectively organised in primary care. The integrated care intervention that was investigated in the ALL-IN trial consisted of (i) structured quarterly check-ups by trained practice nurses, supervised by the GP, with a focus on treatment of comorbidity as well as management of AF itself, (ii) anticoagulation monitoring in primary care, and (iii) close collaboration with cardiologists and anticoagulation clinics. The remaining chapters in this thesis focused on anticoagulation therapy with NOACs, in particular on the occurrence and clinical impact of off-label NOAC dose reduction (Chapter 4 and 5) and the influence of the number of concomitant drugs (Chapter 6).

In this final chapter, the main findings, with a focus on the possible implications of the ALL-IN trial, and remaining questions to be investigated in future studies in this field are discussed. The main findings from the studies included in this thesis are as follows:

- Integrated AF care can be safely orchestrated in primary care. Moreover, the available data show a reduction in mortality, in particular non-cardiovascular mortality.
- Organising integrated AF care in primary care appears to be cost-effective, which offers a promising perspective in managing the increasing burden on the health care system caused by the AF-epidemic.
- Off-label dose reduction occurs in about 15% of all NOAC prescriptions.
- Reducing the NOAC dose in the absence of a clear indication is mainly done in older patients with a high risk of bleeding. This off-label dose reduction, however, did not appear to influence the risk of stroke or, importantly, the risk of major bleeding.
- The number of concomitant drugs prescribed does not appear to modify the safety and effectiveness of NOACs versus VKAs.

THE RESULTS OF THE ALL-IN TRIAL - TOO GOOD TO BE TRUE?

One might view the observed effect of the ALL-IN trial, notably the 45% reduction in all-cause mortality, as surprisingly large, or even 'too good to be true'. Indeed, apart from stroke prevention with anticoagulation, studies have rarely shown any benefit on mortality of other interventions in patients with AF.[3–5] For instance, rhythm

control strategies – such as anti-arrhythmic drugs or ablation techniques – have shown important benefits on quality of life, but not on mortality (except perhaps in patients with AF and severe heart failure in one clinical trial).[3–6] Moreover, when looking at studies on other chronic care programs in primary care, positive effects on mortality (which is unfortunately rarely included as an outcome[7,8]), have not been reported either.

So surprising, yes, but too good to be true? While this question almost touches upon a philosophical discussion on the establishment (or let alone the existence) of 'truth' in science, two arguments are important to highlight when answering this question. First, what is at least 'true' is that the cluster randomised design introduces a complexity with the possibility of post-randomisation selection bias. This is inherently introduced by asking for informed consent of the patients to undergo the index intervention *after* randomisation of the practices (clusters). When comparing the results of the main analysis (adjusted HR 0.55; 95% confidence interval (CI) 0.37-0.82, p=0.003) to the results of the sensitivity analysis that included the patients in the intervention arm who did not sign informed consent and thus did not undergo the index intervention (adjusted HR 0.81; 95% CI 0.61-1.07, p=0.140), it can be concluded that the 'true' HR for all-cause mortality will likely lie somewhere between 0.37 and 1.07. One could argue that there still is a probability of no effect or even a harmful effect of the intervention. This is, however, in the most conservative scenario in which about half of the patients who did not undergo any type of integrated AF care, are included in the analysis. Instead of simply (and wrongly) looking at statistical significance in a dichotomous way, it is more reasonable to interpret the 95% confidence interval in terms of a compatibility interval, in which the point estimate between 0.55 and 0.81 is much more compatible with the data than a point estimate of 1.07.[9]

Second, the results of the ALL-IN trial are in fact in line with previous studies on integrated AF care. In particular a meta-analysis of two nurse-led integrated care interventions for patients with AF coordinated by tertiary care hospitals shows a 49% decrease in all-cause mortality (OR 0.51, 95% CI 0.32 to 0.80), further strengthening our observations.[10]

Nevertheless, doubt should always be an integral part of good and open science. We are still in need for more research, on the one hand to confirm our findings when implemented on a larger scale, and on the other hand to elaborate on possible clinical pathways explaining why integrated AF care appears to be so effective and in whom the intervention is most beneficial. Moreover, it is important to realise that although the

ALL-IN trial appeared lifesaving and cost-effective, hospital admissions still occurred very frequently and were not evidently affected by integrated care, except for urgent hospitalisation (post-hoc analysis, adjusted incidence rate ratio 0.79; 95% CI 0.63 to 1.00). Therefore, the challenge to mitigate the increasing burden from the AF-epidemic remains, and may even increase when patients with AF who receive integrated care live longer and consume more health care resources. In the following paragraphs, I will describe some approaches and issues that are in my view crucial in further developing future integrated care for patients with AF and in future AF research.

THE BROADER APPROACH: RECOGNISING THE 'AF-MULTIMORBIDITY CLUSTER'

When developing future AF care, the starting point needs to be the realisation that AF is part of a systemic condition characterised by multiple interfering cardiovascular *and* non-cardiovascular comorbidities.[11–14] This is endorsed by the striking incidence rate of non-cardiovascular hospitalisation in the ALL-IN trial (19.5 per 100 person-years of follow-up, being more than twice as high as the incidence rate of cardiovascular hospitalisation).[15–17] In analogy with the 'cluster of multi-organ diseases' that is for example recognised in patients with diabetes, affecting for example the kidneys, eyes, nerves, skin and vascular system,[1] we could also speak of a cluster of multimorbidity in patients with AF. This 'AF-multimorbidity cluster' consists of several conditions including heart failure, ischaemic stroke, hypertension, vascular dementia, sleep apnoea, obesity, diabetes and, more in general, frailty. A broad approach with a focus on treatment of comorbidity through integrated AF care orchestrated in primary care, would better suit this idea of an AF-multimorbidity cluster. It is likely that the broad approach of the intervention carried out in the ALL-IN trial was a key factor in explaining the large reduction in all-cause mortality.

IMPLEMENTATION OF FUTURE INTEGRATED CARE FOR PATIENTS WITH AF IN PRIMARY CARE

With the results of the ALL-IN trial, the door to widespread implementation of integrated care for patients with AF in primary care has opened. Suter and colleagues developed ten key principles for successful implementation of integrated health systems, based on a systematic literature review.[18] Besides the comprehensive scope, i.e. the crucial broad approach described above, four of these principles are

particularly relevant to discuss in view of integrated care for patients with AF and the experiences from the ALL-IN trial. These four principles could help to identify priorities and possible barriers and facilitators in the implementation process of future integrated AF care:

1. Patient focus

With a complex condition like AF and the different caregivers involved, it can be difficult for patients to navigate through the health system. For example, practical issues like travel distance, being dependent on relatives to visit the hospital, and financial issues could hamper adherence to AF treatment. This thus may call for integrated care organised predominantly in primary care, close to the home of the patient and with one case manager (e.g. a practice nurse) in the lead. Furthermore, studies show that visits to an outpatient AF clinic can be overwhelming and patient knowledge about AF is currently suboptimal, if not poor, despite extensive information given at outpatient AF clinics.[19–21] If patients are insufficiently aware of the risks of AF and of not taking their prescribed medication, adherence is more difficult to achieve. Therefore, ongoing patient education and patient empowerment may be important in successfully implementing integrated care and in achieving better anticoagulation control.[22]

Lastly, a patient focus should also be pursued in the exact content of the care delivered. Like other authors suggest, one size does not fit all, requiring future management of AF to be stratified and personalized.[2] A certain risk factor, obesity for example, plays a larger role in the development of AF in one patient than in another. Consequently, it should also play a larger role in the *treatment* of AF in one patient compared to another.

2. Standardised care delivery through inter-professional teams

While maintaining a patient focus, integrated care should also be standardised to a certain degree in order to be successful in the long-run. Protocolised and standardised care in terms of guideline adherence and frequent and structured follow-up can very well be provided by nurses. In fact, the RACE-4 trial showed that guideline recommendations were better applied in patients receiving nurse-led care compared to usual care.[23] With the practice nurse as the principle caregiver, a surrounding collaborative, multidisciplinary AF team is necessary to combine the expertise from primary and secondary care. Hereto, it is important that the different care providers know each other and know each other's role. Regular meetings and shared protocols in which these roles are clarified are helpful in this matter. It is important to note that through these multidisciplinary teams, shared care rather than substitution of

care should be pursued, as the latter is not always possible or desirable, for example in patients with complex cardiac comorbidity. One of the lessons learned from the ALL-IN trial is that while substitution of care from cardiologists to primary care was infrequent, the additional quarterly check-ups in primary care were not redundant at all (and still cost-effective). So apparently, many patients with AF benefit from *extra* care or follow-up. To maintain continuity of care, good and frequent communication within the multidisciplinary AF team is required. Initiatives like the Connect AF program, initiated by the Netherlands Society of Cardiology [24] and joint consultations in which cardiologists and GPs evaluate more complex patients together, are promising initiatives to enhance shared care, possibly reducing the number of referrals to the cardiology department.[25] This could also be organised through teleconferencing.

3. Information systems

The current lack of one national, secure, integrated Information Communication Technology (ICT) system where all health care providers involved in the care for a patient (and patients themselves) have access to is probably one of the biggest obstacles to efficient implementation of integrated care. Consulting a specialist in secondary care would be a lot easier and safer when the specialist could access up-to-date information on medication use and laboratory measurements, for example. Awaiting such a fully integrated ICT system, several partially integrated ICT systems are available in many regions, often for patients enrolled in disease or risk management programs in primary care (in Dutch these systems are called "ketenzorg informatiesystemen, KIS"). These systems can often connect primary care ICT systems to laboratory ICT systems, anticoagulation clinic ICT systems, and sometimes even hospital ICT systems. However, the KIS only facilitates *consultation* of hospital specialists, who have access to only a selection of the information in the KIS and can only give an advice to the GP, instead of formally providing shared care. Nonetheless, these developments are important in facilitating collaboration between health care providers and with patients and have the potential to improve guideline adherence and prevent unnecessary diagnostic procedures and costs.[23,26]

4. Financial management

Financial management of integrated care is complex, as it should ideally be a personalised 'package deal' in which multiple health services, both from primary and secondary care, need to be included. In the past decade, the Dutch payment system for existing chronic care programs (type 2 diabetes, COPD and cardiovascular risk management) has changed several times and is currently in transition towards regional organisation and infrastructure (O&I) with a focus on primary care practices. So-called

chain diagnosis treatment combinations (chain-DTCs, or in Dutch: 'keten-DBCs'), are used to reimburse primary care practices, with a fixed price per year per patient included in a chronic care program.[27] But an important downside of the current payment system is that vertical integration (i.e. integration across different levels of care, so for example across primary and secondary care[28]) is not yet structurally reimbursed. Similar to what we saw in the partially integrated ICT systems, hospital specialists are included in the chain-DTC only on a consultation basis, hampering the provision of truly shared-care. In fact, GPs must exclude patients from the chronic care program in primary care once a patient is referred to secondary care, which is counter-intuitive as in particular for these higher risk patients there might be an even stronger need for integrated, shared care across multiple disciplines. Ideally, a separate AF-chain DTC should be created, allowing for reimbursement of shared care, and also including anticoagulation monitoring. Importantly, as the intervention of the ALL-IN trial led to an increase in primary care consultations, it even further increases the already high workload of general practitioners. To lower the threshold for GPs to start providing integrated AF care and to ensure a sustainable situation, adequate financial reimbursement and organisational changes are required, for example more time per patient and less registered patients per GP.[29]

REMAINING UNCERTAINTIES

Now that I have discussed the implications of the promising results of the ALL-IN trial and my view on future integrated care for patients with AF, a remaining question or uncertainty is *why* patients with AF appear to benefit from integrated care? Is it the broad approach? Is it the extra care and structured follow-up facilitating earlier detection of heart failure? Does the combined horizontal *and* vertical integration of care (i.e. integrating care aspects and collaboration *within* primary care and *across* primary and secondary care, respectively) make an important difference? Or all of the above?

The ALL-IN trial is the first study to include both horizontal and vertical integration, treatment of cardiovascular and non-cardiovascular comorbidity, and anticoagulation monitoring. Therefore, perhaps, we can for the first time speak of truly integrated care, which, as I stated in the introduction chapter, aims to overcome care fragmentations. However, one might wonder if all these aspects are equally necessary, as less comprehensive integrated care programs provided at specialised AF clinics have also shown beneficial results.[23,26] This might imply that, for example, the extra follow-up

with earlier detection of heart failure is an important driver for the observed effects on mortality in these studies. However, as these studies only included cardiovascular outcomes, the *added* benefit of a fully integrated, broader approach remains unknown, but could very well be significant given the observed effect on non-cardiovascular mortality in the ALL-IN trial. More research is needed to identify the key responsible factors.

SUGGESTIONS FOR FUTURE RESEARCH ON INTEGRATED AF CARE IN PRIMARY CARE

To confirm the findings of the ALL-IN study, the implementation of integrated care for patients with AF in primary care on a larger scale should be accompanied with a thorough scientific evaluation. This could be done for example with a stepped-wedge design with practices starting providing integrated care sequentially. An alternative would be to include patients with AF receiving integrated care in the large ongoing DUTCH-AF registry, as the primary care practices will need to identify their patients with AF anyway prior to starting integrated care. A pragmatic approach regarding inclusion criteria, both in future evaluations of integrated AF care as well as in AF studies in general, is important to enhance generalizability of future studies, especially since patients with AF are often old and frail. It is quite concerning that in clinical trials, also in the field of AF, patients with multimorbidity are often excluded, as was seen in the NOAC trials.[30,31] This seriously restricts the domain of the trials and limits generalizability of AF studies.

To define which patients benefit most from integrated care and in which setting, further studies in different subgroups of patients with AF are also needed. For example, it would be interesting to compare AF patients with and without concurrent heart failure, or patients with AF aged below and above 75 years, to see if the effect on mortality is predominantly achieved in a particular age group (i.e. exploring floor or ceiling effects). Furthermore, it would be relevant to know if there are certain patients in whom one or two visits per year instead of the quarterly check-ups would be sufficient. If a lower follow-up frequency in certain patients is proven safe and effective, this could increase the feasibility of implementing integrated care for patients with AF.

Lastly, what should be learned from the ALL-IN trial is that future studies in patients with AF should not only include cardiovascular mortality or cardiovascular hospitalisation as outcome parameters of interest. Given that elderly patients

with AF are often affected with multiple comorbidities, it can be very difficult to make a distinction between cardiovascular and non-cardiovascular hospitalisation and mortality. Imagine an elderly patient with AF and comorbid heart failure and COPD, being presented at the emergency department with increasing dyspnoea. When such a patient dies, this could be classified as both cardiovascular and non-cardiovascular death. Including all-cause mortality and all-cause hospitalisation as an outcome avoids possible misclassification and better suits the view that AF is part of a systemic condition characterised by interfering cardiovascular and non-cardiovascular comorbidities.

CONCLUDING REMARK

Justin A. Ezekowitz wrote an editorial at the occasion of the publication of the RACE-4 study[23] in the European Heart Journal. He adapted the quote "All for one, one for all" from Alexandre Dumas' novel The Three Musketeers, by concluding with "All for one, but not one clinic for all",[32] referring to the inconclusive results on the effectiveness of nurse-led care provided at AF-clinics. In light of the results of the ALL-IN trial, my conclusion regarding future care for patients with AF would be: a*ll for one, ALL-IN for all!*

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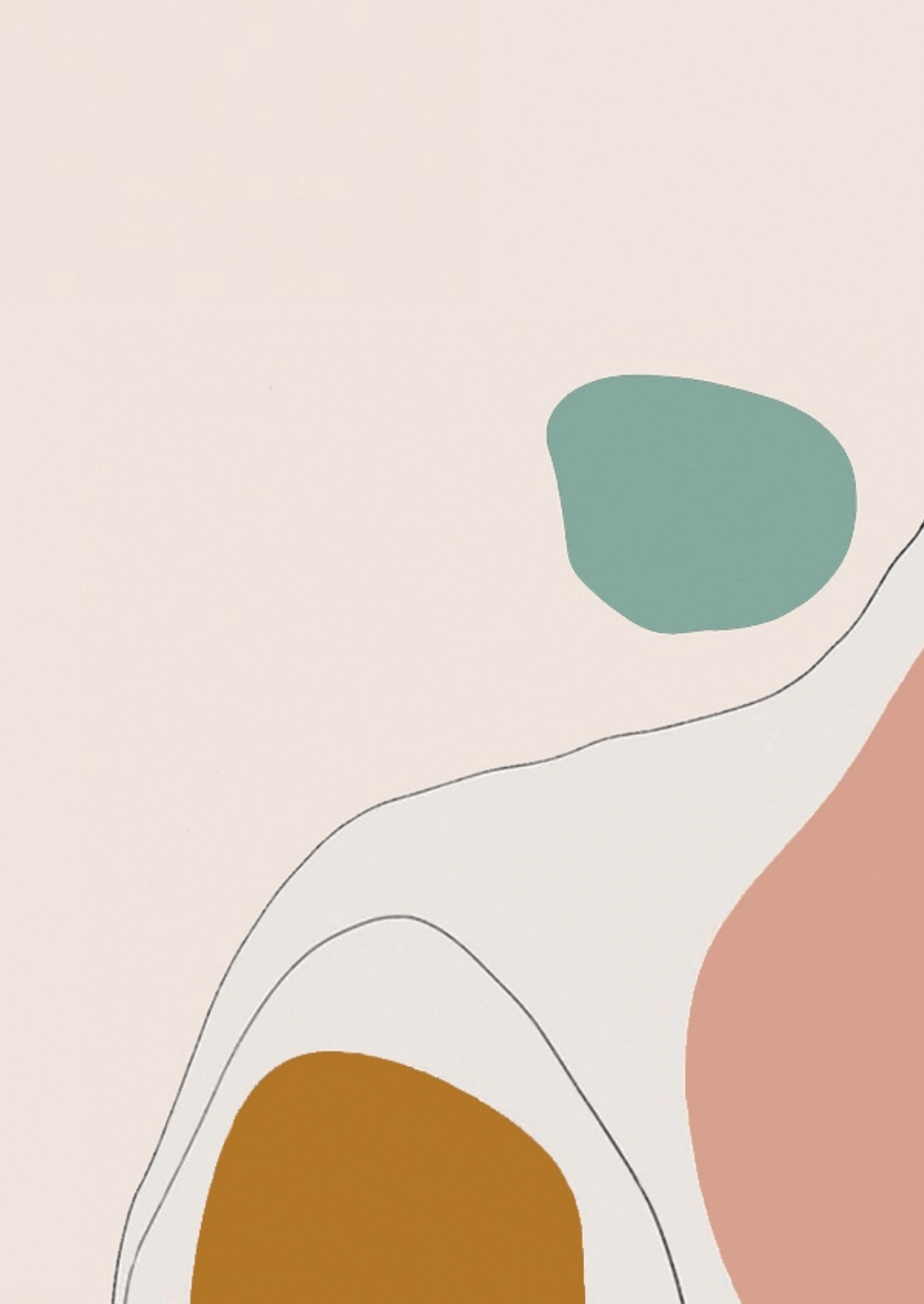

SUMMARY

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence increases with age, up to more than 17% of patients aged 85 years and older. In the next decades, the prevalence of AF is expected to increase dramatically, often referred to as the 'AF epidemic'.[1] Therefore, organisational changes are needed to manage the increasing disease burden of AF.[2] Treatment of AF is generally focused on heart rate or heart rhythm control and treatment with oral anticoagulants to prevent an ischaemic stroke.[3] Importantly, however, AF is more than merely a heart rhythm disorder with an increased risk of stroke, as it often interacts with multiple comorbidities, especially in the elderly.[4–6] Therefore, care for comorbidities like hypertension, heart failure and COPD, should be an integral part of AF management. This gives rise to questions on how to organise care for patients with AF and in which setting.

Besides the AF epidemic, another critical development in the field of AF is the shift in the prescription of oral anticoagulants: from the traditional vitamin K antagonists (VKA), towards non-vitamin K antagonist oral anticoagulants (NOACs). This development also has consequences for the organisation of care for patients with AF, and raises questions about how physicians prescribe these drugs and what the effectiveness and safety of NOACs are in routine clinical practice.

The research objectives of this thesis were:

1. To evaluate if integrated care for patients with AF can be safely and (cost) effectively organised in primary care (the ALL-IN study, Chapters 1-3).
2. To describe the evidence and recommendations for NOAC dose reduction and the occurrence of *off-label* NOAC dose reduction (Chapter 4), as well as the clinical impact of off-label NOAC dose reduction in terms of ischaemic stroke and bleeding complications in routine care patients with AF (Chapter 5).
3. To investigate whether the relative safety and efficacy of NOACs compared to VKAs are influenced by the number of concomitant drugs prescribed to patients with AF treated in routine practice (Chapter 6).

INTEGRATED MANAGEMENT OF PATIENTS WITH AF IN PRIMARY CARE

To improve care for patients with AF, multidisciplinary and coordinated care, so-called *integrated care,* has been recommended in the guidelines[3] and showed beneficial effects on cardiovascular mortality and cardiovascular hospitalisation in patients with newly diagnosed AF treated at experienced outpatient cardiology clinics.[7,8] If integrated AF care could be performed equally effective and safe in *primary care*, this could have important practical and clinical benefits for the often older AF patients with multimorbidity. Moreover, this could be helpful in reducing healthcare costs, especially considering the increasing prevalence of AF. Hence, we developed and evaluated an integrated care program for elderly patients with AF in primary care, with a focus on treatment of comorbidities: the ALL-IN study. The design of this cluster randomised, pragmatic, non-inferiority trial is described in **Chapter 1**.

Chapter 2 describes the main results of the ALL-IN trial. Between 2016 and 2019, 26 Dutch primary care practices close to Zwolle, Hardenberg and Deventer participated in the ALL-IN trial. 15 practices were randomised towards providing the integrated care intervention, and 11 practices were randomised towards providing usual care. Patients with documented AF aged 65 years or older were included. In practices randomised for the intervention group, 527 patients provided informed consent for participating in the intervention and were compared to 713 patients in the usual care group. Median age was 77 (interquartile range 72–83) years. The intervention consisted of three main aspects: (i) quarterly check-ups by the practice nurses, supervised by the GP, for AF and its related cardiovascular *and* non-cardiovascular comorbidities, (ii) anticoagulation monitoring, with International Normalized Ratio (INR) measurements performed in the primary care practice in patients treated with a VKA and special attention for drug compliance and monitoring of kidney function in patients with a NOAC, and (iii) easy-access consultation with anticoagulation clinics and cardiologists. Usual care could vary per patient, but for most patients it involved a once yearly consultation of a cardiologist at the outpatient cardiology department, and, for patients using a VKA, INR measurements performed by anticoagulation clinics.

During a median follow-up time of 2.2 years, the primary outcome all-cause mortality occurred in 39 patients in the intervention arm and 96 patients in the control arm (7.4% and 13.5%, respectively). The hazard ratio (HR) for all-cause mortality, after adjustment for age, sex, and frailty, was 0.55 (95% confidence interval (CI) 0.37 to 0.82, p=0.003). Risk reduction of non-cardiovascular mortality was more pronounced than risk reduction of cardiovascular mortality (adjusted HR for non-cardiovascular

mortality 0.47 (95% CI 0.27 to 0.82) and adjusted HR 0.63 (95% CI 0.37 to 1.06) for cardiovascular mortality). Hospitalisations occurred frequently in both treatment arms, with 38% of all patients having at least one hospital admission (adjusted incidence rate ratio 0.84 (95% CI 0.69 to 1.03)). Non-cardiovascular hospitalisation occurred twice as frequently as cardiovascular hospitalisation. No statistically significant differences were observed for the outcomes major adverse cardiac events, ischaemic stroke, major bleeding, clinically relevant non-major bleeding and health-related quality of life.

In **Chapter 3** of this thesis, we evaluate the cost-effectiveness of the integrated care intervention, as studied in the ALL-IN trial. The number of primary care consultations provided in the intervention and hence, costs in primary care were higher (up to €375 per intervention patient per 2 years), but this was outweighed by cost reductions for other resources, notably home care and assisted living facilities. Altogether, we observed that the integrated care intervention in primary care reduced costs (ranging between -€760 to -€3868 per patient per 2 years) and also provided a small gain in Quality Adjusted Life Years between 0.00 and 0.06 (i.e. up to 22 extra days alive with perfect quality of life per patient over the 2 years). Consequently, our results showed a probability between 42.1% and 89.3% that integrated care for patients with AF in primary care is more effective and less costly.

The results of the ALL-IN trial suggest that the integrated primary care intervention might bring patients with AF to a more stable clinical condition in general, thereby ultimately reducing mortality. Hence, it offers an attractive solution for the increasing disease burden and healthcare costs associated with the increasing prevalence of AF, while improving the accessibility of care for elderly patients with AF and multimorbidity.

OFF-LABEL NOAC DOSE REDUCTION

A complication of anticoagulant therapy that is often feared by both patients and physicians is the inherent risk of bleeding. For each of the four available NOACs, a reduced dose is available for patients fulfilling strict criteria for dose reduction. Concerns have emerged, however, that many patients in routine practice receive a reduced NOAC dose *without* a clear indication, so-called 'off-label dose reduction'. This likely occurs in an attempt to alleviate a presumed increased risk of bleeding, but possibly introduces an unnecessary risk of ischaemic stroke.[9–12]

Chapter 4 describes our clinical review about the current evidence and guidance regarding NOAC dose reduction and a meta-analysis of observational studies on the prevalence of off-label dose reduction and the associated patient characteristics and clinical consequences. First, we describe that NOAC dose reduction criteria are based on pharmacokinetic principles, to achieve a bioavailability that balances effectiveness (reducing stroke risk) and safety (reducing bleeding risk). Reducing the dose solely because of the presence of non-pharmacokinetic bleeding risk factors, for example, prior major bleeding, would result in suboptimal plasma levels, thereby negatively influencing the balance between effectiveness and safety. Next, we performed a meta-analysis including 36 studies, to show that off-label NOAC dose reduction occurred on average in 15.7% (95% CI 13.3% to 18.2%) of patients with AF receiving NOAC therapy. Higher age, a decrease in body weight and a decrease in renal function were generally associated with an off-label reduced NOAC dose. Finally, it appeared that the impact of off-label NOAC dose reduction on outcomes such as ischaemic stroke and bleeding complications was still largely unknown, as the available studies were often small and suffered from methodological shortcomings.

Prompted by the latter observation, we performed a large, population based cohort study on the clinical impact of off-label NOAC dose reduction, described in **Chapter 5**, using observational primary care data from the United Kingdom Clinical Practice Research Datalink (CPRD). We compared 2,466 patients with an off-label reduced NOAC dose (accounting for 8.0% of all NOAC prescriptions), to 18,108 patients with an on-label standard NOAC dose. Physicians appeared to opt for off-label dose-reduction in older patients (median age was 80 years for patients with an off-label reduced dose and 72 years for on-label standard dose users) and patients with more co-morbidity. These patients were indeed at high risk for both stroke and bleeding events, as was reflected in the higher crude incidence rates of these outcomes among patients with an off-label reduced NOAC dose compared to patients with an on-label standard NOAC dose (0.94 versus 0.70 per 100 person years for ischemic stroke, 1.48 versus 0.83 for major bleeding and 6.78 versus 6.16 for non-major bleeding). After adjustment for confounding, however, off-label NOAC dose reduction did not evidently affect the risk of ischaemic stroke (adjusted HR 1.07; 95% CI 0.65 to 1.74) and, importantly, did not appear to reduce the risk of major bleeding (adjusted HR 0.98; 95%CI 0.65 to 1.48). Therefore, our data suggest that off-label NOAC dose reduction is unlikely to be a fruitful strategy when aiming to reduce the, indeed elevated, major bleeding risk in certain older AF patients with multimorbidity.

THE NUMBER OF CONCOMITANT DRUGS AND THE SAFETY OF NOACS IN ROUTINE CARE

In **Chapter 6** of this thesis, we investigated whether the number of concomitant drugs prescribed modifies the effect of NOACs compared to VKAs in routine care CPRD data, as post-hoc analyses of randomised trials showed that the benefit of NOACs versus VKAs on major bleeding appeared less prominent among AF patients with polypharmacy.[13,14] In total, 63,600 patients with AF were included (67% of patients using a VKA and 33% using a NOAC at cohort entry). Effect modification was assessed by stratification of the number of concomitant drugs into three strata (0-5, 6-8 and ≥9 drugs) and by including the continuous variable in an interaction term with the exposure (NOAC versus VKA). The median number of concomitant drugs prescribed was 7. Incidence rates for major bleeding were generally low, and highest in the stratum of 0-5 concomitant drugs (1.39 per 100 person-years for VKA; 1.29 per 100 person-years for NOAC). The adjusted hazard ratio of major bleeding with NOAC versus VKA was 0.98 (95% CI 0.87 to 1.11), with no apparent differences across the 3 strata (interaction p-value 0.65). We therefore conclude that major bleeding risk is comparable between NOACs and VKAs, irrespective of the number of concomitant drugs prescribed.

IMPLICATIONS

Finally, the main findings of the studies included in this thesis are put into perspective in the **General Discussion**, focusing on the implications of the ALL-IN trial. Four key principles for successful implementation of integrated health systems are discussed in light of future implementation of integrated care for patients with AF in primary care: (i) patient focus, (ii) standardised care delivery through inter-professional teams, (iii) integrated information systems, and (iv) financial management. An important question that remains, is *why* patients with AF appear to benefit from integrated care? Although this question cannot be fully answered yet because of the multifaceted nature of the intervention, the results of the ALL-IN trial, especially with regard to non-cardiovascular mortality and hospitalisation, do support the view that AF is part of a systemic condition characterised by multiple interfering cardiovascular *and* non-cardiovascular comorbidities. We therefore suggest the recognition of an 'AF-multimorbidity cluster'. A broad approach with a focus on treatment of multimorbidity through integrated AF care orchestrated in primary care better suits this view and deserves widespread implementation and evaluation.

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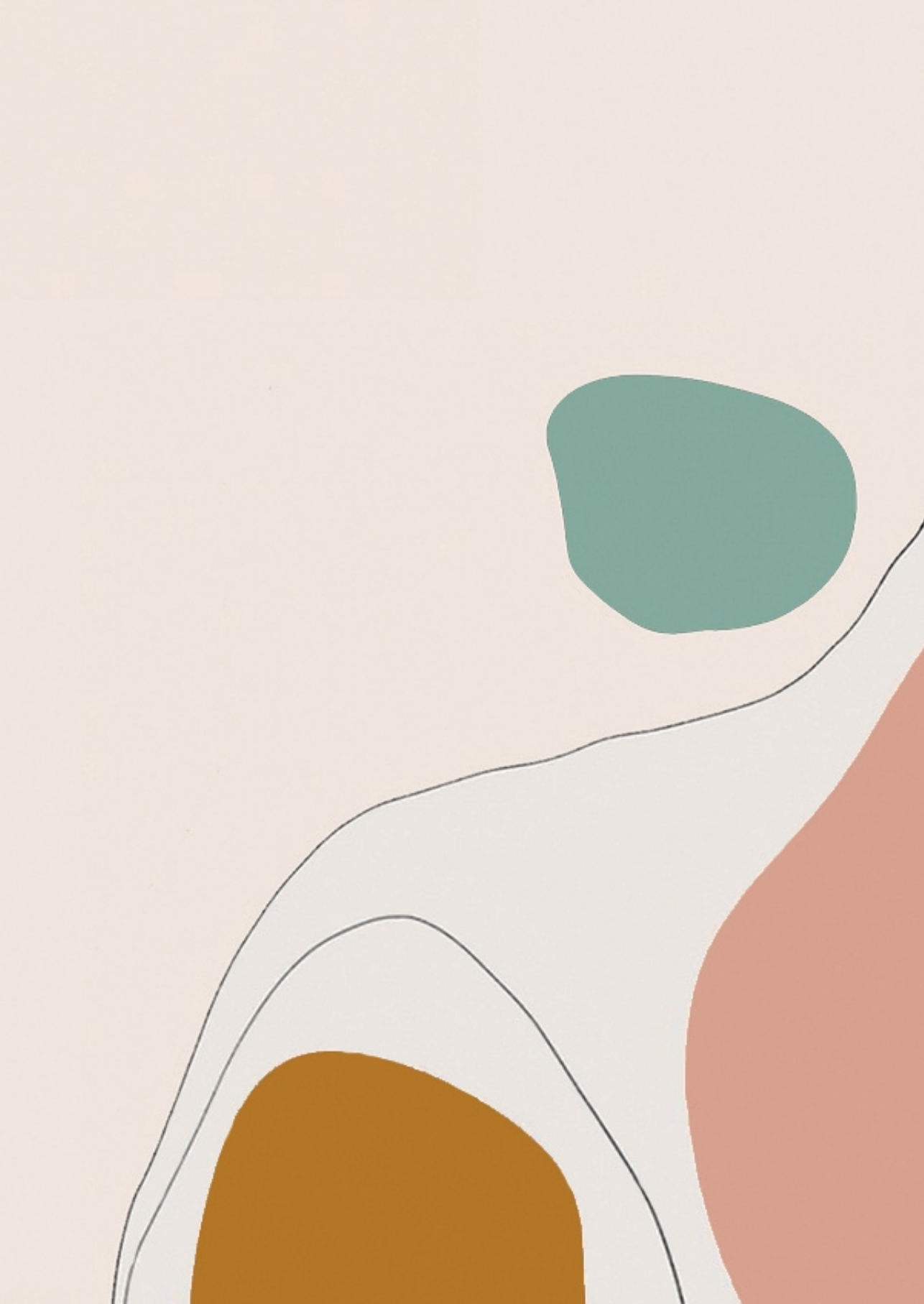

SAMENVATTING

INLEIDING

Atriumfibrilleren (AF), ofwel boezemfibrilleren, is de meest voorkomende hartritmestoornis. De prevalentie neemt toe met de leeftijd, tot meer dan 17% bij patiënten van 85 jaar en ouder. In de komende decennia zal de prevalentie van AF naar verwachting fors toenemen, er wordt daarom ook wel gesproken van een 'AF-epidemie'.[1] Organisatorische veranderingen in de zorg voor patiënten met AF zijn daarom nodig om de toenemende ziektelast van AF te kunnen beheersen.[2] De behandeling van AF richt zich voornamelijk op controle van de hartfrequentie of herstel van sinusritme, evenals het voorkomen van een herseninfarct door middel van orale anticoagulantia.[3] AF is echter meer dan alleen een hartritmestoornis met een verhoogd risico op een herseninfarct. In veel gevallen is er namelijk sprake van een sterke samenhang met andere aandoeningen, zeker bij ouderen.[4–6] Zorg voor deze comorbiditeiten, zoals hypertensie, hartfalen en COPD, zou daarom een integraal onderdeel moeten uitmaken van de zorg voor patiënten met AF. Dit leidt tot de vraag hoe de zorg voor het toenemende aantal patiënten met AF het beste kan worden georganiseerd, en in welke setting.

Naast de dreigende AF-epidemie vindt er momenteel een tweede belangrijke ontwikkeling plaats op het gebied van AF: de verschuiving in het gebruik van orale anticoagulantia, van de traditionele vitamine Kantagonisten (VKA's) naar de niet-vitamine K antagonist orale anticoagulantia (NOAC's). Ook deze ontwikkeling heeft consequenties voor de organisatie van zorg voor patiënten met AF. Daarnaast roept het vragen op over hoe artsen deze middelen voorschrijven en wat de effectiviteit en de veiligheid van NOAC's zijn in de dagelijkse praktijk.

De onderzoeksdoelstellingen van dit proefschrift waren:

1. Onderzoeken of integrale zorg voor patiënten met AF veilig en (kosten)effectief kan worden georganiseerd in de huisartsenpraktijk (het ALL-IN onderzoek, Hoofdstuk 1 t/m 3).
2. Een overzicht creëren van het bewijs en de aanbevelingen voor dosisreductie van NOAC's en nagaan hoe vaak *off-label* dosisreductie van NOAC's voorkomt (Hoofdstuk 4), evenals het onderzoeken van de invloed van off-label dosisreductie van NOAC's op het optreden van herseninfarcten en bloedingscomplicaties bij patiënten met AF in de dagelijkse praktijk (Hoofdstuk 5).
3. Onderzoeken of de veiligheid en effectiviteit van NOAC's in vergelijking met VKA's worden beïnvloed door het totale aantal gelijktijdig voorgeschreven medicijnen bij patiënten met AF in de dagelijkse praktijk (Hoofdstuk 6).

INTEGRALE ZORG VOOR PATIËNTEN MET AF IN DE HUISARTSENPRAKTIJK

Om de zorg voor patiënten met AF te verbeteren wordt multidisciplinaire en gestructureerde zorg, zogenaamde *integrale zorg*, momenteel aanbevolen in de richtlijnen.[3] Onderzoek naar integrale zorg op gespecialiseerde en ervaren AF-poliklinieken in het ziekenhuis toonde namelijk een afname in cardiovasculaire sterfte en cardiovasculaire ziekenhuisopnames.[7,8] Echter, als integrale zorg voor patiënten met AF ook veilig en effectief *in de huisartsenpraktijk* zou kunnen worden georganiseerd, dan heeft dit wellicht belangrijke praktische en klinische voordelen voor de vaak oudere patiënten met AF en multimorbiditeit. Bovendien zou dit kunnen bijdragen aan het beheersen van de zorgkosten, gelet op de stijgende prevalentie van AF. In het ALL-IN onderzoek hebben we daarom een integraal zorgprogramma ontwikkeld en onderzocht voor oudere patiënten met AF in de huisartsenpraktijk, waarbij de interventie zich vooral richtte op behandeling van multimorbiditeit. De opzet van dit cluster-gerandomiseerde, pragmatische, 'non-inferiority' onderzoek wordt beschreven in **Hoofdstuk 1**.

Hoofdstuk 2 beschrijft de belangrijkste resultaten van het ALL-IN onderzoek. Tussen 2016 en 2019 namen 26 Nederlandse huisartsenpraktijken in de regio's Zwolle, Hardenberg en Deventer deel aan dit onderzoek. 15 praktijken werden gerandomiseerd naar de interventiegroep om vervolgens de integrale zorg interventie uit te voeren en 11 praktijken werden gerandomiseerd naar de controlegroep waarin reguliere zorg plaatsvond. Patiënten met AF van 65 jaar of ouder werden geïncludeerd. In de interventiepraktijken wilden 527 patiënten deelnemen aan de interventie. Zij werden vergeleken met 713 patiënten uit de controlepraktijken. De mediane leeftijd was 77 jaar (interkwartielafstand 72–83). De interventie bestond uit drie hoofdonderdelen: (i) kwartaalcontroles door een getrainde praktijkondersteuner (POH) onder supervisie van de huisarts, gericht op behandeling van AF en de gerelateerde cardiovasculaire én niet-cardiovasculaire comorbiditeit, (ii) monitoring van antistollingsbehandeling in de huisartsenpraktijk, inclusief International Normalized Ratio (INR) controles bij patiënten die een VKA gebruikten en aandacht voor therapietrouw en nierfunctiecontrole bij patiënten met een NOAC, en (iii) nauwe samenwerking met de trombosedienst en cardiologen. Reguliere zorg kon per patiënt verschillen, maar voor de meeste patiënten betrof het een jaarlijks consult bij de cardioloog en bij patiënten die een VKA gebruikten controleerde de trombosedienst de INR.

De mediane follow-up duur was 2,2 jaar. In totaal stierven er 39 patiënten in de interventiepraktijken en 96 patiënten in de controlepraktijken (respectievelijk 7,4% en 13,5%). De 'hazard ratio' (HR) voor sterfte ongeacht de oorzaak, na correctie voor leeftijd, geslacht en kwetsbaarheid, was 0,55 (95% betrouwbaarheidsinterval (BI) 0,37-0,82, p=0,003). Voor niet-cardiovasculaire sterfte was het effect groter dan voor cardiovasculaire sterfte (gecorrigeerde HR voor niet-cardiovasculaire sterfte 0,47 (95% BI 0,27-0,82) en gecorrigeerde HR 0,63 (95% BI 0,37-1,06) voor cardiovasculaire sterfte). Ziekenhuisopnames kwamen vaak voor in beide groepen, waarbij 38% van de patiënten ten minste één keer werd opgenomen (gecorrigeerde 'incidence rate ratio' 0.84 (95% BI 0.69-1.03)). Niet-cardiovasculaire ziekenhuisopnames kwamen tweemaal zo vaak voor als cardiovasculaire ziekenhuisopnames. Er werden geen statistisch significante verschillen waargenomen voor de uitkomsten 'major adverse cardiac events', herseninfarct, ernstige bloeding, klinisch relevante niet-ernstige bloeding en gezondheids-gerelateerde kwaliteit van leven.

In **Hoofdstuk 3** van dit proefschrift evalueren we de kosteneffectiviteit van de integrale zorg interventie van het ALL-IN onderzoek. Het aantal consulten in de interventiepraktijken en daarmee ook de kosten in de interventiegroep waren hoger dan in de controlegroep (tot € 375 per interventiepatiënt per 2 jaar), maar dit werd gecompenseerd door kostenbesparingen in andere categorieën, met name thuiszorg en het wonen in een verzorgingshuis. Alles bij elkaar zagen we een kostenbesparing in de interventiegroep (variërend van -€760 tot -€3868 per patiënt per 2 jaar) en ook een kleine winst in voor kwaliteit gecorrigeerde levensjaren, tussen 0,00 en 0,06 (dat wil zeggen, tot 22 gewonnen levensdagen met een perfecte kwaliteit van leven per patiënt in 2 jaar tijd). Daarbij lag de waarschijnlijkheid dat integrale zorg voor patiënten met AF in de huisartsenpraktijk effectiever én goedkoper is tussen 42,1% en 89,3%.

Al met al suggereren de resultaten van het ALL-IN onderzoek dat patiënten die integrale AF-zorg in de huisartsenpraktijk krijgen in 'stabieler vaarwater' terechtkomen, waardoor uiteindelijk ook sterfte kan worden gereduceerd. Het organiseren van integrale AF-zorg in de eerste lijn zou daarom een aantrekkelijke oplossing kunnen bieden voor de stijgende ziektelast en zorgkosten ten gevolge van de stijgende prevalentie van AF, en tegelijkertijd de toegankelijkheid van zorg voor oudere patiënten met AF en multimorbiditeit kunnen verbeteren.

OFF-LABEL DOSISREDUCTIE VAN NOAC'S

Een complicatie van de behandeling met orale anticoagulantia, die door zowel patiënten als artsen wordt gevreesd, is het inherente risico op een bloeding. Voor alle vier de verschillende NOAC's is naast een standaarddosis ook een lagere dosis beschikbaar voor patiënten die voldoen aan strikte criteria voor dosisreductie. Er zijn echter zorgen ontstaan over het voorschrijven van een verlaagde NOAC-dosis aan patiënten die *niet* voldoen aan de criteria voor dosisreductie, zogenaamde 'off-label dosisreductie'. Artsen doen dit vermoedelijk in de hoop een eventueel verhoogd bloedingsrisico te verlagen, maar dit leidt mogelijk tot een onnodig verhoogd risico op een herseninfarct.[9–12]

Hoofdstuk 4 beschrijft onze review over het huidige bewijs en de adviezen met betrekking tot NOAC-dosisverlaging, evenals een meta-analyse van observationele studies naar de prevalentie van off-label dosisreductie van NOAC's en de patiëntkenmerken en klinische consequenties die daarmee zijn geassocieerd. Ten eerste beschrijven we dat de criteria voor dosisreductie van NOAC's gebaseerd zijn op farmacokinetische principes, met als doel een biologische beschikbaarheid te bereiken die de balans tussen effectiviteit (risico op herseninfarct) en veiligheid (risico op bloeding) zo evenwichtig mogelijk houdt. Een dosisreductie puur vanwege niet-farmacokinetische risicofactoren voor een bloeding, bijvoorbeeld omdat iemand in het verleden een ernstige bloeding heeft doorgemaakt, zou leiden tot suboptimale plasmaspiegels en een verstoorde balans tussen effectiviteit en veiligheid. Vervolgens hebben we een meta-analyse van 36 onderzoeken uitgevoerd, waaruit bleek dat off-label dosisreductie van NOAC's gemiddeld optrad bij 15,7% (95% BI 13,3% tot 18,2%) van de patiënten met AF die behandeld werden met een NOAC. Hogere leeftijd, een lager lichaamsgewicht en een afname van de nierfunctie bleken geassocieerd met off-label dosisreductie. Ten slotte bleek dat het effect van off-label dosisreductie van NOAC's op het optreden van herseninfarcten en bloedingen nog grotendeels onbekend was, aangezien de beschikbare onderzoeken vaak klein en matig van kwaliteit waren.

Naar aanleiding van deze laatste conclusie hebben we een groot cohortonderzoek uitgevoerd naar de gevolgen van off-label NOAC-dosisverlaging in de dagelijkse praktijk, beschreven in **Hoofdstuk 5**. Hiervoor maakten we gebruik van observationele data uit huisartsenpraktijken uit het Verenigd Koninkrijk: de Clinical Practice Research Datalink (CPRD). We vergeleken 2.466 patiënten (8,0%) die een off-label verlaagde NOAC dosis kregen, met 18.108 patiënten (58,5%) die terecht (on-label) een standaard NOAC dosis kregen. Artsen bleken vaker te kiezen voor off-label dosisreductie bij

oudere patiënten (de mediane leeftijd was 80 jaar voor patiënten met een off-label verlaagde NOAC dosis en 72 jaar voor gebruikers van een on-label standaard NOAC dosis) en bij patiënten met multimorbiditeit. Dat dit inderdaad een hoog risicogroep is voor zowel herseninfarcten als bloedingen, bleek wel uit de hogere incidentie-dichtheid ('incidence rate',IR) van deze uitkomsten onder patiënten met een off-label verlaagde NOAC dosis (0,94 versus 0,70 per 100 persoonsjaren voor herseninfarcten; 1,48 versus 0,83 voor ernstige bloedingen; en 6,78 versus 6,16 voor niet-ernstige bloedingen). Na correctie voor confounding bleek off-label dosisverlaging van NOAC's echter geen duidelijke invloed te hebben op het risico op herseninfarcten (gecorrigeerde HR 1,07 (95% BI 0,65-1,74)) en, belangrijker nog, ook niet op het risico op ernstige bloedingen (gecorrigeerde HR 0,98 (95% BI 0,65 tot 1,48)). Daarom suggereren deze resultaten dat off-label dosisverlaging van NOAC's waarschijnlijk geen veelbelovende strategie is om het (wel degelijk) verhoogde bloedingsrisico bij oudere patiënten met AF en multimorbiditeit te kunnen verminderen.

HET AANTAL GELIJKTIJDIG VOORGESCHREVEN MEDICIJNEN EN DE VEILIGHEID VAN NOAC'S IN DE DAGELIJKSE PRAKTIJK

In **Hoofdstuk 6** van dit proefschrift hebben we onderzocht of het *aantal* voorgeschreven medicijnen de veiligheid van NOAC's in vergelijking met VKA's beïnvloedt. Hierbij maakten we net als in Hoofdstuk 5 gebruik van CPRD-data. Uit post-hoc-analyses van gerandomiseerde onderzoeken is namelijk gebleken dat de afname in ernstige bloedingen bij behandeling met NOAC's ten opzichte van VKA's minder groot was bij patiënten met polyfarmacie.[13,14]

In totaal includeerden we 63.600 patiënten met AF van wie 67% een VKA gebruikte en 33% een NOAC. Effectmodificatie werd onderzocht door drie groepen te creëren op basis van het aantal gelijktijdig voorgeschreven medicijnen (0-5, 6-8 en ≥9 medicijnen) en door het aantal medicijnen als continue variabele op te nemen in een interactieterm met de determinant (NOAC's versus VKA's). De mediaan van het aantal gelijktijdig voorgeschreven medicijnen was 7. De IR van ernstige bloedingen was over het algemeen laag en het hoogst in de groep van 0-5 medicijnen (1,39 per 100 persoonsjaren voor VKA's; 1,29 per 100 persoonsjaren voor NOAC's). De gecorrigeerde HR voor ernstige bloedingen met NOAC's versus VKA's was 0,98 (95% BI 0,87-1,11), waarbij geen duidelijke verschillen tussen de 3 groepen werden gezien (interactie p-waarde 0,65). We concluderen daarom dat het risico op ernstige bloedingen vergelijkbaar is tussen NOAC's en VKA's, ongeacht het aantal gelijktijdig voorgeschreven geneesmiddelen.

IMPLICATIES

Ten slotte worden in de **General Discussion** van dit proefschrift de belangrijkste bevindingen van de onderzoeken uit dit proefschrift bediscussieerd, met de nadruk op de mogelijke implicaties van het ALL-IN onderzoek. Vier principes die essentieel zijn voor succesvolle implementatie van integrale gezondheidzorg worden besproken vanuit het perspectief van toekomstige implementatie van integrale AF zorg in de huisartsenpraktijk: (i) patiëntgerichtheid, (ii) gestandaardiseerde zorgverlening door multidisciplinaire teams, (iii) geïntegreerde informatiesystemen en (iv) financieel management.

Een belangrijke vraag die overblijft, is *waarom* patiënten met AF precies zouden profiteren van integrale zorg? Deze vraag is niet gemakkelijk te beantwoorden omdat de onderzochte interventie uit het ALL-IN onderzoek uit meerdere onderdelen bestond. Desalniettemin ondersteunen de resultaten van het ALL-IN onderzoek, met name de resultaten voor niet-cardiovasculaire sterfte en ziekenhuisopname, de visie dat AF deel uitmaakt van een systemische aandoening, die wordt gekenmerkt door onderling samenhangende cardiovasculaire én niet-cardiovasculaire multimorbiditeit. We pleiten daarom voor het herkennen van een 'AF-multimorbiditeitscluster'. Een generalistische benadering van patiënten met AF en behandeling van multimorbiditeit door middel van integrale zorg in de huisartsenpraktijk sluit goed aan bij deze visie en is rijp voor grootschalige implementatie en evaluatie.

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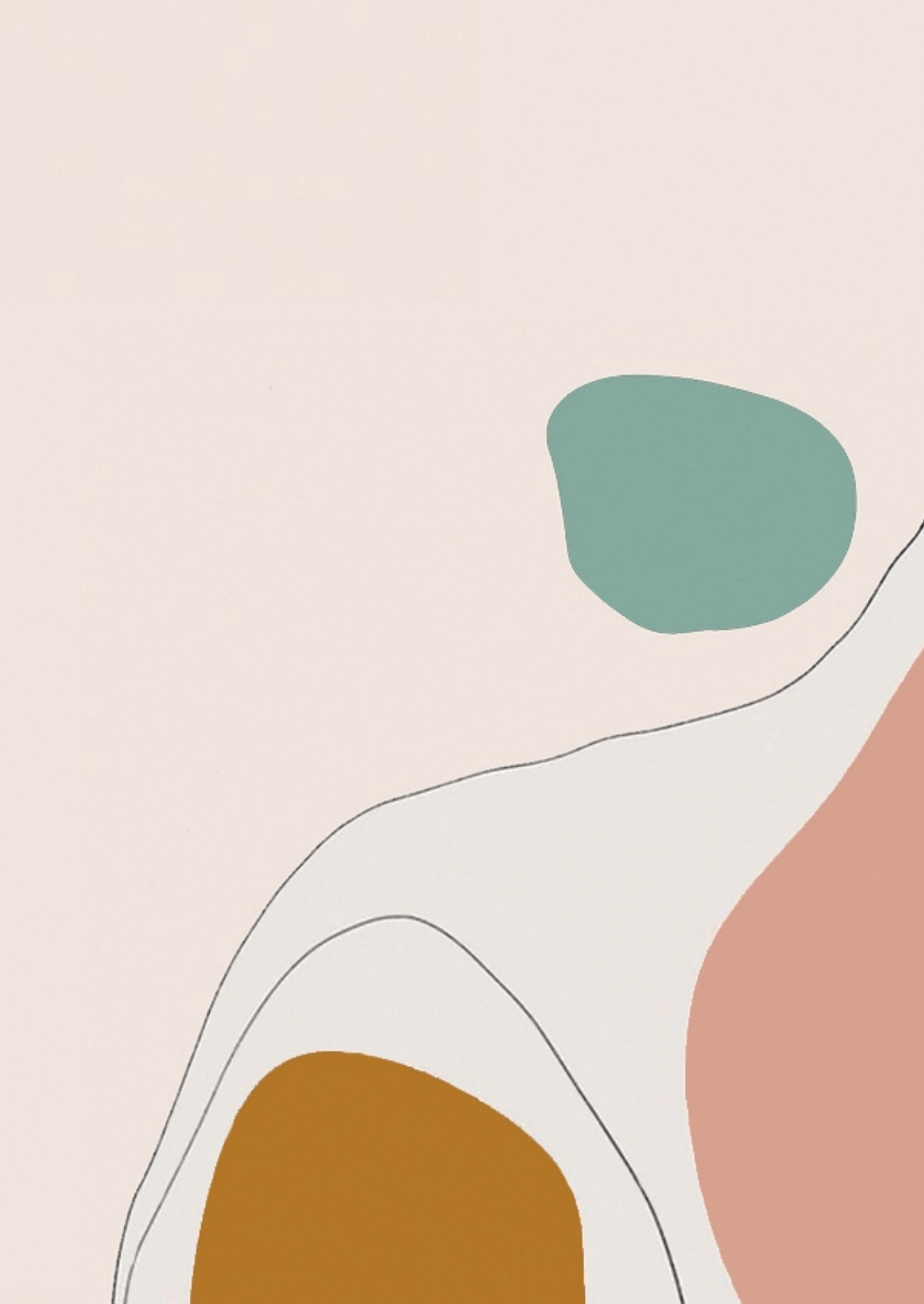

DANKWOORD

DANKWOORD

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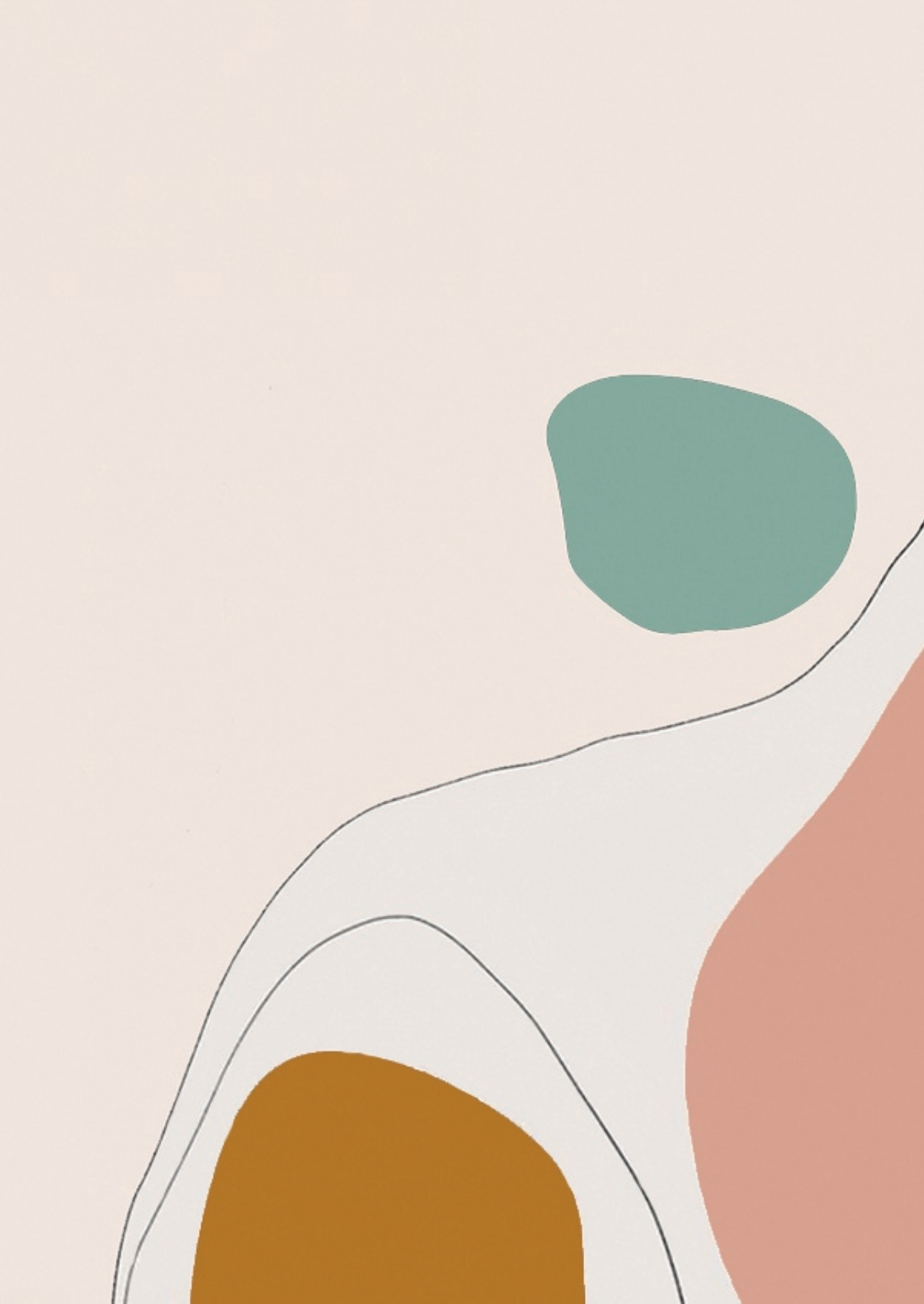
Het is AF.



ABOUT THE AUTHOR

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Carline Jo van den Dries was born in Zuid-Scharwoude, Noord-Holland, on September 15th 1989. After graduation from secondary school in 2007 (Trinitas College Han Fortmann, Heerhugowaard) she studied medicine at the VU University Medical Center Amsterdam, where she obtained her medical degree cum laude in December 2013.

In 2014-2015, she worked as a resident in Internal Medicine at the Spaarne Gasthuis in Haarlem. In June 2015, she started her PhD trajectory at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht/Utrecht University, under supervision of prof. dr. K.G.M. Moons, prof. dr. A.W. Hoes, dr. G.J. Geersing and dr. S. van Doorn, which resulted in the articles presented in this thesis. In 2019, she completed the postgraduate master Clinical Epidemiology at Utrecht University. Since 2017, she has combined her research projects with the general practitioner training, of which she is currently at the end of the second year.