Quality of contemporary anticoagulation management in atrial fibrillation

QUALITY OF CONTEMPORARY ANTICOAGULATION MANAGEMENT IN ATRIAL FIBRILLATION

JAAP SEELIG

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Cover: This work shows a timeline of the first isolation of naturally occurring anticoagulants which provided the foundation for the creation of the oral anticoagulants used in practice currently. This work by Jaap Seelig is a derivative of 1) "Fig 1" from 'Solving a Bloody Mess: B-Vitamin Independent Metabolic Convergence among Gammaproteobacterial Obligate Endosymbionts from Blood-Feeding Arthropods and the Leech Haementeria officinalis' by Alejandro Manzano-Marin et al, used under CC BY-NC 4.0, source: https://tinyurl.com/yargbwbt and 2) "Figure 1" from 'Possibilities for Relapsing Fever Reemergence' by Sally J Cutler, Public Domain, source: https://tinyurl.com/ybe3jda2 and 3) "Hookworms", which comes from the Centers for Disease Control and Prevention's Public Health Image Library (PHIL) with identification number #5205, Public Domain, source: https://tinyurl.com/yazmfbuu and 4) "leech-1055446_1920" by EllWi (https://tinyurl.com/y9dtp4z6/) from Pixabay and 5) "Melilotus officinalis 002" by H. Zell, used under CC BY-SA 3.0, source: https://tinyurl.com/y7u6caw7.

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CHAPTER 1

General introduction and outline of the thesis

INTRODUCTION

Thrombosis is one of the leading causes of death and global disease burden.[1] In 2010, it was estimated that one in five deaths worldwide is caused by ischemic stroke or ischemic heart disease, a 32% increase since 1990.[1] Many underlying conditions can be a cause of thrombosis, such as atrial fibrillation (AF) or the presence of a mechanical heart valve. The factors related to thrombosis have classically been described as 'Virchow's triad', and consist of 1) disrupted blood flow (i.e. stasis), 2) an alteration in blood constitution causing hypercoagulability and 3) vascular endothelial disruption.[2] Traditionally, thrombosis in AF has been assigned to stasis, primarily in the atrial appendages. In reality, thrombosis in AF is a complex orchestration of coagulation factors, platelets, leukocytes, extracellular vesicles, cytokines and many more factors involved.[3] Drugs such as statins, ACE-inhibitors or colchicine can therefore also prevent thrombosis to some extent by primarily targeting factors involved with inflammation, while not directly interfering with the coagulation pathways.[4-9] However, in most AF patients the risk of thrombosis is so high that inhibition of the coagulation cascade with oral anticoagulants (OAC) is recommended.[10,11] As OACs hereby increase bleeding risk, it is important to carefully treat and monitor these patients, as both bleeding and thrombosis can have severe consequences. Research, however, has markedly contributed to the improvement of both the safety and effectiveness of antithrombotic management in a relative short period of human history. However, there are still many questions that need answers to guide us to further improvement of OAC care. As the incidence of AF continues to rise as a result of an ageing population, it is essential to identify where potential improvements in OAC care in AF can be made.[12]

This thesis therefore aims to further elucidate and expand current knowledge on the safety and effectiveness of real-world OAC treatment in patients with AF.

—— ORAL ANTICOAGULANTS ——

A BRIEF HISTORY

Anticoagulants have been around since the discovery of the parenterally administered heparphosphatide by medical student Jay McLean in 1916, which was later renamed to heparin by William Henry Howell in 1918.[13] The first OAC was discovered two decades later by Karl Link in 1939, after a farmer from Wisconsin brought him a diseased cow, a bucket of the cow's unclotted blood and one hundred pounds of spoiled clover hay.[14,15] This cattle disease, which had a drastic impact on blood coagulation, would later be known as sweet clover disease, and was the result of the oxidization of coumarin in sweet clover to dicoumarol. In contrast to coumarin, dicoumarol has strong anticoagulant properties and was the first discovered vitamin K antagonist (VKA). The clinical relevance of this compound was argued at that time, and a variation on dicoumarol called warfarin (named after the Wisconsin Alumni Research Foundation) was marketed by Karl Link in 1948 as rat poison.[15] Although this compound was 5-10 times more potent than dicoumarol, was faster acting and had a more uniform anticoagulant response, the branding of warfarin as a rodenticide limited its medical use initially.[14,15] However, after president Dwight D. Eisenhower was treated in 1955 for a myocardial infarction with warfarin, the use of this OAC rapidly increased.[14] Also in the 1950s, other variations on dicoumarol such as acenocoumarol and phenprocoumon were developed, which are currently the two VKAs mainly used in the Netherlands. The target international normalized ratio (INR; a measure of clotting time which is used to dose VKAs) in the Netherlands have been higher compared to other countries for many years, namely low-intensity range 2.5-3.5 vs 2.0-3.0 and high-intensity range 3.0-4.0 vs 2.5-3.5. A higher target INR range was thought to provide a net clinical benefit as the rate of ischemic stroke increases sharply when INR drops below 2.0, while (intracranial) bleeding risk seems to remain comparable between INR ranges 3.0-3.5 and 2.0-3.0.[16,17] However, target INR ranges in the Netherlands have been lowered in 2016 to comply with international guidelines, as strong evidence for this alternate approach was lacking.

IMPROVING VKA CARE

Nowadays, we know undoubtedly that OACs are very effective at preventing thrombosis for a variety of morbidities such as AF. However, sweet clover disease also showed us the risks accompanied with OACs, of which the most feared complication is intracranial bleeding. Moreover, treatment with VKAs is challenging given the multiple drug and food interactions and the necessity for frequent monitoring by INR measurements.[18] Fluctuations in INR had a significant impact on hospitalization duration in patients with deep venous thrombosis back in the 1940s. This led to the foundation of the first outpatient anticoagulation clinic in Utrecht, the Netherlands, by prof. Jordan in 1949.[19] As a result of the formation of this specialized

clinic, patients who were treated with a VKA could be discharged much sooner. Due to its success, the Dutch Red Cross established in 1954 a committee for the formation of a nationwide network of similarly specialized anticoagulation clinics.[20] In order to connect all these anticoagulation clinics, the Dutch Federation of Anticoagulation Clinics (FNT) was established in 1971. After more than 50 years of existence, the FNT continues to improve the quality of OAC care by registration and comparison of clinical care data, as well as providing guidelines, education and research. As of 2020, there are over 40 anticoagulation clinics based in the Netherlands, taking care of over 300.000 patients treated with VKAs.[21]

RISE OF THE NOACS

Although the organization of VKA care has greatly improved, the issue of INR fluctuations, bleeding complications and multiple drug and food interactions remained. These issues gave incentive to study possible alternatives. The direct thrombin inhibitor (DTI) ximelagatran, developed in the 1990s, was the first of the non-vitamin K oral anticoagulants (NOAC), otherwise also referred to as direct oral anticoagulants (DOAC). However, its European market application was withdrawn in 2006 due to the risk of severe liver injury when using this drug.[22,23] Research and development continued and in 2008 the DTI dabigatran was the first NOAC to be approved by the European Medicines Agency (EMA).[24] Concurrently, the possibility of directly inhibiting factor Xa (FXa) was studied, as an alternative to direct thrombin inhibition. The FXa inhibitors rivaroxaban, apixaban and edoxaban were approved by the EMA in 2011, 2011 and 2015, respectively.[25-27] In contrast to ximelagatran, these four NOACs were shown to be a safe and effective alternative to VKA for stroke prevention in AF.

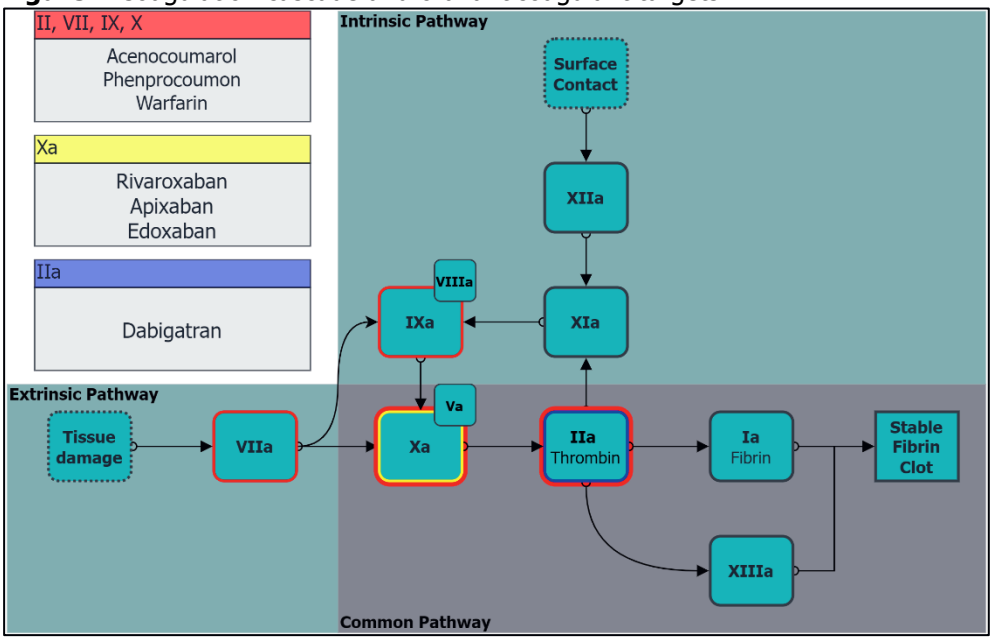
ANTICOAGULANTS MECHANISMS OF ACTION

Currently, there are two types of OAC available in the Netherlands, namely VKAs (acenocoumarol and phenprocoumon) and NOACs (dabigatran, rivaroxaban, apixaban and edoxaban). All OACs target the coagulation cascade and inhibit the formation of stable fibrin clots (Figure 1), but they achieve this in different ways. VKAs inhibit the formation of activated vitamin K_1 (quinol) by inhibiting the enzyme vitamin K epoxide reductase (VKOR).[28] The active vitamin K_1 is needed for the gamma-carboxylation of the inactive coagulation factors II, VII, IX, X and protein C, S and Z into their respective, active form.[28] This extensive inhibition severely impacts blood coagulation, as these activated factors are crucial components of the coagulation cascade (Figure 1).

Unlike VKAs, NOACs target a specific coagulation factor in the coagulation cascade directly. Dabigatran etexilate is a non-active prodrug which is converted in the liver and plasma into the active substance dabigatran. Dabigatran reversibly and directly

binds to activated factor II (thrombin), hereby inhibiting free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.[24] In contrast to dabigatran, the FXa inhibitors are orally administered in an active form. These drugs directly bind to activated factor X, which inhibits the activation of factor II (prothrombin) into thrombin (Figure 1).[25-27]

Figure 1 Coagulation cascade and oral anticoagulant targets



This figure portrays a simplified version of the coagulation cascade. Only activated (a) coagulation factors are displayed. The arrows indicate which coagulation factor activates the next. Factor Va and VIIIa are cofactors and increase the speed of activation of the next coagulation factor. The target of oral anticoagulants (legend) is depicted by the coloured borders around the affected coagulation factors.

—— ANTICOAGULATION IN ATRIAL FIBRILLATION ——

AF is the most common sustained cardiac arrhythmia and is associated with a near fivefold increased risk of stroke in untreated patients.[29] In the Netherlands, approximately over 400,000 people currently have AF.[30] The prevalence is estimated to rise towards 550,000 by 2050, with especially an increase in patients aged ≥75 years.[12] In most patients, AF occurs due to a combination of 1) an abnormal supraventricular impulse formation, and 2) the presence of an underlying anatomical and/or electrophysiological substrate in which the abnormal impulse can sustain.[31] Due to the formation of multiple wavelet re-entry circuits, the atrial myocardium fibrillates resulting in a functional stand still of the atria. The resultant irregular and often rapid beating of the heart in combination with the loss of an 'atrial kick' can cause symptoms such as palpitations, dyspnoea, fatigue and chest pain. In patients with AF, the left atrium is often dilated and the blood flow velocity in the left atrial appendage reduced.[32] The subsequent stasis of blood promotes thrombus formation, which occurs primarily in the left atrial appendage.[33] Besides this classic explanation for thrombogenesis in AF, there is also a clear association with a hypercoagulable state and endothelial dysfunction, completing Virchow's triad.[34,35] For instance, in AF factors associated with platelet activation, coagulation activation and fibrinolysis are upregulated, such as β-thromboglobulin, d-dimer and tissue plasminogen activator, respectively.[35] The upregulation of coagulation activity can be measured as early as six hours after onset of AF.[36] Also, the hypercoagulable state during AF has previously been shown to cause pro-fibrotic and pro-inflammatory responses in atrial fibroblasts, further promoting the development of a substrate for AF. [34,37] Besides, AF is strongly associated with cardiovascular disease and cardiovascular risk factors such as hypertension and diabetes mellitus, which presence concomitantly with AF increases thrombotic risk and promote a substrate for AF.[38]

Oral anticoagulants are the cornerstone for treatment of patients with AF, except for those with absent additional stroke risk factors as currently indicated by the CHA_2DS_2-VASc score.[10,38] Both VKAs and NOACs are on-label for stroke prevention in AF. Although nowadays an absence of OACs in AF management would be unthinkable, it is only until the last decades that we have come to better understand the relationship of AF with ischemic stroke, and how to reduce this associated risk.

A BRIEF HISTORY

As far as we know, AF was first described in Huang Ti Nei Ching Su Wên, an ancient Chinese medical text on conversations between the legendary Yellow Emperor (mythical reign: 2698-2598 BCE) and his ministers.[39] In response to a question of the Emperor, one of his ministers answered: "When the pulse is irregular and tremulous and the beats occur at irregular intervals, then the impulse of life fades;".[39] Despite the multiple descriptions of this phenomenon in ancient times, it was only until 1628 when William Harvey, most recognized for his appropriate and complete description of the circulatory system, first described fibrillation of the auricles in animals.[40,41] In 1906, the Dutch physician Willem Einthoven was the first to show a single lead electrocardiographic recording of AF, which he described as 'pulsus inaequalis et irregularis'.[41] Despite its long history, only as of 1978 a clear association was shown between non-rheumatic AF and an increased stroke risk in the Framingham Heart Study.[42] As previously mentioned, at first the primary reason for thrombosis in AF was hypothesized to be a resultant of the stasis of blood flow in primarily the left atrial appendage during fibrillation. However, in the early 2000s the RACE I and AFFIRM trials showed us the non-inferiority of a rate control strategy to rhythm control on thrombosis and mortality.[43,44] Moreover, the pattern of AF (i.e. paroxysmal, persistent or permanent) or successful ablation of AF does not seem to independently influence stroke risk.[45,46] These results indicate that there is more to stroke risk in AF than the mere presence of AF and stasis of blood flow.[34] Underlying comorbidities such as hypertension, heart failure, obesity and diabetes mellitus attribute to the lifetime risk of AF and also influence stroke risk.[38,47] Therefore, besides anticoagulation, an integrated approach with management of cardiovascular risk factors has become one of the mainstays of AF treatment as AF should be regarded a vascular disease.[48]

In 1989, the first randomized controlled trial on OAC in non-rheumatic AF was performed (AFASAK-I), which showed a distinct benefit regarding the occurrence of thrombosis but also vascular mortality with warfarin treatment over placebo or aspirin.[49] Since then, warfarin and other VKAs such as acenocoumarol or phenprocoumon have become the mainstay of treatment in AF patients with a high risk of stroke.[50] Nowadays, NOACs are increasingly prescribed in AF, as is also shown in this thesis. A meta-analysis of the four pivotal NOAC trials showed an overall 20% reduction in stroke or systemic embolism (SE) and a 50% reduction in intracranial bleeding, compared to warfarin.[51] Major bleeding was more difficult to pool given high heterogeneity (I^2=83%), but all NOACs were non-inferior in this respect to warfarin, with superiority for apixaban and edoxaban.[51] Since NOACs also have the benefit of a steady daily dosage regimen without monitoring of drug levels, NOACs have replaced VKAs as the primary treatment choice in AF.[10,48,52] However, there are concerns about the safety of NOACs in real-world practice.

REAL-WORLD SAFETY OF ANTICOAGULANT TREATMENT

When the first NOAC, dabigatran, was approved in the Netherlands in 2011, discussion arose about the safety of these novel agents in daily clinical practice.[53] In response to parliamentary questions, the Dutch minister of Health, Welfare and Sport (in Dutch: Volksgezondheid, Wetenschap en Sport (VWS)) asked the Health Council of the Netherlands ('Gezondheidsraad') for an advisory report hereon.[54] Subsequently, the Health Council advised a careful introduction of NOACs given the lack of real-world data, the lack of an antidote and the risk of poor compliance since no drug level monitoring is needed.[54] A need for more research was also advised, which led to the initiation of the nationwide DUTCH-AF registry (this thesis). This project is a combination of an observational study and a long-term registry program, of which the latter was made possible by collaboration with the Netherlands Heart Registration (NHR). The main aim of the DUTCH-AF registry is to investigate the safety and effectiveness of contemporary OAC treatment in AF in the Netherlands, with a focus on NOAC non-adherence.

Indeed, studying anticoagulant adherence is important as several studies have shown an increased risk of thrombosis with suboptimal OAC treatment.[55,56] Also, concerns about real-world NOAC non-adherence are reasonable as previous studies have shown that overall medication non-adherence is very common in chronic diseases.[57] Moreover, results of randomized controlled trials do not directly translate into real-world results. In randomized controlled trials, patients are selected (e.g. expected drug non-compliance is a common exclusion factor in trials), and are actively monitored for non-compliance during the study, which influences outcomes. Although real-world anticoagulant non-adherence is common in VKA users worldwide, these patients are actively monitored by specialized anticoagulation clinics, in the Netherlands.[58,59] This reminds patients of the need for drug compliance as well as that INR levels can be used as a proxy to identify non-compliant VKA users, which reduces real-world safety concerns. For NOAC users, however, no such monitoring system exists.

Unfortunately, determining real-world drug adherence is difficult.[60,61] There are various ways in which non-adherence can be measured, but each method has its limitations.[60] Direct measurement of drug or metabolite levels, counting left-over pills from patients and/or the usage of Electronic Medication Packages (EMP) (which senses when the drug container is opened) are the most accurate methods.[60] However, these methods are expensive and are overall not feasible for usage in daily clinical practice. In real-world studies, medication adherence is almost always determined by using pharmacy dispensing data or with the use of medication adherence questionnaires. With pharmacy dispensing data, the Proportion of Days Covered (PDC) can be calculated, which is the number of days patients were covered

by the medication supplies divided by the total number of prescription days. Medication Possession Ratio (MPR) is another frequently used calculation, but given several disadvantages of MPR, calculating PDC is generally considered to be the preferred method.[62] Usually, with PDC a cut-off value of ≥80% is used as an indication for drug adherence.[63] A clear disadvantage of this method, however, is that patients can collect their medication from the pharmacy, but not take their medication, which overestimates PDC count. However, a low PDC count would appear to be specific for non-adherence, as not collecting medication from the pharmacy means the patient cannot have taken it. Concerning the use of questionnaires, a similar problem exists. Patients can be untruthful about their therapy adherence, but if patients state that they did not take their drugs, that statement is more likely to be true than the contrary. Thus, these methods can identify non-adherence with a certain reliability, although not all non-adherent patients can be found in this way. When non-adherence is studied, it is therefore recommended to use a multimeasure approach to improve the overall combined test's ability.[60] However, a multimeasure approach to identify OAC non-adherent patients in newly diagnosed AF has not been investigated as of yet, but will be used in DUTCH-AF.

Another important aspect of safe drug use is to assess guideline adherence, as anticoagulation guideline non-adherence in AF is common worldwide and is associated with increased rates of all-cause mortality, bleeding and thrombosis.[55,64-66] However, the extent of AF guideline OAC non-adherence throughout the Netherlands is unclear, although a few small studies have evaluated AF guideline non-adherence in Dutch primary care practices.[67-70] Similarly, it is important to assess if NOACs are prescribed according to the dose recommendations as stated in their respective Summary of Product Characteristics (SmPC) from the European Medicines Agency (EMA).[24-27] These are the dose recommendations as used and proven safe and effective in the large randomized controlled NOAC trials.[71-74] Following these recommendations is important, as the effect of prescribing off-label doses on thrombosis and bleeding in AF is uncertain. Moreover, several reports have shown that off-label dosing is frequent and associated with increased mortality, stroke and worse bleeding events, although these results should be interpreted with caution as selection bias is likely to have occurred.[66,75-77] Similar to AF guideline adherence to OAC, the extent of this issue for the Netherlands is largely unknown.[78]

—— OUTLINE OF THE THESIS ——

In this thesis, nationwide research on the contemporary safety and effectiveness of real-world OAC management for AF is described.

In **Chapter 2**, the design and rationale of the nationwide DUTCH-AF registry is described, which aims to investigate the safety and effectiveness of OAC treatment in patients with newly diagnosed AF in the Netherlands, with a focus on anticoagulation non-adherence. In **Chapter 3**, the extent and determinants of over- and underdosing of NOACs in newly diagnosed AF is described, using data from the DUTCH-AF registry. In **Chapter 4**, the adherence to AF anticoagulation guidelines in newly diagnosed AF patients from the DUTCH-AF registry is described, with a focus on sex differences in anticoagulation management. In **Chapter 5**, Dutch results from the worldwide GARFIELD-AF registry are shown, which described trends in OAC use in recent-onset AF in the Netherlands, with a focus on guideline adherence. In **Chapter 6**, Dutch outcomes from the GARFIELD-AF registry are compared with Belgian outcomes. As anticoagulant management between these neighbouring countries has been noticeably different, these results provide an important insight into the impact of these differences on rates of stroke, bleeding and mortality. In **Chapter 7**, available evidence on the safety and effectiveness of anticoagulant treatment in patients with a high risk of bleeding are reviewed, as withholding OAC treatment in these patients, despite the presence of often a concomitantly high ischemic stroke risk, is not uncommon and a frequent topic of discussion. Finally, in **Chapter 8 and 9** the results of this thesis are summarized and discussed.

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CHAPTER 2

Design and rationale of DUTCH-AF: a prospective nationwide registry program and observational study on long-term oral antithrombotic treatment in patients with atrial fibrillation

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ABSTRACT

INTRODUCTION

Anticoagulation therapy is pivotal in the management of stroke prevention in atrial fibrillation (AF). Prospective registries, containing longitudinal data are lacking with detailed information on anticoagulant therapy, treatment adherence, and AF-related adverse events in practice-based patient cohorts, in particular for non-vitamin K oral anticoagulants (NOAC). With the creation of DUTCH-AF, a nationwide longitudinal AF registry, we aim to provide clinical data and answer questions on the (anticoagulant) management over time and of the clinical course of patients with newly diagnosed AF in routine clinical care. Within Dutch-AF, our current aim is to assess the effect of non-adherence and non-persistence of anticoagulation therapy on clinical adverse events (e.g. bleeding, stroke), to determine predictors for such inadequate anticoagulant treatment, and to validate and refine bleeding prediction models. With DUTCH-AF, we provide the basis for a continuing, nationwide AF registry, which will facilitate subsequent research, including future registry based clinical trials.

METHODS AND ANALYSIS

The DUTCH-AF registry is a nationwide, prospective registry of patients with newly diagnosed 'non-valvular' AF. Patients will be enrolled from primary, secondary and tertiary care practices across the Netherlands. A target of 6000 patients for this initial cohort will be followed for at least 2 years. Data on thromboembolic and bleeding events, changes in antithrombotic therapy and hospital admissions will be registered. Pharmacy dispensing data will be obtained to calculate parameters of adherence and persistence to anticoagulant treatment, which will be linked to AF-related outcomes such as ischemic stroke and major bleeding. In a subset of patients, anticoagulation adherence and beliefs about drugs will be assessed by questionnaire.

ETHICS AND DISSEMINATION

This study protocol was approved as exempt for formal review according to Dutch law by the Medical Ethics Committee of the Leiden University Medical Centre, Leiden, the Netherlands. Results will be disseminated by publications in peer-reviewed journals and presentations at scientific congresses.

INTRODUCTION

As a consequence of the increasing prevalence of atrial fibrillation (AF) in our ageing society, its associated adverse events, and the overall societal health care burden, there is a need for optimization of AF management.[1] Collecting data on case-mix, treatment and outcomes of AF patients has been shown to be valuable for improving the management of AF patients.[2-4]

DUTCH-AF is a nationwide, prospective registry designed to gather information on the (anticoagulation) management and clinical course of patients with newly diagnosed AF. Virtually all newly diagnosed AF patients in the Netherlands are eligible for this registry, and patients will be included throughout all levels of care across. By collecting these data, DUTCH-AF will provide a base for future research (notably registry-based randomized trials) and will provide benchmark data for care providers. This will strengthen the cooperation between different care providers and improve quality of AF care and research.

Aside from collecting registry data, a prospective study assessing non-adherence and non-persistence to anticoagulation therapy in this AF population will be performed simultaneously, under the hypothesis that non-adherence and non-persistence to anticoagulation therapy increases the risk of AF- and anticoagulant-related adverse events, such as stroke and bleeding. As a recent meta-analysis has shown, primary therapy non-adherence is frequently seen in common chronic diseases.[5] For instance, in patients with therapy-resistant hypertension, non-adherence was seen in over two-thirds of patients.[6] In line with these findings, multiple studies have shown in recent years that non-adherence and non-persistence to anticoagulation therapy occur frequently in AF patients as well, which subsequently affects safety and efficacy outcomes negatively.[7-12] Based on these findings, identifying predictors of non-adherence and non-persistence is highly needed, as these patients could be targeted for adherence-improving interventions in the future.

Furthermore, one important complication of anticoagulation therapy, which could also affect patient adherence and persistence, is bleeding. Identifying AF patients with high risk of bleeding could potentially help decision making and follow-up strategies in anticoagulant management, in particular to flag or identify potentially modifiable risk factors for bleeding. Unfortunately, current existing AF bleeding prediction models perform moderately well and have few clinical implications.[3,13-16]

With this prospective study, DUTCH-AF aims to (i) determine the clinical impact of non-adherence and non-persistence to anticoagulation therapy in AF patients, (ii)

identify predictors for non-adherence and non-persistence to OAC therapy, and (iii) validate and refine current bleeding prediction models.

By combining subsequent research with a quality registry, DUTCH-AF aims to provide important insights into contemporary (anticoagulation) management of AF and the clinical impact of non-adherence and non-persistence to anticoagulation therapy.

METHODS

DESIGN

DUTCH-AF is a prospective, observational, multicentre, nationwide study of a representative sample of Dutch patients with newly diagnosed AF. The registry started as of January 2018, with a planned 3 years of patient recruitment. The intended duration of patient follow-up will be at least 2 years.

DUTCH-AF is an integral part of a nationwide cardiovascular data registration strategy. The creation of this nationwide registry was conducted in collaboration with the Dutch society of cardiology (NVVC), the Dutch association of cardiothoracic surgery (NVT), the Dutch college of general practitioners (NHG), the Netherlands Heart Registry (NHR), and the Dutch Heart Foundation. Prior experience of the Netherlands Heart Network (NHN) was incorporated in the design as well.[17] The data gathered in DUTCH-AF is managed by the NHR and will be the basis of a continuous, ongoing AF registry, enabling the possibility to conduct registry-based trials by applying the trials within cohort-design (TWiC).[18-20] This is done with the ambition to enhance scientific evaluation in AF research, and bring valuable, promising interventions easier and faster to patients, at lower study costs and burden.

STUDY POPULATION

Investigators enroll consecutive patients aged ≥ 18 years with newly diagnosed non-valvular AF (initial AF diagnosis < 6 months before the inclusion date). Patients with valvular AF (i.e. moderate to severe mitral stenosis or a mechanical heart valve), an anticipated life expectancy < 6 months, or with documented AF developed within 14 days after cardiothoracic surgery will be excluded. AF following cardiothoracic surgery is an exclusion criterion for this registry due to its high incidence (in 20-40% of all surgeries) and its self-limiting nature (80% reverts back to sinus rhythm within 24 hours).[21,22] All patients are asked to provide written informed consent for participation and permission (i) to collect their baseline and predefined follow-up data, (ii) to be approached for future studies, e.g. registry-based trials (TWiC design), and (iii) for participation in a paper survey on anticoagulation adherence and beliefs about drugs.

SITE SELECTION

Sites from all over the Netherlands participate in this registry, consisting of but not limited to a broad mix of hospitals (secondary and tertiary centres), anticoagulation clinics and GP practices. All Dutch centres treating AF patients are encouraged to join the registry. Centres are informed on the registry through symposia, newsletters, mailings, and word of mouth, with the help of the Dutch Federation of Anticoagulation Clinics (FNT), the Netherlands Society of Cardiology (NVVC), the Netherlands Heart Registration (NHR), general practitioner networks, and NVVC Connect-AF. In this way, we aim to enrol a representative sample of all Dutch newly diagnosed AF patients, minimizing selection and allowing for a broad generalizability of findings.

DATA COLLECTION AND FOLLOW-UP

Data will be primarily collected from electronic medical records of the enrolled patients, and will mainly consist of routine care data. At baseline, data will be collected on patient demographics, pattern of AF, date and location of the initial AF diagnosis, secondary causes of AF, EHRA classification, relevant medical history with items that contribute to the CHA_2DS_2-VASC score and bleeding risk assessment, and the (cardiovascular) medical treatment.[23] Follow-up is scheduled at 12 and 24 months after inclusion. At follow-up, data will be collected from electronic medical records, accompanied with telephone interviews. Follow-up data will be complemented with pharmacy dispensing data from the Foundation for Pharmaceutical Statistics (SFK).[24] Table 1 provides an overview of the data collected during baseline and follow-up. Table 2 provides an overview of the causes of secondary AF.[23]

Table 1 Overview of baseline and follow-up variables

Baseline
Demographics: gender, age, ethnicity
Weight, height and blood pressure
Recent haemoglobin and kidney function
Medical history (including all parameters in CHA_2DS_2-VASC, sleep apnoea, chronic lung disease, malignancy, prior bleeding history).
Date of AF diagnosis
Location of AF diagnosis (primary or specialist care)
Complaints of AF – EHRA symptom classification
Pattern: paroxysmal or persistent AF
Treatment: none, rhythm or rate control
Secondary causes of AF: infection/inflammation, non-cardiothoracic surgery, MI, alcohol consumption, thyrotoxicosis, pericardial and myocardial disease, acute pulmonary embolism
Anticoagulation prior to AF diagnosis: none, antiplatelet agents, VKA and/or NOAC
Anticoagulation after AF diagnosis: none, antiplatelet agents, VKA and/or NOAC
Follow-up
Weight, blood pressure
Recent haemoglobin and kidney function
Pattern: paroxysmal, persistent, long-standing persistent, permanent AF
Occurrence of bleeding events: MB, CRNMB Location: intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intramuscular, gastrointestinal, urogenital, nasal, pulmonary.
Occurrence of ischemic events: TIA, ischemic stroke, ATE, MI
Healthcare utilization (emergency department visits, hospital admission for AF-treatment)
Side effects to antithrombotic treatment
Changes in anticoagulation treatment and CHA_2DS_2-VASC
Prescription data from SFK: - Dispensing data (type, dosage) - Concomitant medical therapy
Adherence and persistence
In a subset of patients: MARS-5/BMQ/DGSS questionnaires

ATE Arterial thrombotic event; *BMQ* Beliefs in Medicine Questionnaire; *CRNMB* Clinically relevant non-major bleeding; *DGSS* Dutch General Self-efficacy Scale; *EHRA* European Heart Rhythm Association; *MARS-5* Medication Adherence Report Scale; *MB* Major bleeding; *MI* Myocardial infarction; *NOAC* Non-vitamin K antagonist oral anticoagulant; *SFK* Foundation of Pharmaceutical Statistics; *TIA* Transient ischemic attack; *VKA* Vitamin K antagonist.

Table 2 Definition of secondary AF used in the DUTCH-AF registry

Secondary AF
AF that is triggered within 14 days after 1) infection or inflammation, 2) non-cardiothoracic surgery, 3) myocardial infarction, or 4) pericarditis/myocarditis, or 5) exacerbation chronic pulmonary disease, or 6) hyperthyroidism, or 7) pulmonary embolism, or 8) cardiac tamponade, or 9) or acute alcohol intoxication. If AF was triggered by any amount of alcohol use, as stated in the medical records by the treating physician, this was also scored as 'acute alcohol intoxication'.

OUTCOMES

The following clinical outcomes will be registered during follow-up: (i) thromboembolic adverse events (i.e. transient ischemic attack, ischemic stroke, arterial thrombotic event, myocardial infarction), (ii) bleeding (i.e. major, clinically relevant non-major (CNRMB), and minor bleeding), (iii) AF-related visits to the emergency department or hospital admissions, (iv) all changes in antithrombotic therapy, (v) adherence to antithrombotic therapy, and (vi) all-cause mortality**.** Outcome definitions of all major cardiovascular and bleeding endpoints will be assessed as stated in Supplementary Table 1.[16,25,26] Thromboembolic adverse events, clinically relevant bleeding, and myocardial infarction will be judged by a blinded, independent adjudication committee, consisting of a neurologist, a cardiologist, and a vascular internist.

Data on adherence and persistence to OAC will be acquired in two ways. First, the SFK, which has a coverage of >95% of all community pharmacies, will provide medication dispensing data of all included patients.[24] Adherence and persistence rates to OAC will be calculated using these data. The various measures are explained in section Statistical Analysis. Second, a subset of patients will be sent a composite questionnaire regarding anticoagulation adherence and beliefs about drugs at one point in time. The composite questionnaire consists of the Beliefs about Medicine Questionnaire (BMQ), the Medication Adherence Rating Scale (MARS-5), and the Dutch General Self-Efficacy Scale (DGSS).[27-30] The composite questionnaire is sent randomly after 1, 6, 12 or 24 months after inclusion if patients 1) agreed to participate when consulted at inclusion, and 2) used antithrombotic therapy within 1 month after inclusion. Table 3 provides an overview of the various items asked in the questionnaires.[27-31]

Table 3 Questionnaires for the assessment of patients' beliefs, attitudes and behaviour regarding anticoagulants in English and Dutch language

Beliefs about Medicine Questionnaire Specific (BMQ-S)	
This eleven-item scale asks the patient to rate their beliefs regarding anticoagulation therapy. Respondents indicate their degree of agreement with each statement on a 5-point Likers scale, ranging from 1 = strongly disagree to 5 – strongly agree. Scores obtained for individual items are summed and divided by the total number of items in the scale to give a scale score of 1-5. Higher scores indicate stronger beliefs.	
1.	My health at present depends on my anticoagulation therapy. In Dutch: Op het moment hangt mijn gezondheid af van mijn bloedverdunners.
2.	Having to take anticoagulants worries me. In Dutch: Ik maak me zorgen over het feit dat ik bloedverdunners moet nemen.
3.	My life would be impossible without anticoagulants. In Dutch: Mijn leven zou erg moeilijk zijn zonder bloedverdunners.
4.	I sometimes worry about the long-term effects of anticoagulation therapy. In Dutch: Soms maak ik me zorgen over de effecten die mijn bloedverdunners op de lange termijn kunnen hebben.
5.	Without anticoagulation therapy, I would be very ill. In Dutch: Zonder mijn bloedverdunners zou ik heel ziek zijn.
6.	My anticoagulation therapy is a mystery to me. In Dutch: Ik ben onvoldoende op de hoogte van wat mijn bloedverdunners doen.
7.	My health in the future depends on anticoagulation therapy. In Dutch: Mijn toekomstige gezondheid hangt af van mijn bloedverdunners.
8.	My anticoagulation therapy disrupts my life. In Dutch: Mijn bloedverdunners ontwrichten mijn leven.
9.	I sometimes worry about becoming too dependent on anticoagulants. In Dutch: Soms ben ik bang dat ik te afhankelijk zal worden van mijn bloedverdunners.
10.	Anticoagulation therapy protects me from becoming worse. In Dutch: Mijn bloedverdunners voorkomen dat ik verder achteruit ga.
11.	This anticoagulation therapy cause me unpleasant side-effects. In Dutch: Deze bloedverdunners hebben onplezierige bijwerkingen.
Medication Adherence Report Scale, 5-item (MARS-5)	
This five-item scale asks the patient to rate the frequency with which he/she engages in each of the five aspects of non-adherent behaviour. Each item is rated on a 5-point Likers scale, where 1 = always to 5 = never. Score for each of the five items are summed and divided by five to give a scale score of 1-5, where higher scores indicate higher levels of reported adherence.	
1.	I forget to take my anticoagulants. In Dutch: Ik vergeet mijn bloedverdunners in te nemen.
2.	I modify the doses of my anticoagulants. In Dutch: Ik wijzig de dosering van mijn bloedverdunners.
3.	I stop taking medications during a certain period. In Dutch: Ik stop een tijdje met bloedverdunners te nemen.
4.	I decide to miss a dose. In Dutch: Ik besluit een dosering over te slaan.

5.	I take less than what is prescribed. In Dutch: Ik neem minder dan is voorgeschreven.
Dutch General Self-efficacy Scale (DGSS)	
The DGSS is a ten-item Likert-type scale, where 1 = is not true at all to 4 = exactly true, that assesses general self-efficacy. Higher scores represent higher levels of general self-efficacy	
1.	I can always manage to solve difficult problems if I try hard enough. In Dutch: Het lukt me altijd om moeilijke problemen op te lossen, als ik er genoeg moeite voor doe.
2.	If someone opposes me, I can find the means and ways to get what I want. In Dutch: Als iemand mij tegenwerkt, vind ik toch manieren om te krijgen wat ik wil.
3.	It is easy for me to stick to my aims and accomplish my goals. In Dutch: Het is voor mij makkelijk om vast te houden aan mijn plannen en mijn doel te bereiken.
4.	I am confident that I could deal efficiently with unexpected events. In Dutch: Ik vertrouw erop dat ik onverwachte gebeurtenissen doeltreffend aanpak.
5.	Thanks to my resourcefulness, I know how to handle unforeseen situations. In Dutch: Dankzij mijn vindingrijkheid weet ik hoe ik in onvoorziene situaties moet handelen.
6.	I can solve most problems if I invest the necessary effort. In Dutch: Ik kan de meeste problemen oplossen als ik er de nodige moeite voor doe.
7.	I can remain calm when facing difficulties because I can rely on my coping abilities. In Dutch: Ik blijf kalm als ik voor moeilijkheden kom te staan omdat ik vertrouw op mijn vermogen om problemen op te lossen.
8.	When I am confronted with a problem, I can usually find several solutions. In Dutch: Als ik geconfronteerd word met een probleem, heb ik meestal meerdere oplossingen.
9.	If I am in trouble, I can usually think of a solution. In Dutch: Als ik in een benarde situatie zit, weet ik meestal wat ik moet doen
10.	I can usually handle whatever comes my way. In Dutch: Wat er ook gebeurt, ik kom er wel uit.

DATA MANAGEMENT

All clinical data are accumulated using a web-based Electronic Data Capture System and are registered in electronic case report forms (e-CRF). All e-CRF records will be pseudonymized and patients are assigned a unique study identifier. Personal data of all included patients will be collected in order to send the composite questionnaire on medication adherence and beliefs about drugs, for linkage with the SFK, and for approach of the patients for future research. All personal data will be handled according to the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the GDPR, and will be stored separately from the e-CRF. By using an application for the storage of personal data, the risk of including the same patient twice is negligible. Data monitoring will be performed by the coordinating

researchers to ascertain completeness and accuracy of the entered data. Source data verification will be undertaken in 1-10% of all cases. A comprehensive plan has been developed to monitor the quality of data entered into the electronic database during the course of the program. Linkage of the pharmacy dispensing data with the corresponding study participants will be performed by a Trusted Third Party using pseudonymized data.

STATISTICAL ANALYSIS

RESEARCH AIM 1: ASSOCIATION BETWEEN OAC ADHERENCE/PERSISTENCE, DOSAGE AND CLINICAL OUTCOMES

To evaluate adherence and persistence of NOACs, subsequent dispensing of NOACs will be assessed. If the prior prescription ended prior to the subsequent dispensing date, it would be considered a gap. The length of the gap will be measured in days. To improve the accuracy of our adherence assessment, we will correct for patients stacking their medication at home, and account for the carry-over of oversupply. Patient adherence to NOAC will be expressed through the medication possession rate (MPR) and the proportion of days covered (PDC). The proportion of days covered is obtained by dividing the number of daily doses dispensed from the first prescription until, but not including, the last refill with the number of days in that interval and expressed as a percentage. Patients will be classified as adherent or non-adherent dependent on various PDC cut-off points, including the PDC >80%, in line with previous publications.[32] Other measures of patient adherence will be assessed, including the gap length and the total gap days. As a proxy of patient adherence to VKA, patient adherence to VKA will be expressed through the time in therapeutic range (TTR) of INR. Patients will be classified as adherent dependent on various TTR cut-off points. The TTR will be calculated with the Rosendaal method.[33]

Persistence will be defined as the time, in days, between the first dispension until the day of treatment discontinuation. As patients can switch to another anticoagulant therapy, we will assess persistence to the prescribed anticoagulant in particular and to anticoagulant therapy in general as well. Persistence rates for both VKA and NOACs will be calculated for various time intervals. Kaplan-Meier curves will be used to graphically display persistence over time.

OAC adherence and persistence will be linked to risks of both thrombo-embolic and bleeding outcomes. First, patients with such occurrences will be matched with patients without occurrences on time, since start of follow-up. We will classify adherence and persistence measures as described above. Odds ratios (ORs) with 95% confidence intervals (CI) will be calculated using conditional multivariate logistic regression to assess the association between adherence and persistence to the anticoagulation therapy and the risk of event.

Research aim 2: Predictors of NOAC non-adherence/non-persistence

NOAC non-adherence will first be defined as a PDC below 80%, similarly as above. Next, using this binary outcome, a logistic model is fitted to quantify correlations of clinical variables with NOAC non-adherence. From the collected data, the following variables are considered, based upon clinical likeliness to be correlated with NOAC-adherence: age, sex, comorbidity, and co-medication.[34] This list of variables that potentially correlate with NOAC-adherence will continuously be expanded based on the latest publications regarding this subject. As clinical outcomes, such as bleeding or thromboembolism, may affect adherence and persistence afterwards, secondary analyses will be performed in which the impact of such clinical outcomes on adherence and persistence measures will be assessed. Furthermore, we will assess whether the predictors of non-adherence prior to or after an event differ. If the impact of such clinical outcomes on adherence are of relevance, we will perform similar prediction analyses considering only the PDC measures prior to or without an event. Missing values are imputed using existing multiple imputation techniques and subsequently pooled using Rubin's rule, assuming that the missing at random assumption is met. Using backward selection, variables are eliminated from the list of potential predictors if they do not have independent predictive ability in the model (criterion $p < 0.15$). To prevent overfitting, we will apply bootstrapping techniques. Model performance is subsequently assessed by estimations of the discriminative power of the model (Harrell's C-statistic, graphically illustrated in ROC space) and its calibration, illustrated in a calibration plot (predicted against observed risk).

Research aim 3: Validation of bleeding models

All variables of VTE-BLEED (active cancer, male gender with uncontrolled hypertension, anaemia, history of bleeding, age ≥60 years, and renal dysfunction) will be included in the study database in accordance with the definitions used in the derivation study.[35] Next, for each individual patient predicted risk of the VTE-BLEED model will be calculated, using the intercept and betas from the original derivation study. Subsequently, similar as above, model performance of VTE-BLEED is assessed by quantifying its discriminative power (Harrell's C-statistic, graphically illustrated in ROC space) and its calibration, illustrated in a calibration plot (predicted against observed risks). Finally, to quantify the ability to predict the risk of major bleeding, we will run univariate logistic regression models with major bleeding as binary outcome. Hereto, ORs and 95% CI are obtained for the VTE-BLEED high-risk score class (threshold >2) versus low-risk class serving as the reference group.

Should model performance of VTE-BLEED be disappointing (given that VTE-BLEED model was originally derived to predict bleeding complications in patients with venous thrombo-embolism, this may occur), simple updating techniques will be applied to optimize model performance for use in AF patients (rather than developing

a new model). They may include, with increasing complexity, an adjustment of the intercept of the model, re-estimating the betas for the variables from the original regression model, or including novel variables if needed.

STUDY SIZE

The registry has a target enrolment of 6,000 patients with a follow-up of at least two years. We expect 5500 NOAC users. Based on a 1-year non-persistence in a third of the NOAC users, 1815 patients on NOACs will be non-persistent.[36] If we assume a 50% increased risk of ischemic stroke/systemic embolism in these patients, we can expect on average a 3% yearly risk compared to the 2% in the 3685 patients who will continue to use their drug.[7] During 2-year follow-up, we expect 250 patients will develop ischemic stroke/systemic embolism.

If we assume 30% of the remaining NOAC users to be non-adherent, we can expect 1105 non-adherent NOAC users. With an expected yearly risk of 3.5% major bleeding in adherent patients and a 2.5% for non-adherent patients, we expect 176 major bleeding events annually.[37-39] For cardiovascular death, we expect a risk of about 1.5% in all NOAC users, leading to 135 deaths in 2 years. Therefore, we expect a total of about 600 patients meeting one of our pre-specified major cardiovascular endpoints consisting of ischemic stroke/systemic embolism, major bleeding including intracranial bleeds and all-cause mortality. These numbers will be sufficient to (i) determine risk groups, (ii) construct a prediction model for non-adherence, and (iii) validate and develop bleeding risk scores.

ADMINISTRATIVE STRUCTURE

A steering committee (SC), comprised of experts in cardiology, vascular medicine, pharmaceutics and medication adherence, neurology, general practice and epidemiology, is responsible for the study design and study conduct. A user committee, together with the NHR and the SC, evaluates and oversees the inclusion of patients and follow-up within the registry.

PATIENT AND PUBLIC INVOLVEMENT (PPI)

Two patient advisory groups are involved in DUTCH-AF. Harteraad was involved in the grant application process for funding from The Netherlands Organisation for Health Research and Development (ZonMw). The Cliëntenraad Nederlandse Trombosediensten (CTDN) has joined the steering committee of DUTCH-AF. At the end of the study, the patient advisory groups will be involved to present the results to their peers and patient groups.

ETHICS AND DISSEMINATION

The Medical Ethics Review Committee of Leiden University Medical Centre approved this study and concluded that the (Dutch) Medical Research Involving Human Research Act (WMO) does not apply, as strictly speaking no experimental interventions are studied or imposed upon patients. The study is conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice and local regulatory requirements. All patients provide written consent to participate after being informed about the study. Participants are free to withdraw at any time. This study is registered in the Netherlands Trial Register (Trial NL7467, NTR7706). Results of the study will be disseminated to healthcare professionals and to the scientific community, through publications in peer-reviewed journals as well as presentations at scientific congresses.

DISCUSSION

In the DUTCH-AF registry, baseline characteristics, current anticoagulant treatment practices, medication adherence and clinical outcome of real-life AF patients in the Netherlands will be described. Data are collected from newly diagnosed patients with AF. Patients will be represented across all levels of care in the Netherlands, irrespective of treatment strategies.

In cooperation with the NHR, this registry constitutes an essential framework for improving quality of care and for patient-centred research, including the opportunity of registry-based randomized controlled trials (RCT). Participating centres can continuously evaluate and benchmark their current practice on guideline implementation and guideline non-adherence. The minimal dataset has been designed to minimize registration burden, but will be sufficient for answering important current and future research questions. In the near future, our minimal dataset will be implemented in Dutch electronic medical records to minimize double-registration. This will improve the quality of the continuing quality registry, as the dataset will be entered by healthcare professionals, instead of using traditional methods with disease or treatment codes. The incorporation of the DUTCH-AF registry within the centralized network structure of the NHR will allow for cross-talk between registries through data linkage and through the adoption of a standardized set of definitions. Data collected for the AF registry could provide valuable information for other registries in which a patient is enrolled, without the need for additional follow-up.

A strong feature of this registry includes the inclusion of patients from all levels of care across the Netherlands, including patients from general practices. In the

Netherlands, most AF patients will be referred back to the general practitioner (GP) after the initial management by a cardiologist. The GP will have the responsibility for further AF care including routine monitoring of anticoagulant adherence, kidney function, and side effects, to ensure safe continuation of anticoagulation therapy. The participation of general practices will provide further information on patients who are never referred to specialist care, which are presumably more 'frail' and at an increased risk of stroke and bleeding.

The registry will also provide insights into the effects of (non-)adherence and persistence of the anticoagulant therapy on clinical adverse outcomes such as stroke and major bleeding. Current guidelines on NOACs are predominantly based on the NOAC RCTs, which showed high discontinuation rates even despite stringent monitoring.[40-43] Recent observational data showed similar or higher rates of discontinuation.[44,45] Due to the short half-life of NOACs, interruptions are suggested to increase the risk for strokes, as was seen in historical VKA studies.[46-49] However, long-term prospective studies assessing the effects of non-adherence to NOACs on adverse outcomes are lacking. Hence, DUTCH-AF is essential for providing patient-based information on adherence/persistence and dosage of anticoagulant treatment with NOACs in daily practice.

There are inherent limitations to this registry due to its design. First, the minimal dataset of this registry is designed to specifically answer the predefined research aims regarding dosing, adherence and persistence of anticoagulants. To minimize registration burden, concise echocardiographic data were for example not registered. Furthermore, interpreting differences in outcome between hospitals or between the different (anticoagulant) treatment modalities must be done with caution. Confounding by indication cannot be entirely captured in the minimal datasheet. Also recall bias can occur during the telephone conversation with the patient as part of follow-up. Besides, there is a risk of misclassification (this risk will however be minimalized by monitoring of the data as prescribed before). Another potential pitfall could occur when patients are not equally enrolled from primary and secondary/tertiary care, which could limit the extrapolation and generalizability of this registry.

The feasibility to derive a prediction model for VKA non-adherence will be determined by the number of novel AF patients treated with VKA. In the Netherlands, NOACs have overtaken VKA as the primary anticoagulant, with the number of starters on VKA decreasing rapidly.[37] Hence, deriving a prediction model for VKA non-adherence was not stated as a research aim; the feasibility of such an analysis will have to be assessed in the future.

Finally, as no other study utilizes the same methods to assess dosing, adherence and, persistence of anticoagulants in AF patients, future external validation could, for example, be performed in patients included after the required 6000 patients. Options for external validation in other studies or registries will have to be assessed in the future, based on the comparability between study designs and aims.

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CHAPTER 3

Determinants of label non-adherence to non-vitamin K oral anticoagulants in patients with newly diagnosed atrial fibrillation

Submitted

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ABSTRACT

AIMS

We aimed to evaluate the extent and determinants of off-label NOAC dosing in newly diagnosed Dutch AF patients.

METHODS

In the DUTCH-AF registry patients with newly diagnosed AF (<6 months) are prospectively enrolled. Label adherence of NOAC dosing was assessed using the European Medicines Agency labelling. Factors associated with off-label dosing were explored by multivariable logistic regression analyses.

RESULTS

From July 2018 to November 2020, 4,500 patients were registered. Mean age was 69.6±10.5 years, and 41.5% were female. Of the 3,252 patients in which NOAC label adherence could be assessed, underdosing and overdosing was observed in 4.2% and 2.4%, respectively.

In the 2,916 (89.7%) patients with a full dose NOAC recommendation, 4.6% were underdosed, with a similar distribution between NOACs. Independent determinants (with 95%-CI) were higher age (OR 1.01 per year, 1.01-1.02), lower renal function (OR 0.96 per ml/min/1.73m^2, 0.92-0.98), lower weight (OR 0.98 per kg, 0.97-1.00), active malignancy (OR 2.46, 1.19-5.09), anaemia (OR 1.73, 1.08-2.76), and concomitant use of antiplatelets (OR 4.93, 2.57-9.46).

In the 336 (10.3%) patients with a reduced dose NOAC recommendation, 22.9% were overdosed, most often with rivaroxaban. Independent determinants (with 95%-CI) were lower age (OR 0.92 per year, 0.88-0.96) and lower renal function (OR 0.98 per ml/min/1.73m^2, 0.96-1.00).

CONCLUSION

In newly diagnosed Dutch AF patients, off-label dosing of NOACs was seen in only 6.6% of the patients, most often underdosing. In this study, determinants of off-label dosing were age, renal function, weight, anaemia, active malignancy and concomitant use of antiplatelets.

INTRODUCTION

Oral anticoagulants (OAC) are used for stroke prevention in atrial fibrillation (AF). For most AF patients, non-vitamin K oral anticoagulants (NOAC) are currently the anticoagulants of first choice.[1] These drugs are non-inferior to vitamin K antagonist (VKA) treatment with respect to mortality, bleeding and thromboembolism, with the benefit of not requiring routine laboratory monitoring as is needed with VKAs. However, NOACs do require dose adjustment based on patient characteristics including renal function, weight and age.

Despite clear dosing recommendations, off-label dosing of non-vitamin K oral anticoagulants (NOAC) is frequently reported.[2-5] Real-world patients are often different from patients enrolled in clinical trials, and as a result of individually balancing thrombosis and bleeding risk there can be a valid rationale for deviating from the labelled dosing recommendation. However, it is unclear what the effect of non-recommended dose adjustments is on the risk of thrombosis and bleeding. Non-randomized studies suggest an increased rate of adverse events, but as selection bias has likely influenced results, these studies should be interpreted with caution.[2-4,6]

Nonetheless, given the potential for an increased risk of bleeding with overdosing and thrombosis with underdosing, it is important to identify determinants of such off-label use. This could help our understanding on how the safety of NOAC use in contemporary practice may be improved. Although the body of literature on off-label dosing in NOAC recipients is increasing, prospective studies evaluating label adherence to NOAC dosing at initiation of AF treatment are scarce, yet of great importance since this is the moment physicians make a critical first choice for the type of NOAC and its dose. Moreover, most current studies relied on retrospective healthcare registries or claims data, thus inherently suffering from misclassification or missing data for important variables, such as body weight or renal function.

Therefore, this study sought to determine the frequency of off-label dosing in newly diagnosed AF patients receiving their initial NOAC prescription, using data from a nation-wide prospective and harmonized data collection registry of AF patients in the Netherlands. Moreover, we explored determinants of such off-label dosing.

METHODS

In the prospective DUTCH-AF registry, patients with AF or atrial flutter aged ≥18 years were eligible for inclusion if AF or atrial flutter was diagnosed within the previous six months. Excluded were patients with 1) moderate or severe mitral valve stenosis, 2) mechanical valve(s), 3) a life expectancy of less than six months, or 4)

patients in whom AF or atrial flutter was only documented within two weeks following cardiothoracic surgery. Enrolment started in July 2018. For the current analyses, we used the data available up till November 2020. DUTCH-AF also incorporates a subsample of AF patients in whom retrospectively data were gathered from the already existing Netherlands Heart Network (NHN). These patients were diagnosed earlier with AF in the period November 2014 to December 2018, and they were prospectively followed after informed consent was obtained. Inclusion and exclusion criteria of these patients were the same as for the other participants in the DUTCH-AF registry, as were the gathered patient characteristics. The design of the DUTCH-AF registry was reported previously.[7]

Label adherence of NOAC dosing was determined by comparing the prescribed dose at diagnosis with the recommended dose based on age, weight and/or renal function, as mentioned in the respective summaries of product characteristics (SmPC) from the European Medicines Agency (EMA) (see Supplementary Table S1 for an overview).[8] Of note, comedication such as verapamil or strong P-glycoprotein inhibitors can influence the recommended NOAC dose, but were not available in this registry. Overdosing was defined as the prescription of a full dose NOAC (i.e. dabigatran 150mg, rivaroxaban 20mg, apixaban 5mg or edoxaban 60mg) in patients with a dose reduction recommendation according to the labelled criteria. Underdosing was defined as the prescription of a reduced dose NOAC (i.e. dabigatran 110mg, rivaroxaban 15mg, apixaban 2.5mg or edoxaban 30mg) in patients with no dose reduction recommendation according to the labelled criteria.[8] Creatinine clearance was calculated using the CKD-EPI formula.[9] The sponsor and coordinating centre of DUTCH-AF is Leiden University Medical Centre (LUMC) and the study is registered at the Netherlands Trial Register (NL7464). Data management was overseen by the Netherlands Heart Registration (NHR).

STATISTICAL ANALYSIS

Categorical variables are described as numbers (%), and continuous variables as mean ± standard deviation. A t-test or Mann-Whitney U test was performed for comparison of continuous variables, depending on normal distribution. To explore determinants for off-label dosing, patients were categorized in two subgroups: 1) patients with a full dose recommendation, comparing full dose NOAC prescribed on-label versus reduced dose NOAC prescribed off-label (i.e. underdosed) and 2) patients with a reduced dose recommendation, comparing reduced dose NOAC prescribed on-label versus full dose NOAC prescribed off-label (i.e. overdosed). Patient characteristics possibly related to over- or underdosing were selected based on previous studies and clinical relevance, including age, renal function, weight, characteristics from the CHA_2DS_2-VASc score and characteristics associated with bleeding risk (see Supplementary Table S2 for a full overview). Only characteristics

which are univariably associated with off-label dosing are displayed in table 2 and 3. Next, we performed multivariable logistic regression to assess the individual adjusted odds ratios. Variables were checked for non-linearity and interaction. Odds ratios (OR) are presented with 95%-confidence intervals (CI). A two-tailed p-value of <0.05 was considered significant. As missing data was uncommon (see Supplementary Table S3), a complete case analysis was performed. Analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (Armonk, NY: IBM corp.).

RESULTS

In total, 4,500 patients from 22 hospitals, 5 anticoagulation clinics and 18 primary care practices were enrolled in DUTCH-AF, of whom 3,588 (79.7%) patients were enrolled prospectively. Mean age was 69.6±10.5 years and 1,867 (41.5%) were female. The mean CHA_2DS_2-VASc stroke risk score was 2.7±1.6, and 5.9% of patients were classified as high risk of bleeding according to the HAS-BLED bleeding risk score.[10,11] The most common comorbidities were hypertension (55.7%), diabetes mellitus (14.2%) and coronary artery disease (13.7%) (Table 1). At diagnosis, 3,440 (76.4%) of 4,500 patients were prescribed NOACs, and 317 (7.0%) VKAs (Table 1). The most common NOAC prescribed was apixaban (31.0% of NOAC users), followed by rivaroxaban (22.7% of NOAC users). Antiplatelet monotherapy was prescribed in 128 (2.8%), and 582 (12.9%) of patients were not treated with antithrombotics. Combination therapy of antiplatelets with OAC was prescribed in 120 (2.7%).

Table 1 Patient characteristics at diagnosis

	N=4,500	Missing
Female sex	1,867 (41.5)	0 (0.0)
Age, years	69.6±10.5	0 (0.0)
≥80 years	715 (15.9)	
Weight, kg	85.1±18.2	331 (7.4)
<60 kg	226 (5.4)	
Comorbidities		
Congestive heart failure	267 (6.0)	41 (0.9)
Hypertension	2,495 (55.7)	23 (0.5)
Diabetes mellitus	638 (14.2)	5 (0.1)
Ischaemic stroke or TIA	495 (11.0)	19 (0.4)
Venous thromboembolism*	181 (4.1)	40 (0.9)
Coronary artery disease†	614 (13.7)	6 (0.1)
Peripheral artery disease	246 (5.5)	34 (0.8)

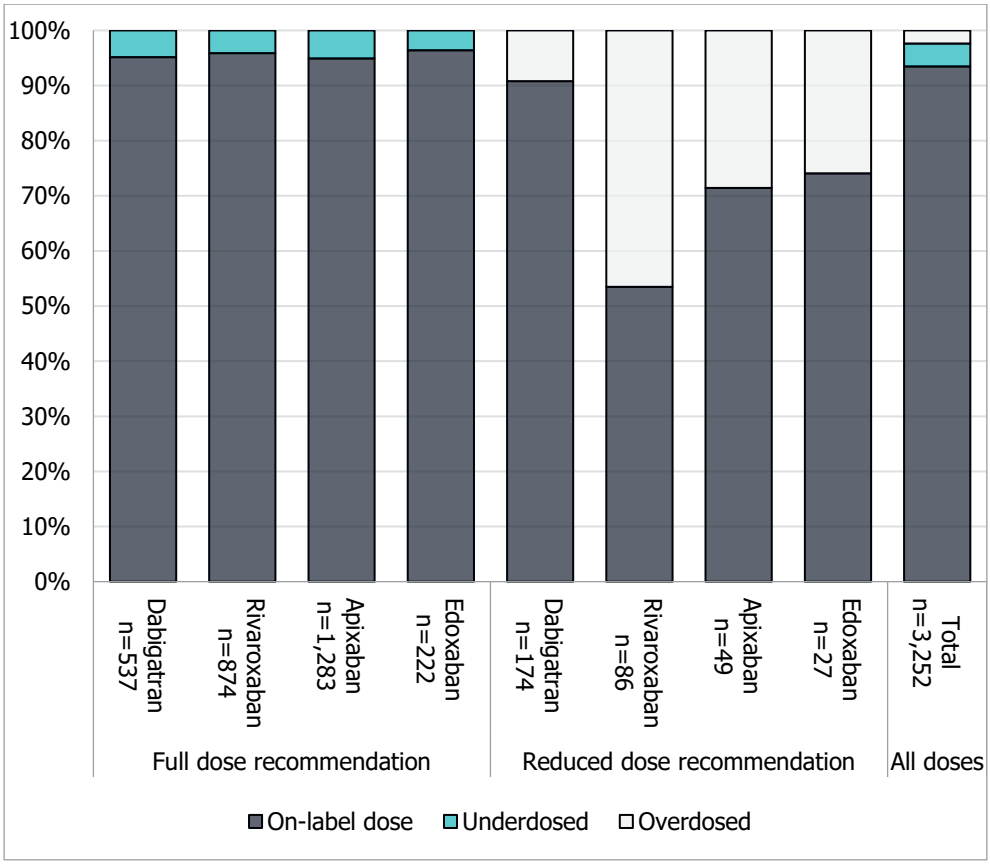
Anaemia‡	526 (12.7)	356 (7.9)
CrCl, ml/min/1.73m^2	74.0±18.3	239 (5.3)
<50 ml/min/1.73m^2	426 (10.0)	
History of bleeding	80 (1.8)	42 (0.9)
Active malignancy	156 (3.5)	24 (0.5)
Risk scores		
CHA_2DS_2-VASc[11]	2.7±1.6	111 (2.5)
Low risk (male: 0, female: 1)	537 (12.2)	
Intermediate risk (male: 1, female: 2)	943 (21.5)	
High risk (male: ≥2, female: ≥3)	2,909 (66.3)	
HAS-BLED[10]§	1.1±0.9	569 (12.6)
Low risk (0-2)	3,701 (94.1)	
High risk (3-6)	230 (5.9)	
Antithrombotics at diagnosis		0 (0.0)
None	582 (12.9)	
NOAC	3,440 (76.4)	
Dabigatran	749 (16.6)	
Rivaroxaban	1,020 (22.7)	
Apixaban	1,397 (31.0)	
Edoxaban	274 (6.1)	
VKA	317 (7.0)	
Acenocoumarol	252 (5.6)	
Phenprocoumon	65 (1.4)	
Other (e.g. heparin)	33 (0.7)	
Antiplatelet monotherapy	128 (2.8)	
OAC concomitant with antiplatelets	120 (2.7)	

Categorical data is presented as n (%) and continuous data as mean±standard deviation. *History of pulmonary embolism or deep venous thrombosis. †History of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting. ‡Haemoglobin in mmol/l of <8.1 in males, <7.5 in females. §Calculated without availability of liver function, international normalized ratio, concomitant use of nonsteroidal anti-inflammatory drugs or alcohol use. *CrCl* Creatinine clearance; *NOAC* Non-vitamin K oral anticoagulant; *OAC* Oral anticoagulant; *TIA* Transient ischaemic stroke; *VKA* Vitamin K antagonist.

LABEL ADHERENCE

Of the 3,440 patients treated with a NOAC, four patients had a contraindication for NOAC use due to a severely impaired renal function. In 184 patients NOAC label adherence could not be determined due to missing variables, most often a missing recent renal function (141 of 184 patients). Of the remaining 3,252 patients, a full dose NOAC was prescribed in 2,858 patients (87.9%), and a reduced dose NOAC in 394 (12.1%) patients. In total, 212 (6.5%) received their NOAC dose off-label, of which 77 (2.4%) were overdosed and 135 (4.2%) were underdosed (Figure 1).

Figure 1 Label adherence per NOAC



Underdosing

Of the 2,916 (89.7%) patients with a recommendation for a full dose NOAC, 135 (4.6%) were underdosed. This proportion was comparable between the four NOACs, ranging between 3.6% for edoxaban and 5.1% for apixaban (Figure 1). Compared to patients using a full dose NOAC on-label, underdosed patients were older (75.3±9.0 vs 69.1±8.9 years, p <0.001) and had an overall higher predicted risk of stroke (CHA_2DS_2-VASc 3.3±1.4 vs 2.7±1.5, p <0.001) and bleeding (HAS-BLED 1.6±0.8 vs 1.1±0.8, p <0.001). Characteristics which had a univariable association with underdosing are displayed in table 2. After multivariable analysis, higher age, lower renal function, lower weight, active malignancy, anaemia, and concomitant use of antiplatelets were significantly associated with underdosing (Table 2).

Table 2 Patient characteristics associated with underdosing of NOACs

	On-label full dose	Off-label reduced dose	Unadjusted		Adjusted	
	N=2,781	N=135	Odds Ratio	P-value	Odds Ratio	P-value
Age, years	69.1±8.9	75.3±9.0	1.10 (1.07-1.12)	<0.001	1.01 (1.01-1.02)	<0.001
CrCl, ml/min/1.73m^2	76.5±15.1	63.1±19.3	0.95 (0.94-0.96)	<0.001	0.96 (0.91-0.98)	<0.001
Weight, kg	86.2±18.0	79.5±16.7	0.98 (0.97-0.99)	<0.001	0.98 (0.97-1.00)	0.008
Coronary artery disease	355/2777 (12.8)	29/135 (21.5)	1.87 (1.22-2.86)	0.004	1.09 (0.63-1.88)	0.77
Peripheral artery disease	131/2764 (4.7)	12/133 (9.0)	1.99 (1.07-3.70)	0.03	1.26 (0.63-2.51)	0.52
Active malignancy*	84/2,767 (3.0)	10/134 (7.5)	2.57 (1.30-5.07)	0.01	4.25 (1.58-11.42)	0.004
Anaemia*	257/2,660 (9.7)	32/130 (24.6)	3.05 (2.01-4.64)	<0.001	1.67 (1.00-2.82)	0.05
OAC concomitant with antiplatelets	60/2,781 (2.2)	16/135 (11.9)	6.10 (3.41-10.90)	<0.001	4.28 (1.99-9.17)	<0.001

Underdosing according to EMA labelling. Categorical data is presented as n (% of total) and continuous data as mean±standard deviation. Odds ratios are displayed with 95% confidence intervals, for continuous variables per unit increase. *Significant interaction between anaemia and active malignancy, p=0.04. *CrCl* Creatinine clearance.

Overdosing

Of the 336 (10.3%) patients with a recommendation for a reduced dose NOAC, 77 (22.9%) were overdosed. This proportion varied between the four NOACs, ranging from 9.2% for dabigatran to 25.9% for edoxaban, 28.6% for apixaban, and 46.5% for rivaroxaban (Figure 1). Compared to patients using a reduced dose NOAC on-label, overdosed patients were younger (76.7±8.9 vs 80.9±5.9 years, p <0.001) and had an overall lower predicted risk of stroke (CHA_2DS_2-VASc 3.5±1.5 vs 4.1±1.3, p=0.001) but a comparable predicted risk of bleeding (HAS-BLED 1.4±0.6 vs 1.6±0.7, p=0.11). Characteristics which had a univariable association with overdosing are displayed in table 3. After multivariable analysis, lower age and lower renal function were significantly associated with overdosing (Table 3).

Table 3 Patient characteristics associated with overdosing of NOACs

	On-label reduced dose	Off-label full dose	Unadjusted		Adjusted	
	N=259	N=77	Odds Ratio	P-value	Odds Ratio	P-value
Age, years	80.9±5.9	76.7±8.9	0.92 (0.89-0.96)	<0.001	0.93 (0.89-0.96)	<0.001
CrCl, ml/min/1.73m^2	57.6±17.9	51.4±17.6	0.98 (0.97-1.00)	0.008	0.98 (0.97-1.00)	0.03

Overdosing according to EMA labelling. Categorical data is presented as n (% of total) and continuous data as mean±standard deviation. Odds ratios are displayed with 95% confidence intervals, for continuous variables per unit increase. *CrCl* Creatinine clearance.

DISCUSSION

We performed this study to explore the extent and determinants of off-label NOAC dosing in newly diagnosed patients with AF. Our findings show that label adherence of NOACs was high, and only 2.4% and 4.2% of NOAC users were over- and underdosed, respectively. Given that in these NOAC users only a small subset is in need for NOAC dose reduction, overdosing was uncommon overall; yet, over a fifth of patients with a recommendation for a reduced dose received a full dose. The proportion of patients who were underdosed was similar between NOACs, but a significant variation between NOACs was observed in overdosed patients, most often in rivaroxaban. Patient characteristics associated with off-label dosing - either over- or underdosing - were age and renal function, while for underdosing also weight, anaemia, active malignancy and concomitant use of antiplatelets were independent determinants.

The low proportion of off-label NOAC dose prescription in the Netherlands has previously been observed in smaller Dutch cohort studies. Data from a single-centre study on 3,231 NOAC naïve AF patients from the Netherlands showed only marginally higher proportions compared to our observations (4.5% overdosed and 5.4% underdosed).[2] Also, in the worldwide GARFIELD-AF registry, which registered patients with newly diagnosed AF and one or more risk factors for stroke, the Dutch cohort had a similarly low rate of off-label dosing. This was in contrast to the worldwide GARFIELD-AF cohort, which reported 3.8% overdosing and 23.2% underdosing among all AF patients on NOAC.[6] In the ORBIT-AF II registry, which enrolled U.S. patients with recent-onset AF and novel NOAC therapy, 3.4% of NOAC users were overdosed and 9.4% underdosed.[5] A large, cross-sectional study from the U.K., which included patients with AF and a novel prescription of NOAC, showed overdosing as high as 16.9% with dabigatran and underdosing as high as 21.6% with apixaban.[3] Overall, off-label NOAC dosing in AF, including not newly diagnosed AF, seems to range between 25-50% globally.[4] The reasons for the low off-label use of NOACs in the Netherlands cannot be derived from this study. However, we postulate that it is possibly a result of a high awareness of the issue in combination with differences in case mix. In addition, a study effect could have been of influence.

Notably, the proportion of overdosing within patients with a reduced dose recommendation was high. The lowest rate of overdosing was seen for dabigatran, which is to be expected given the non-absolute dosing criteria for this NOAC, as physicians are free to choose between the 150mg and 110mg dose of dabigatran in selected patients (see Supplementary Table S1).[8] Overdosing was more often seen in patients initiated on a Factor Xa-inhibitor, in which 61 out of 162 (37.7%) patients with a recommendation for using a reduced dose were overdosed. In patients using

apixaban, the observed relative high frequency of overdosing could be due to the more complex dosing criteria in which 2 out of 3 criteria must be present to justify dose reduction. Nevertheless, overdosing was similar to edoxaban and less than in rivaroxaban that have more straightforward dosing criteria. The reasons for this relatively high proportion of overdosing cannot be determined from this study, but it might be in part due to an unintentional dosing error. Although it is true that the vast majority (89.7%) of NOAC-eligible patients should be prescribed a full dose NOAC according to the dosing criteria, it is of importance to always check the patients age, renal function and/or weight to see whether dose adjustment is needed. Notably in frail patients prescribing physicians should be alert as these patients are often at a high risk of both stroke and bleeding.[12,13]

In previous studies as in this study, underdosing of NOACs is more common than overdosing.[2-6] The type of NOAC does not seem to matter, as no clear variation in underdosing between the different NOACs was observed in this study. The most important determinants associated with underdosing are factors associated with an increased bleeding risk, i.e. anaemia, an active malignancy and concomitant use of antiplatelets, this besides higher age, lower renal function and lower weight. In patients with a high predicted bleeding risk, the choice between on-label vs off-label dosing can be difficult, as the phase III trials in which the dosing criteria were validated largely excluded such patients. Moreover, the stroke risk in patients with an increased intrinsic risk of bleeding is often high too. Given these uncertainties, it is still uncertain whether some patients seen in clinic, who are deemed to be at high risk of bleeding, would be better served with an on- or off-label NOAC prescription. Importantly, however, previous observational studies have shown that off-label reduced dosing of NOACs in general is associated with more cardiovascular hospitalization, mortality and thrombosis, however, without an apparent reduction in major bleeding compared to on-label dosing.[5,6] Of note, these results should be interpreted with caution as selection bias and unblinded assessment of outcomes may have occurred.

A pooled post-hoc analysis of the pivotal NOAC trials reported 31% more major bleeds in patients using a NOAC concomitant with an antiplatelet agent versus NOAC monotherapy.[14] Therefore, combining a reduced NOAC dose concomitant with antiplatelet therapy seems intuitive to lower bleeding risk, but inherently could increase stroke risk. The vast majority of patients in DUTCH-AF receiving antiplatelet therapy had undergone coronary revascularization. Evidence regarding the effectiveness and safety of reducing NOAC dose in the presence of antiplatelet therapy after percutaneous coronary intervention (PCI) in AF is mainly comprised of the RE-DUAL PCI and PIONEER AF-PCI trials.[15,16] In the RE-DUAL PCI trial,

dabigatran 110mg b.i.d. plus a $P2Y_{12}$ inhibitor regimen resulted in significantly lower bleeding rates than dabigatran 150mg b.i.d. plus a $P2Y_{12}$ inhibitor, or warfarin plus dual antiplatelet therapy.[15] In the PIONEER AF-PCI trial, rivaroxaban 15mg o.d. plus a $P2Y_{12}$ inhibitor also resulted in significantly lower bleeding rates compared to warfarin plus dual antiplatelet therapy, whereas a rivaroxaban 20mg cohort was not included.[16] Based on these trials, the 2020 AF guideline from the European Society of Cardiology recommends that a reduced dose dabigatran or rivaroxaban concomitantly with a $P2Y_{12}$ inhibitor after PCI may be considered in patients with a high bleeding risk (i.e. HAS-BLED ≥3).[1] Although the 2020 ESC AF guidelines were published at the end of our study observation period, physicians could have already implemented the results of the RE-DUAL PCI and PIONEER AF-PCI trials into their practices. It should be noted however that both trials were underpowered to detect the observed between-group differences in their efficacy endpoints. Therefore, reducing NOAC dose outside of the EMA labelling when antiplatelet therapy is initiated should always be done with caution.

STRENGTHS AND LIMITATIONS

A major strength of this study is that we prospectively enrolled a large cohort of everyday patients from different levels of care, including academic and non-academic hospitals (both out- and inpatients), primary outpatient clinics, as well as outpatient anticoagulant clinics. Our cohort is therefore likely an accurate reflection of Dutch everyday AF practice. Moreover, our contemporary data was registered at diagnosis, and we recorded the initial choice regarding antithrombotic therapy.

The most important limitations of this study are those related to the observational and pragmatic design of this registry. For example, we did not collect data on the use of strong P-glycoprotein inhibitors or other drugs included in the labelled dosing criteria of the individual NOACs, which could have resulted in misclassification of label adherence. Another limitation is the inclusion of retrospectively collected data in 912 patients from this cohort.

CONCLUSION

In newly diagnosed Dutch AF patients, off-label dosing of NOACs was seen in only 6.6% of the patients, most often underdosing. In this study, determinants of off-label dosing were age, renal function, weight, anaemia, active malignancy and concomitant use of antiplatelets.

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CHAPTER 4

Unequal prescription of anticoagulants among females and males with atrial fibrillation and similar stroke risk

Should we omit sex category from the CHA_2DS_2-VASc score?

Heart Rhythm (2022)

Seelig J, Chu G, Trinks-Roerdink EM, Pisters R, de Vries TAC, ten Cate H, Geersing GJ, Rutten FH, Huisman MV, Hemels MEW

LETTER

The CHA_2DS_2-VASc stroke risk score has been recommended by the European Society of Cardiology atrial fibrillation (AF) guidelines to guide decision on oral anticoagulation (OAC) prescription in AF patients. Whereas female sex was initially considered an individual risk factor warranting antithrombotic treatment in all female AF patients independent of other risk factors, this recommendation was revised as growing evidence showed that female sex is rather a risk modifier as sex does not contribute to stroke risk in the absence of other risk factors.[1] Currently, a CHA_2DS_2-VASc of 2 in females and 1 in males has a class IIa recommendation for OAC (i.e. should be considered), and a CHA_2DS_2-VASc of ≥3 in females or ≥2 in males has a class I recommendation for OAC (i.e. indicated).[1]

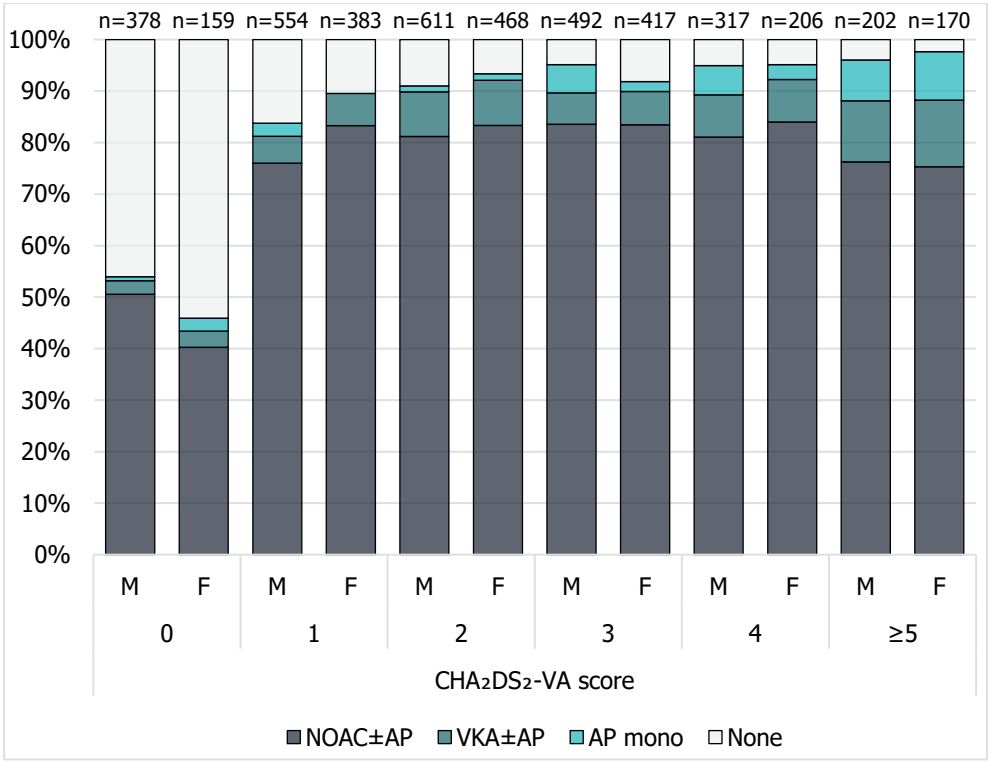
In the prospective, nationwide DUTCH-AF registry, we investigated whether the current guideline recommendations on OAC treatment are followed in daily clinical practice. This registry started in 2018 and consists of patients with newly diagnosed AF (<6 months old), excluding patients with moderate-to-severe mitral stenosis or a mechanical valve.[2] Antithrombotic therapy as prescribed at diagnosis was recorded.[2] The study protocol was approved by the ethics committees of all participating centers, and all patients provided informed consent. Of 4,500 patients enrolled, adherence to guidelines could be determined in 4,357 patients (96.8%), mean age of which was 69.5±10.5 years, and 1,803 (41.4%) were female. Mean CHA_2DS_2-VASc score was 2.2±1.5 in males and 3.4±1.5 in females.

Of the 2,883 (66.2%) patients with a class I recommendation for OAC treatment, 90.9% of females and 89.5% of males were treated with OAC (p=0.20) (see Figure). Of the 937 patients (21.5%) with a class IIa recommendation, 89.6% of females and 81.2% of males received OAC (p<0.001). Regarding these 937 patients, a logistic regression model with OAC prescription as a binary outcome including each stroke risk factor of the CHA_2DS_2-VASc score (heart failure, hypertension, age per year, diabetes mellitus, vascular disease, female sex) as well as renal function (per ml/min/1.73m^2) as determinants, showed that only male sex was associated with no OAC treatment (adjusted odds ratio 2.1, 95%-confidence interval 1.4-3.2).

This seemingly unwarranted difference in OAC prescription between sexes at AF diagnosis might indicate that females with a CHA_2DS_2-VASc score of 2 are perceived to be at a higher stroke risk than males with a CHA_2DS_2-VASc score of 1. However, this observation is remarkable as previous large-scale registries from Sweden and Denmark have shown that males and females with AF and no or only one non-sex stroke risk factor have equal rates of ischemic stroke, despite a numerically different CHA_2DS_2-VASc score.[3] As sex category should not influence the guideline recommended decision on OAC initiation, the CHA_2DS_2-VA score (excluding sex

category as a risk modifier) has been proposed as an alternative for the CHA_2DS_2-VASc score, and has for instance been implemented in the most recent Australian AF guideline.[1,3,4] Although previous studies have shown OAC undertreatment in females with AF across multiple CHA_2DS_2-VASc scores, we did not observe this in our contemporary cohort (Figure), and using a CHA_2DS_2-VA score would not influence the decision around OAC initiation when the guidelines are followed. The CHA_2DS_2-VASc score – not limited to – is more appropriate for stroke risk estimation, but the CHA_2DS_2-VA score is sufficient for the sole purpose of guiding OAC initiation and could help prevent the prevent the observed difference in OAC treatment between sexes.[1,3]

Figure 1 Antithrombotic treatment in relation to CHA_2DS_2-VA score



AP Antiplatelet agent; *F* Females; *M* Males; *VKA* Vitamin K antagonist; *NOAC* non-vitamin K oral anticoagulant.

In conclusion, we observed a significant and unwarranted difference in OAC treatment between males and females with a similar stroke risk at a decision point of starting OAC. Applying a CHA_2DS_2-VA score to guide the decision on OAC initiation could be useful to avoid such a difference.

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CHAPTER 5

Changes in anticoagulant prescription in Dutch patients with recent-onset atrial fibrillation: observations from the GARFIELD-AF registry

Thrombosis Journal (2020)

Seelig J, Verheugt FWA, Hemels MEW, Illingworth L, Lucassen A, Adriaansen H, Bongaerts MCM, Pieterse M, Herrman JPR, Hoogslag P, Hermans W, Groenemeijer BE, Boersma LVA, Pieper K, ten Cate H

ABSTRACT

BACKGROUND

For the improvement of AF care, it is important to gain insight into current anticoagulation prescription practices and guideline adherence. This report focuses on the largest Dutch subset of AF-patients, derived from the GARFIELD-AF registry.

METHODS

Across 35 countries worldwide, patients with newly diagnosed 'non-valvular' atrial fibrillation (AF) with at least one additional risk factor for stroke were included. Dutch patients were enrolled in five, independent, consecutive cohorts from 2010 until 2016.

RESULTS

In the Netherlands, 1189 AF-patients were enrolled. The prescription of non-vitamin K antagonist oral anticoagulants (NOAC) has increased sharply, and as per 2016, more patients were initiated on NOACs instead of vitamin K antagonists (VKA). In patients with a class I recommendation for anticoagulation, only 7.5% compared to 30.0% globally received no anticoagulation. Reasons for withholding anticoagulation in these patients were unfortunately often unclear.

CONCLUSIONS

The data from the GARFIELD-AF registry shows the rapidly changing anticoagulation preference of Dutch physicians in newly diagnosed AF. Adherence to European AF guidelines in terms of anticoagulant regimen would appear to be appropriate. In absence of structured follow up of AF patients on NOAC, the impact of these rapid practice changes in anticoagulation prescription in the Netherlands remains to be established.

INTRODUCTION

In the Netherlands, AF patients on vitamin K antagonist (VKA) therapy are routinely managed by specialized anticoagulation clinics. Back in 2012, a report from the health council of the Netherlands endorsed the careful introduction of NOACs, given the lack of real-world data, absence of specific antidotes, and a substantial risk of non-compliance due to a lack of monitoring.[1] These factors resulted in a slower uptake of a NOAC-based approach in comparison to other countries.[2] However, based on a decision-related Markov model, it was recently calculated that an increase in NOAC prescription in the Netherlands would result in higher quality of life.[3,4] Moreover, given the increasing real-world data on NOACs versus VKAs, uncertainties about the safety of these drugs have diminished. It is therefore important to monitor anticoagulation prescription trends for AF in the Netherlands, which are currently unknown. This will give insights in how to further improve our AF care.

Moreover, insight in adherence to AF-guidelines could also help to improve AF care. In the Netherlands, it is estimated that the prevalence of AF is around 2.0% in 2020, expected to increase to 3.2% by 2050.[5] In parallel, in subjects with AF the ischemic stroke rate will rise, primarily due to ageing and an increase in patients with multiple morbidities.[5-7] This increases health-care related costs and reduces quality of life. To minimise these aspects, it is important that AF guidelines are adhered to, as non-adherence is associated with increased ischemic stroke and mortality rates.[8,9]

This report expands on previously published Dutch GARFIELD-AF data, and demonstrates changes in antithrombotic treatment initiation in newly diagnosed AF in the Netherlands.[2] We compare the results with the global GARFIELD-AF cohort, and with recommendations of the most recent European AF-guidelines.[10]

METHODS

DESIGN

GARFIELD-AF was a multicentre, prospective registry of patients with recent onset non-valvular AF from over a 1000 centres in 35 countries worldwide. Globally, the recruitment of patients started in December 2009 and was completed in August 2016. In the Netherlands, patients were included as of November 2010. Patients were enrolled in five independent, consecutive cohorts 1) 2009-2011, 2) 2011-2012, 3) 2013-2014, 4) 2014-2015, and 5) 2015-2016. Data used was from the October 2017 dataset.

POPULATION

Patients diagnosed with 'non-valvular' AF within the previous 6 weeks, aged ≥ 18 years, and with at least one investigator-determined risk factor for stroke were considered eligible for inclusion. Patients were excluded if; 1) follow-up with a physician was considered unlikely or impossible, 2) there was a potentially reversible, transient cause for AF, or 3) they were enrolled in a controlled clinical trial. For each country, a sufficient number of investigator sites from different care settings were identified.

DATA COLLECTION

All data were made anonymous and were imported to a secured, electronic case report form (eCRF), which was designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, UK). Oversight of operations and data management were done by the Thrombosis Research Institute [TRI] (London, UK), which is the sponsor and coordinating centre. A detailed description of the methods can be found elsewhere.[11] The study is registered at ClinicalTrials.gov (unique identifier: NCT01090362).

At inclusion, patient characteristics such as demographics, medical history, vital signs, and type and dose of antithrombotic therapy were recorded. Amongst others, the components of the CHA_2DS_2-VASc stroke risk and HAS-BLED bleeding risk scores were collected.[12,13] Vascular disease was defined as the combination of a history of acute coronary syndrome with peripheral and/or coronary artery disease. Chronic kidney disease was defined according to the National Kidney Foundation guidelines.[14]

ANALYSIS

Continuous variables are expressed as means with standard deviation, and categorical variables as frequencies with percentages. Data from patients with missing values were not removed from the analyses. Follow-up data was not analysed due to a lack of power. Similarly, no p-values were calculated. Data analysis was performed with SAS Enterprise Guide, version 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

POPULATION

In the Netherlands, 1189 out of 52,014 patients (2.3%) were enrolled across 16 sites. Across the different Dutch cohorts were 199 (1; 2009-2011), 410 (2; 2011-2012), 357 (3; 2013-2014), 155 (4; 2014-2015), and 161 (5; 2015-2016) AF patients enrolled. In the Netherlands and worldwide, the mean age was 70.7 and 69.7 years, respectively, and 42.4% compared to 44.2% of patients were female. At baseline, hypertension (65.5%), hypercholesterolemia (36.0%), diabetes mellitus (20.0%), and coronary artery disease (18.7%) were the most common comorbidities in the Dutch cohorts. The mean CHA_2DS_2-VASc (3.1 vs. 3.2) and HAS-BLED (1.4 vs. 1.4) scores were comparable between the Dutch and overall cohort, respectively. Compared to the worldwide cohort, more patients were enrolled in cardiology departments (90.2% vs. 65.7%) in the Dutch subset. Further baseline characteristics are described in Table 1.

CHANGES IN ANTITHROMBOTIC THERAPY

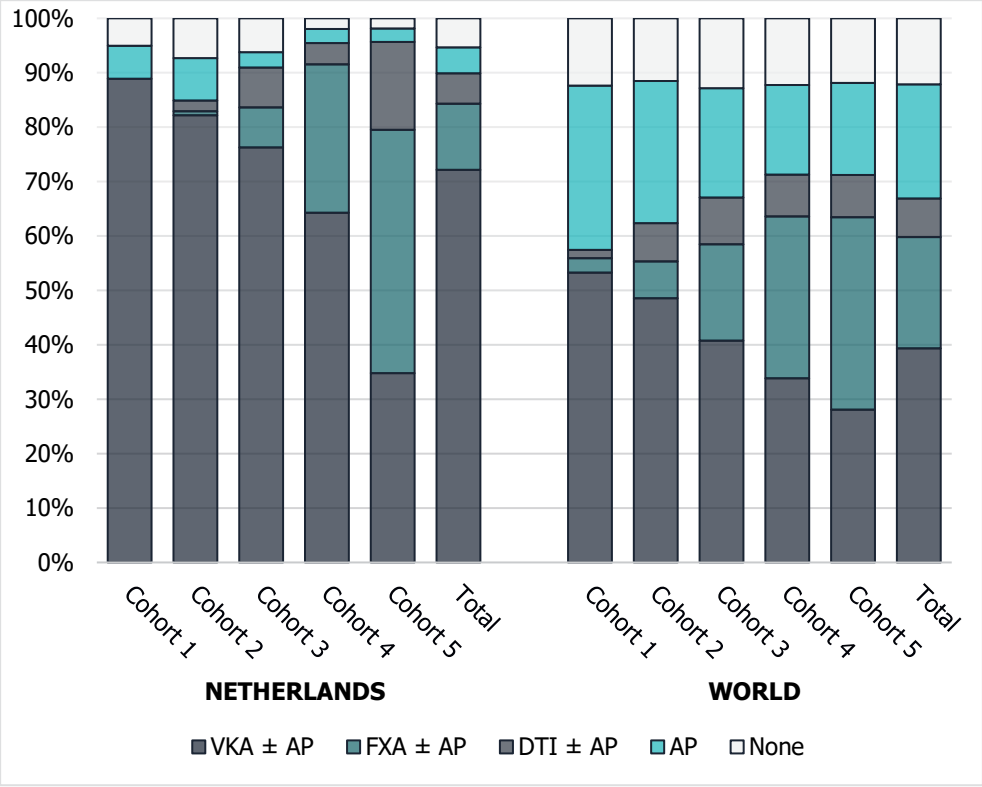
Of all 35 participating countries, the percentage of patients on oral anticoagulation at AF diagnosis was on average highest in the Netherlands (89.9%). A comparison of anticoagulation treatments (with or without concomitant antiplatelet therapy) between the five different cohorts, demonstrates a rise in the prescription of NOACs from 0.0% to 60.9% over the years (Figure 1). Conversely, a decrease in VKA prescription from 88.9% to 34.8% was observed. The proportion of patients on antiplatelet monotherapy decreased from 6.1% to 2.5%. The proportion of patients not treated with antithrombotics reduced from 5.1% to 1.9%. In the most recent cohort, the proportion of patients on antiplatelet drug therapy (2.5%) or no antithrombotic therapy (1.9%) were both the lowest of all participating countries.

Table 1 Baseline characteristics of Dutch and all included patients

	Netherlands (N=1189)	World (N=52014)
Female sex, n (%)	504 (42.4)	22987 (44.2)
Age, mean (sd)	70.7 (9.9)	69.7 (11.5)
< 65, n (%)	311 (26.2)	15693 (30.2)
65-74, n (%)	426 (35.8)	16948 (32.6)
≥ 75, n (%)	452 (38.0)	19373 (37.2)
BMI (kg/m^2), mean (sd)	28.5 (5.3)	27.8 (5.7)
Congestive Heart Failure, n (%)	82 (6.9)	10397 (20.0)
Hypertension, n (%)	775 (65.5)	39585 (76.3)
Diabetes Mellitus, n (%)	238 (20.0)	11540 (22.2)
Stroke/TIA, n (%)	137 (11.5)	5954 (11.4)
PE or DVT, n (%)	22 (1.9)	1356 (2.6)
Coronary artery disease, n (%)	222 (18.7)	11232 (21.6)
Acute Coronary Syndrome, n (%)	166 (14.0)	4895 (9.5)
Chronic Kidney Disease, n (%)		
None	377 (31.7)	23919 (46.0)
Stages 1 to 2	629 (52.9)	16508 (31.7)
Stages 3 to 5	118 (9.9)	5373 (10.3)
History of Bleeding, n (%)	25 (2.1)	1317 (2.5)
Hypercholesterolemia, n (%)	422 (36.0)	20940 (41.6)
CHA_2DS_2-VASc	3.1 (1.5)	3.2 (1.6)
HAS-BLED	1.4 (0.9)	1.4 (0.9)
Care Setting Speciality at Diagnosis, n (%)		
Cardiology	1097 (92.3)	34165 (65.7)
Other Hospital Departments	30 (2.5)	10434 (20.1)
Primary Care	62 (5.2)	7410 (14.2)

BMI Body mass index; *VKA* Vitamin K antagonist; *NOAC* Non-vitamin K antagonist oral anticoagulant; *TIA* Transient ischaemic attack; *PE* Pulmonary embolism; *DVT* Deep venous thrombosis.

Figure 1 Treatment at diagnosis by cohort



VKA Vitamin K Antagonist; *AP* Antiplatelet Drug; *FXa* Factor Xa inhibitor; *DTI* Direct Thrombin Inhibitor.

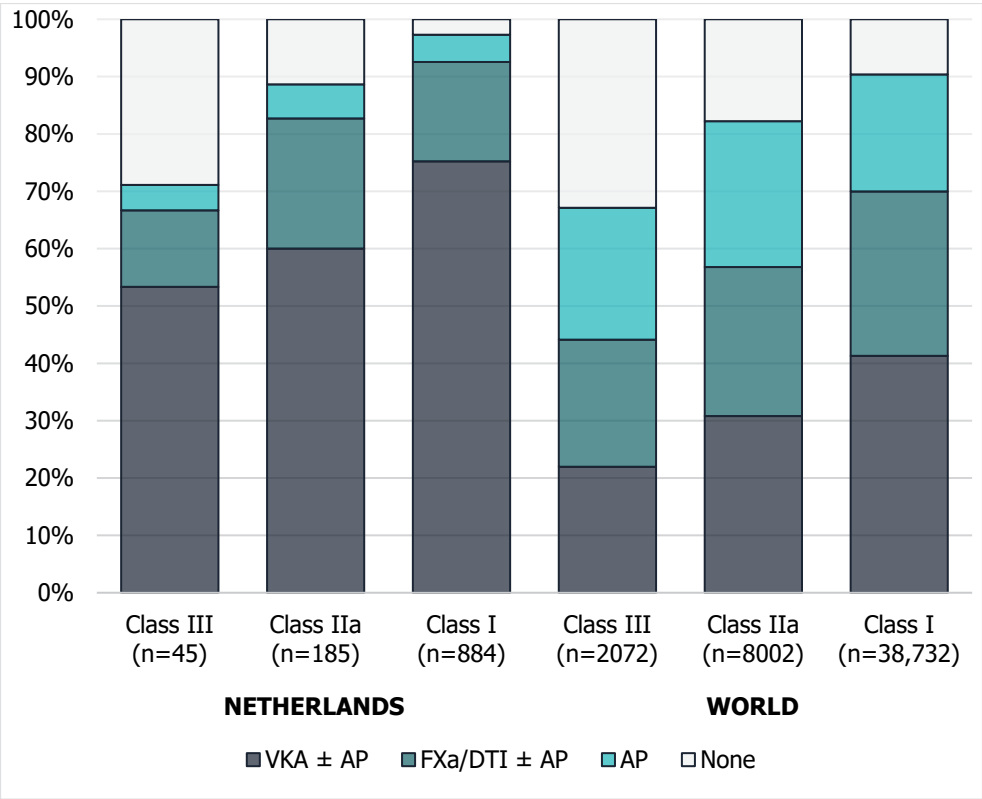
GUIDELINE ADHERENCE AND REASONS OF NOT PRESCRIBING ANTICOAGULATION

Within the Dutch cohorts, 79.4% of patients had a class I recommendation for anticoagulation for stroke prevention in AF (i.e. males CHA_2DS_2-VASc ≥ 2, and females CHA_2DS_2-VASc ≥ 3), according to ESC guidelines.[10] Of these patients, 92.5% were treated with oral anticoagulants, 4.8% with antiplatelet monotherapy, and 2.7% with no antithrombotic therapy (Figure 2). In patients with a class IIa recommendation for stroke prevention in AF (i.e. males CHA_2DS_2-VASc = 1, and females CHA_2DS_2-VASc = 2; 16.6% of patients), 82.6% of patients were treated with oral anticoagulants, 6.0% with antiplatelet monotherapy, and 11.4% with no antithrombotic therapy. In patients with no increased stroke risk according to the CHA_2DS_2-VASc score (i.e. males CHA_2DS_2-VASc = 0, and females CHA_2DS_2-VASc = 1; 4.0% of patients), 66.7% were treated with oral anticoagulants, 4.4% with antiplatelet monotherapy, and 28.9% with no antithrombotic therapy.

Unfortunately, in the Netherlands and worldwide, reasons for not prescribing anticoagulants in males with CHA_2DS_2-VASc ≥ 2, and females with CHA_2DS_2-VASc ≥ 3 were often recorded as 'unknown' (28.8% versus 39.4%) or 'other' (40.9 versus

22.4%). Excluding these options, the most frequently reported reasons in the Netherlands were 'low stroke risk' (12.1%) and 'bleeding risk' (7.6%) (Table 2). In the worldwide cohort, excluding Dutch patients, the main reasons for not prescribing anticoagulants were 'patient refusal' (7.8%), 'bleeding risk' (7.2%), 'low risk of stroke' (5.8%) and 'already taking antiplatelet drugs for other medical condition' (5.4%).

Figure 2 Treatment at diagnosis by Class of Recommendation according to the 2016 ESC AF-guidelines



VKA Vitamin K Antagonist; *AP* Antiplatelet Drug; *FXa* Factor Xa inhibitor; *DTI* Direct Thrombin Inhibitor.

Table 2 Main reasons anticoagulant not used in males with CHA_2DS_2-VASc ≥2, and females with CHA_2DS_2-VASc ≥3

	Netherlands (N=66)	World (N=11630)
Alcohol abuse	0 (0.0)	48 (0.4)
Already taking AP for other medical condition	3 (4.5)	628 (5.4)
Patient refusal	1 (1.5)	911 (7.8)
Previous bleeding event	2 (3.0)	211 (1.8)
Taking medication contraindicated or cautioned for use with OAC	1 (1.5)	78 (0.7)
Other	12 (18.2)	1682 (14.5)
Unknown	19 (28.8)	4588 (39.4)
Physician's choice	28 (42.4)	3484 (30.0)
Bleeding risk	5 (7.6)	836 (7.2)
Concern over patient compliance	0 (0.0)	412 (3.5)
Guideline recommendation	0 (0.0)	237 (2.0)
Fall risk	0 (0.0)	401 (3.4)
Low risk of stroke	8 (12.1)	677 (5.8)
Other	15 (22.7)	921 (7.9)

Data are displayed in n (%). *AP* Antiplatelet drug; *OAC* Oral anticoagulation.

DISCUSSION

GARFIELD-AF was the largest, worldwide, prospective registry of newly diagnosed AF patients. In the Netherlands, 1189 patients were enrolled, making it the largest Dutch AF-cohort available to date. This manuscript provides a unique insight in the rapid changes in anticoagulation management of novel AF, which had not been described since the introduction of the NOACs in the Netherlands. The comparison between NOAC uptake rates in the Netherlands vs other countries is important, as this could have influenced the quality of Dutch AF care. Future studies will have to analyse how these differences have impacted the safety and efficacy of AF care. Moreover, this is the first report describing nationwide adherence to AF-guidelines in the Netherlands and explores reasons for withholding oral anticoagulation in AF, which gives insight in how to further improve our AF care. Also, this country-specific evaluation may also be of help in improving care when comparisons are made with anticoagulant management in other countries.

In the Netherlands, there was initially a slow shift to more NOAC prescription, compared to the rest of the world. However, as of 2014-2015, the anticoagulation landscape has changed rapidly, resulting in more newly diagnosed AF patients treated with NOACs than VKA as of 2016. Our findings were comparable to a recent analysis of anticoagulant pharmaceutical dispensing data of naïve oral anticoagulation starters for any indication in the Netherlands.[15] A possible explanation for this initial slow shift could be that there is a well-organized system of specialized anticoagulation clinics in the Netherlands. In these clinics, the monitoring of compliance and complications of VKA treatment through regularly scheduled follow-up checks is aimed at minimising risks accompanying VKA treatment. Although NOACs have been repeatedly shown to be at least as effective and safe as VKAs in both randomized controlled trials and real-world data, a lack of monitoring could have contributed to a hesitation to shift to a more NOAC based approach. This is not unreasonable, as without a regular check of factors such as renal function, weight or age, patients are often (± 10% in two recent Dutch AF-studies), treated with a too high or too low NOAC dose.[16,17] Moreover, early discontinuation of (N)OAC treatment can be as high as 50% at 6 months in certain patient groups.[18,19] Frequently mentioned reasons for early discontinuation are (minor) bleeding, other anticoagulant-related side-effects, and a lack of the perceived need for anticoagulation.[20,21] Therefore, international guidelines recommend structured follow up of patients on NOACs (ESC) including assessment of adherence to medication, complications, interactions and regular (at least annual, but more often on indication) check on renal and liver functions.[22] For the Netherlands, much of this burden will come down on the shoulders of prescribers (mainly cardiologists) and for the long term on general practitioners. It is imperative

that, based on national guidance documents such as the "Landelijke Standaard Ketenzorg Antistolling" (LSKA) 2.0 and the updated "Landelijke Transmurale Afspraak antistolling" (manuscript in preparation), the chronic care for patients on NOACs becomes well organized.[23]

In GARFIELD-AF, the Netherlands had the highest proportion of patients on oral anticoagulation at diagnosis (89.9%). In the most recent cohort, Dutch patients had the lowest proportions of antiplatelet monotherapy (2.5%) or no antithrombotic therapy (1.9%). For patients with a class I recommendation for anticoagulation, 7.5% of patients were undertreated according to the ESC guidelines.[10] Compared to the worldwide cohort (30.0%), this proportion is relatively low. In patients with a class III recommendation for anticoagulation (i.e. CHA_2DS_2-VASc 0 in males, CHA_2DS_2-VASc 1 in females), the proportion of patients on anticoagulation is high (66.6%).[10] Although there is no chronic indication for anticoagulation in these patients, the guideline recommends at least three weeks of pre-treatment with oral anticoagulation in late cardioversions.[10] The ACWAS trial showed that in patients with recent-onset (<36 hours) AF, a delayed cardioversion strategy led to spontaneous conversion within 48 hours in 69% of patients.[24] In a post-hoc analysis of the ACUTE trial, nearly 50% of patients with pre-existing AF of ≤ 1 week had a spontaneous cardioversion.[25] It is likely that patients with recent-onset, newly diagnosed AF without risk factors for stroke are often 'overtreated' with anticoagulation, given the high rate of spontaneous conversion. It is therefore worth researching if there are possibilities to safely limit the prescription of anticoagulants in these patients.

Although the proportion of undertreated patients in the Netherlands was relatively low, there is still room for improvement. In GARFIELD-AF, main reasons for not prescribing anticoagulants in patients with a class I recommendation for anticoagulation for stroke prevention in AF were often not clear. In patients with a clear recorded reason for withholding anticoagulation, a 'low risk of stroke' (12.1%) and 'bleeding risk' (7.6%) were the most common reasons in the Dutch cohort. Depicting patients with 2 or more non-sex related stroke risk factors as having a 'low risk of stroke' is contradictory, and the precise reasoning behind it is unknown. It would be valuable to gather more information on reasons for withholding anticoagulation, and to evaluate if withholding anticoagulation in these groups is a safe approach.

This study has several limitations. As described before, the high proportion of patients included in Dutch cardiology departments limits the external validity of this study to nationwide clinical practice. Moreover, the number of patients was too low, and the mean follow-up was too short, to relate major adverse events to CHA_2DS_2-

VASc scores or changes in anticoagulant treatment practices. Moreover, reasons for not prescribing anticoagulants were extracted from the medical records and were not confirmed by the prescribing physician, and a large proportion of reasons could not be recorded and were classified as 'other'. Further research without these limitations is necessary. DUTCH-AF (Dutch trial register number: NL7464) is a largescale registration of newly diagnosed AF-patients in the Netherlands, which does not have these limitations and could provide further answers.[26]

CONCLUSION

The data from the GARFIELD-AF registry shows the rapidly changing anticoagulation preference of Dutch physicians in newly diagnosed AF. Adherence to European AF guidelines in terms of anticoagulant regimen would appear to be appropriate. In absence of structured follow up of AF patients on NOAC, the impact of these rapid practice changes in anticoagulation prescription in the Netherlands and in relation to other countries remains to be established.

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CHAPTER 6

Impact of different anticoagulation management strategies on outcomes in atrial fibrillation: Dutch and Belgian results from the GARFIELD-AF registry

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ABSTRACT

BACKGROUND

The uptake rate of non-vitamin K oral anticoagulants (NOAC) for the treatment of non-valvular atrial fibrillation (AF) was far lower in the Netherlands (NL) compared to Belgium (BE). Also, patients on VKA in NL were treated with a higher target INR range of 2.5-3.5.

OBJECTIVES

To explore the effect of these differences on thromboembolism (TE) and bleeding.

METHODS

Data from the GARFIELD-AF registry was used. Patients with new-onset AF and ≥1 investigator-determined risk factor for stroke were included between 2010-2016. Event rates from two years of follow-up were used.

RESULTS

In NL and BE, 1186 and 1705 patients were included, respectively. Female sex (42.3% vs 42.2%), mean age (70.7 vs 71.3 years), CHA_2DS_2-VASc (3.1 vs 3.1) and HAS-BLED score (1.4 vs 1.5) were comparable between NL and BE. At diagnosis in NL vs BE, 72.1% vs 14.6% received vitamin K antagonists (VKA) and 17.8% vs 65.5% NOACs, varying greatly across cohorts. Mean INR was 2.9 (±1.0) and 2.4 (±1.0) in NL and BE, respectively. Event rates per 100 patient-years in NL and BE, respectively, of all-cause mortality (3.38 vs 3.90; HR 0.86 95%-CI 0.65-1.15), ischemic stroke/TE (0.82 vs 0.72; HR 1.14 95%-CI 0.62-2.11) and major bleeding (2.06 vs 1.54; HR 1.33 95%-CI 0.89-1.99) did not differ significantly.

CONCLUSIONS

In GARFIELD-AF, despite similar characteristics, patients on anticoagulants were treated differently in NL and BE. Although the rate of major bleeding was 33% higher in NL, variations in bleeding, mortality and TE rates were not statistically significant.

INTRODUCTION

In the neighbouring countries the Netherlands (NL) and Belgium (BE), oral anticoagulation (OAC) treatment strategies in atrial fibrillation (AF) have been noticeably different. In these countries, non-vitamin K oral anticoagulants (NOAC) were approved for AF in 2011 and 2012, respectively. In 2012, more than 50% of patients with newly diagnosed AF were treated with NOACs in BE, compared to around 3% in NL.[1,2] One of the reasons for the lower uptake rate in NL was an advisory report from the Health Council of the Netherlands warranting a careful introduction of NOACs, given the uncertainties of the safety and efficacy of these drugs in a real-world setting, and a lack of systematic monitoring hereon.[3] Also, more experience with anticoagulant management by physicians in BE in comparison to NL could have influenced NOAC uptake rates, as VKA care in BE is organized by general physicians (GP), but in NL is organized by specialized anticoagulation clinics. Moreover, before 2012, cardiologists in BE already had experience with NOACs due to the availability of dabigatran through compassionate use programs.[4]

A second difference in OAC treatment strategy between these countries was that before 2016, the majority of AF patients on VKA were treated with a target INR range of 2.5-3.5 in NL (therapeutic INR range: 2.0-3.5), compared to the internationally used range of 2.0-3.0 in BE. It was hypothesized that aiming for a higher target INR range would give a higher net clinical benefit of VKA treatment. As of 2016 however, target INR range in NL lowered to correspond with international guidelines.

It is important to research how these differences in treatment strategy relate to thromboembolism and bleeding in AF. Since the populations in these countries are quite similar, a comparative analysis can provide us with some unique insights. In this article, we will explore differences in patient characteristics, treatment strategies and outcomes in newly diagnosed AF patients between NL and BE. For these analyses, data from the worldwide GARFIELD-AF registry was used, comprising the largest Dutch and Belgian AF cohort to date.

METHODS

GARFIELD-AF is the largest, prospective, worldwide registry of patients with a new diagnosis of atrial fibrillation. Patients were enrolled in five independent, consecutive cohorts: 1) 2009 to 2011, 2) 2011 to 2012, 3) 2013 to 2014, 4) 2014 to 2015, and 5) 2015 to 2016. In NL and BE, patients were included as of November 2010 and May 2012, respectively. Patients aged ≥18 years were eligible for inclusion if they were diagnosed with non-valvular AF within the previous 6 weeks, and had ≥1 investigator-determined risk factor for stroke. Patients with transient AF due to a reversible cause were excluded. Follow-up data was collected every 4 months for 2 years. During follow-up, data on mortality, ischemic stroke, thromboembolism (TE) and major or clinically relevant non-major bleeding (CRNMB) were registered. Major bleeding and CRNMB were both defined according to ISTH criteria.[5,6] Chronic kidney disease (CKD) was defined according to the guidelines of the National Kidney Foundation (NKF).[7] The study sponsor and coordinating centre is the Thrombosis Research Institute (TRI) based in London, United Kingdom. The study methods have been described elsewhere.[8] The study was approved by the ethical committees of all participating centres and is registered at ClinicalTrials.gov (NCT01090362).

STATISTICAL ANALYSIS

Continuous variables are expressed as means with standard deviation, and categorical variables as frequencies with percentages. Data from patients with missing values were removed from the respective analyses. For statistical comparison, a t-test was used for continuous variables and a chi-squared test for categorical variables. TTR was calculated using the Roosendaal method.[9] For BE, an INR range of 2.0-3.0 was applied in the calculations. For NL, TTR was calculated using two definitions. The first was applying the range of 2.0-3.0 and the second an INR range of 2.0-3.5 for INR values before January 1st 2016, and 2.0-3.0 hereafter. Only the first occurrence of each adverse event within the first 2 years of follow-up was analysed. Events are described as number of events per 100 patient-years. A Cox proportional hazards model was used for comparison of time-to-event, described as unadjusted hazard ratios (HR) with 95%-confidence intervals (CI). A density plot was made for a comparison of INR and TTR measurements, with a histogram and an illustration of the density curve applying a kernel smoothing function to the INR and TTR data. A two-tailed p-value of <0.05 was considered significant. Data analysis was performed with SAS Enterprise Guide, version 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

PATIENT CHARACTERISTICS

In NL and BE, 1186 and 1705 patients were included in GARFIELD-AF, respectively. Mean follow-up was 1.9 years in both countries. Mean age (70.7 vs 71.3 years), female sex (42.3% vs 42.2%), CHA_2DS_2-VASc (3.1 vs 3.1) and HAS-BLED score (1.4 vs 1.5) were comparable between NL and BE, respectively.[10,11] Congestive heart failure (15.4% vs 9.3%) and CKD (13.3% vs 10.0%) were more common in BE, compared to NL. Diabetes mellitus (20.1% vs 16.4%) and acute coronary syndrome (14.7% vs 9.6%) were more common in NL, compared to BE (Table 1).

Table 1 Baseline characteristics by country

	Netherlands (N=1186)	Belgium (N=1705)	P-value[a]
Female sex	502 (42.3)	720 (42.2)	0.96
Age	70.7±10.0	71.3±10.8	0.14
BMI	28.5±5.3	28.8±5.7	0.27
Care setting specialty			<0.0001
Cardiology	1094 (92.2)	1484 (87.0)	
Other hospital departments	30 (2.5)	90 (5.3)	
General practice	62 (5.2)	131 (7.7)	
CHF	110 (9.3)	263 (15.4)	<0.0001
Hypertension	775 (65.5)	1160 (68.2)	0.14
Diabetes Mellitus	238 (20.1)	279 (16.4)	0.01
Stroke/TIA	134 (11.3)	169 (9.9)	0.22
PE or DVT	22 (1.9)	41 (2.4)	0.33
CAD	221 (18.6)	289 (17.0)	0.24
PVD	86 (7.3)	135 (8.0)	0.51
ACS	174 (14.7)	164 (9.6)	<0.0001
CKD, moderate or severe	118 (10.0)	224 (13.3)	0.01
Previous bleeding	25 (2.1)	46 (2.7)	0.31
Risk scores			
CHA_2DS_2-VASc	3.1±1.5	3.1±1.6	0.22
HAS-BLED	1.4±0.9	1.5±0.9	0.25
Antithrombotic treatment			<0.0001
NOAC±AP	209 (17.8)	1110 (65.5)	
DTI±AP	66/209 (31.6)	267/1110 (24.1)	
FXa±AP	143/209 (68.4)	843/1110 (75.9)	
VKA±AP	847 (72.1)	247 (14.6)	

Acenocoumarol±AP	744/847 (87.8)	54/247 (21.9)
Phenprocoumon±AP	99/847 (11.7)	36/247 (14.6)
Warfarin±AP	1/847 (0.1)	155/247 (62.8)
Other or unknown±AP	3/847 (0.4)	2/247 (0.8)
AP monotherapy	56 (4.8)	179 (10.6)
None	63 (5.4)	158 (9.3)

The aggregated data of all cohorts are displayed. Categorical data is presented in n (% of total) and continuous data in mean ± standard deviation, unless stated otherwise. [a]P-values calculated using chi-square tests for categorical variables and t-tests for continuous variables. *ACS* Acute coronary syndrome; *AP* Antiplatelet agents; *BMI* Body mass index (kg/m^2); *CAD* Coronary artery disease; *CHF* Congestive Heart Failure; *CKD* Chronic Kidney Disease; *DTI* Direct Thrombin Inhibitor; *DVT* Deep venous thrombosis; *FXa* Direct Factor Xa inhibitor; *NOAC* Non-vitamin K antagonist oral anticoagulant; *PE* Pulmonary embolism; *PVD* Peripheral Vascular Disease; *TIA* Transient ischaemic attack; *VKA* Vitamin K antagonist.

DIFFERENCES IN ANTITHROMBOTIC TREATMENT

Overall, at diagnosis in NL vs BE 72.1% vs 14.6% received VKA and 17.8% vs 65.5% NOAC, which varied significantly across time (Figure 1). At diagnosis in the most recent cohort in NL (N=158) and BE (N=406), 33.5% vs 7.7% were treated with VKA, 62.0% vs 76.9% with NOAC, 2.5% vs 6.5% with antiplatelet monotherapy and 1.9% vs 9.0% with no antithrombotic therapy. Overall in NL and BE, antiplatelet therapy was used on top of OAC in 13.4% vs 14.8% of patients, respectively.

Figure 1 NOAC and VKA treatment distribution by year of enrolment and country

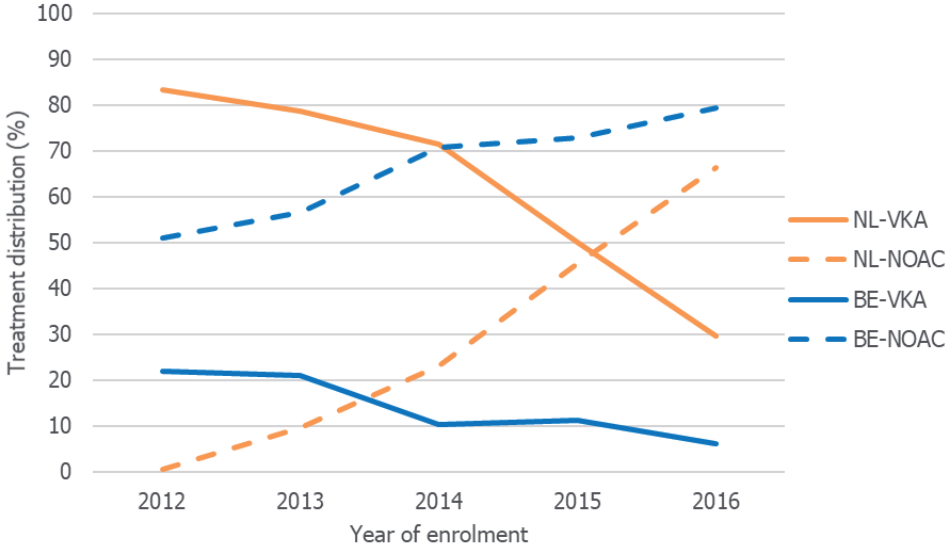
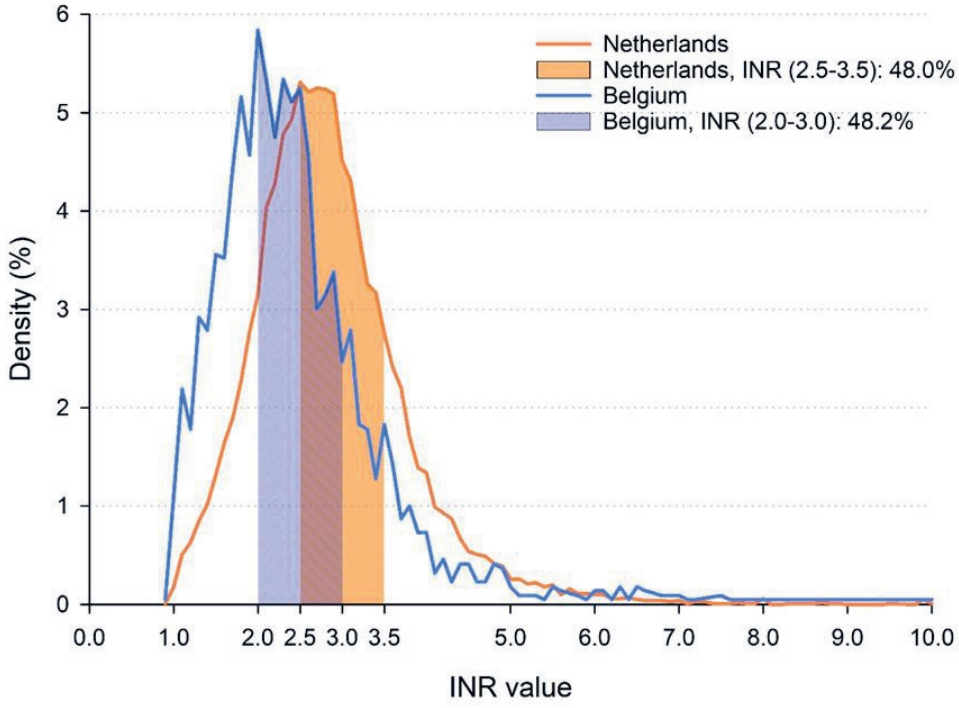


Figure 2 The distribution of all INR values for the Netherlands and Belgium. Percentage of INR values in their respective target range are displayed by country.



During the first two years of follow-up from all cohorts, mean INR was significantly higher in NL (2.9±1.0 vs 2.4±1.0) compared to BE. Of all INR values recorded in NL and BE, 35.0% vs 19.7% were above 3.0, 51.9% vs 48.2% between 2.0-3.0 and 13.1% vs 32.1% below 2.0 (Figure 2 and Table 2). Mean TTR in NL (range 2.0-3.5 before 2016 and 2.0-3.0 as of 2016) and BE (range 2.0-3.0) was 75.5±14.9 and 48.7±23.8, respectively (Table 2). The proportion of patients with a TTR ≥65% was 79.4% and 28.9% in NL and BE, respectively. Density plots of TTR for NL and BE are displayed in Figure 3 and 4.

Table 2 INR and TTR distribution by country

	Netherlands (N=705)	Belgium (N=121)
TTR INR method 1[a]	75.5±14.9	48.7±23.8
≥65	79.4%	28.9%
TTR INR method 2[b]	55.4±16.9	48.7±23.8
≥65	28.2%	28.9%
INR	2.9±1.0	2.4±1.0
<2.0	13.1%	32.1%
<2.5	34.3%	58.5%
2.0-3.0	51.9%	48.2%
2.5-3.5	48.0%	31.3%
2.0-3.5	69.2%	57.7%
>3.0	35.0%	19.7%
>3.5	17.7%	10.2%

Only cases with at least one INR measurement were analysed. All INR measurements were treated independently. Categorical data is presented in % and continuous data in mean ± standard deviation. [a]Method 1: For BE TTR was calculated using an INR range of 2.0-3.0 and for NL TTR was calculated using INR range of 2.0-3.5 for INR values before January 1st 2016, and 2.0-3.0 hereafter. [b]Method 2: For both countries TTR was calculated using INR range of 2.0-3.0. *INR* International normalized ratio; *TTR* Time in therapeutic range.

Figure 3 Kernel-smoothed density of TTR (INR range 2.0-3.0) by country

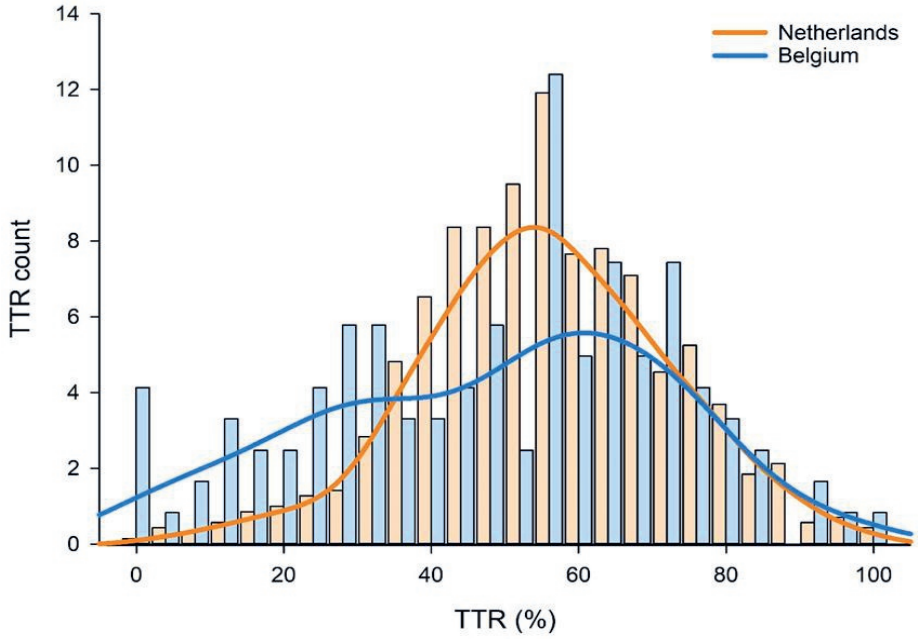
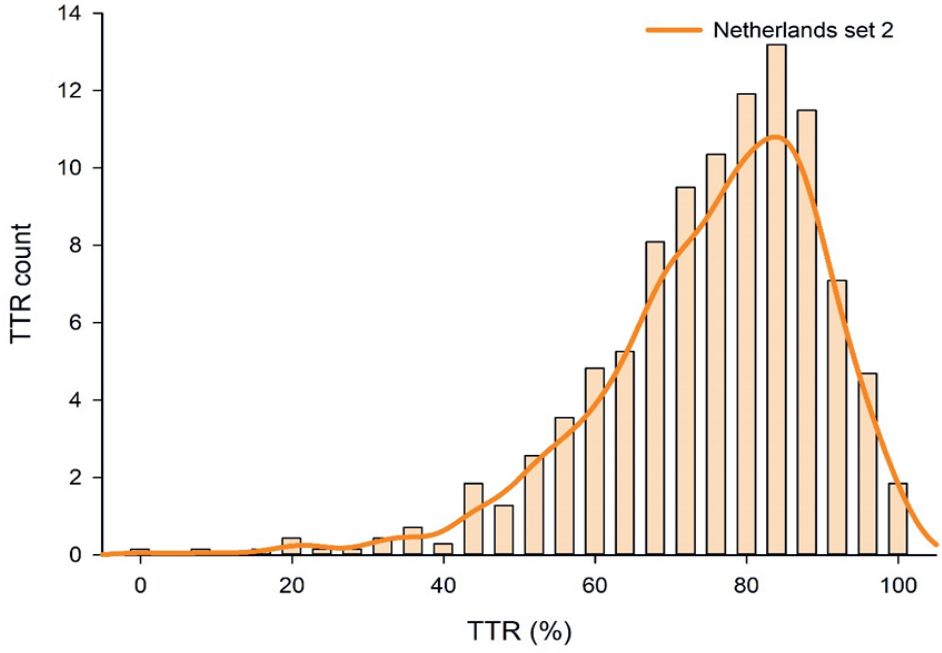


Figure 4 Kernel-smoothed density of TTR (INR range 2.0-3.5) for the Netherlands



OUTCOMES

Overall, event rates per 100 patient-years in NL vs BE of all-cause mortality (3.38 vs 3.90; HR 0.86 95%-CI 0.65-1.15), ischemic stroke/TE (0.82 vs 0.72; HR 1.14 95%-CI 0.62-2.11) and major bleeding (2.06 vs 1.54; HR 1.33 95%-CI 0.89-1.99) were not significantly different (Table 3). Moreover, there were no statistically significant differences between NL and BE in the rates of cardiovascular mortality (0.95 vs 1.05; HR 0.89 95%-CI 0.52-1.54), non-cardiovascular mortality (1.53 vs 2.17; HR 0.71 95%-CI 0.47-1.06), or CRNMB (2.13 vs 1.80; HR 1.18 95%-CI 0.80-1.74). In NOACs vs VKAs, the rates of major bleeding (1.31; 95%-CI 0.93-1.85 vs 2.10; 95%-CI 1.56-2.85) and CRNMB (1.68; 95%-CI 1.24-2.27 vs 2.38; 95%-CI 1.79-3.17) were non-significantly lower with NOACs in comparison to VKAs, respectively (online: Table S1 & S2).

Table 3 Unadjusted event rates per 100 person-years by country

Outcome	Netherlands (N=1186)	Belgium (N=1705)	Hazard Ratio (95%-CI)
All-cause mortality	3.38 (2.70-4.24)	3.90 (3.28-4.65)	0.86 (0.65-1.15)
Cardiovascular	0.95 (0.62-1.45)	1.05 (0.75-1.47)	0.89 (0.52-1.54)
Non-cardiovascular	1.53 (1.10-2.15)	2.17 (1.71-2.74)	0.71 (0.47-1.06)
Undetermined	0.90 (0.58-1.40)	0.68 (0.45-1.03)	1.33 (0.72-2.43)
Ischemic stroke/TE	0.82 (0.51-1.30)	0.72 (0.48-1.08)	1.14 (0.62-2.11)
Major bleeding	2.06 (1.54-2.76)	1.54 (1.16-2.04)	1.33 (0.89-1.99)
Intracranial bleeding	0.41 (0.21-0.78)	0.25 (0.12-0.50)	-
CRNMB	2.13 (1.59-2.84)	1.80 (1.39-2.33)	1.18 (0.80-1.74)

Data are displayed as event rates per 100 person-years and unadjusted hazard ratios with 95%-confidence intervals. No hazard ratio for intracranial bleeding was calculated due to low number of events. *CRNMB* Clinically relevant non-major bleeding; *TE* Thromboembolism.

DISCUSSION

The GARFIELD-AF registry is the largest, prospective registry of patients with newly diagnosed AF in NL and BE to date, which included 1186 and 1705 patients, respectively. This report provides a unique comparison between outcome rates in AF, since AF patient characteristics between the Netherlands and Belgium are quite similar, while OAC management strategy in terms of target INR range and OAC preference differed greatly. Despite the above-mentioned differences in treatment strategy, rates of all-cause mortality (HR 0.86; 95%-CI 0.65-1.15), stroke/TE (HR 1.14; 95%-CI 0.62-2.11) and CRNMB (HR 1.18; 95%-CI 0.80-1.74) did not differ significantly between NL and BE. Although the rate of major bleeding was 33% higher in the Netherlands (HR 1.33; 95%-CI 0.89-1.99), the difference was not statistically significant, albeit the number of events were low.

In this study, the rates of major bleeding and stroke/TE were comparable to previous nationwide AF studies, although mortality rates vary. The XANTUS registry, a prospective registry of rivaroxaban in AF, enrolled 899 patients between 2012-2013 in NL.[12] Event rates per 100 patient-years of major bleeding and thromboembolism were 2.4 (95%-CI 1.4-3.7) and 1.6 (95%-CI 0.9-2.8), respectively. The rate of all-cause mortality was lower in XANTUS (1.0; 95%-CI 0.4-2.0), which is likely due to a younger population with fewer comorbidities in XANTUS. A Dutch study which compared dabigatran with acenocoumarol included 920 AF patients between 2010-2013.[13] This study reported event rates of dabigatran vs acenocoumarol for major bleeding of 2.1%/year (95%-CI 1.0-3.8) vs 4.3%/year (95%-CI 2.9-6.2), for stroke/TE 0.8%/year (95%-CI 0.2-2.1) vs 1.0%/year (95%-CI 0.4-2.1) and for all-cause mortality 2.0%/year vs 1.6%/year. A prospective registry in older patients from general practice offices in NL reported on 2068 AF-patients on OAC (97% VKA, 3% dabigatran) between 2013-2014.[14] Event rates per 100 patient-years of mortality was higher (6.7), while stroke (1.7), major bleeding (1.7) and CRNMB (2.7) seemed similar, although no CIs were reported. Stroke and bleeding rates from The Belgian Improvement Study on OAC Therapy were higher (4.9 and 5.9, respectively). However, patients for any OAC indication were enrolled and the study dates back to 2005.[15]

Patients in NL and BE had overall relatively similar characteristics, with a similar predicted stroke and bleeding risk (Table 1). In NL, patients on VKA in GARFIELD-AF were treated using target INR range 2.5-3.5 until January 2016 and 2.0-3.0 hereafter, the latter being equivalent to practice in Belgium and worldwide. This difference in practice is reflected by a significantly higher mean INR (2.9±1.0 vs 2.4±1.0) in NL in this study. It was Dutch practice for years to target a higher INR range, which was hypothesized to provide a net clinical benefit since the rate of ischemic stroke increases sharply when INR drops below 2.0, while (intracranial)

bleeding risk seems to remain quite similar with INR 3.0-3.5 vs 2.0-3.0.[16-18] However, randomized study data hereon has always been lacking. Indeed, in this study the proportion of INR measurements below 2.0 is far lower (13.1% vs 32.1%) in NL vs BE, with the counter effect of more INR measurements above 3.0 (35.0% vs 19.7%) and 3.5 (17.7% vs 10.2%) (Table 2). Despite this difference in VKA intensity, no significant difference in rates of ischemic stroke/TE, bleeding and mortality were observed between BE and NL. These results should be interpreted with caution, as differences in the proportion of NOAC vs VKA users, but also differences in VKAs used between countries could influence results. Given the low proportion of VKA use in Belgium, there were too few Belgian VKA patients with an adverse event to be able to adjust for confounders for this comparison.

As reflected in Figure 1, the proportion of patients on NOAC therapy was much higher in BE, but the difference diminished significantly as the years progressed. In the most recent cohort in NL and BE, 33.5% vs 7.7% were treated with VKA and 62.0% vs 76.9% with NOAC, respectively. When the NOACs were introduced in NL, discussion arose around the safety of these agents for usage in daily practice.[3,19] One of the concerns was a lack of monitoring for therapy adherence or side-effects with NOACs, especially given the high mean time in therapeutic ranges (TTR) as an indicator for therapy adherence and low bleeding rates already being achieved by the specialized Dutch anticoagulation clinics.[20] This, combined with a lack of real-world data, resulted in a careful introduction of NOACs in NL, as seen in this study. Moreover, until 2016 NOACs could only be prescribed by cardiologists and the drugs were only reimbursed with a physician's statement form. As of 2016, Dutch GPs were allowed to prescribe NOACs, and as of 2018, all NOACs were reimbursed without the need of a physician's statement form. In BE, patients on VKA are treated and monitored mainly by GPs and NOACs were adopted very early. BE entered the GARFIELD-AF registry from cohort 2, which coincided with reimbursement of the first available NOAC dabigatran. Furthermore, NOACs were made available to cardiologists (who included most GARFIELD-AF patients) the year before by means of so-called 'compassionate use and medical need' programs.[4] These programs allow the use of drugs with an approved European indication although not yet commercially available. So, Belgian physicians were already familiar with the use of these drugs.

However, since then there is robust evidence showing the safety of these agents in the real-world, although issues such as medication adherence and off-label dosing persist.[21] Also, NOACs have proven to be a cost-effective alternative to VKAs.[22] Since NOACs reduce ischemic stroke rate by 20% and intracranial bleeding rate by 50% in comparison to warfarin, one could hypothesize that a faster NOAC uptake could have prevented more adverse events.[23] When comparing patients on NOAC vs VKA

in the combined NL-BE cohort, the rate of major bleeding per 100 patient-years (1.3; 95%-CI 0.9-1.9 vs 2.1; 95%-CI 1.6-2.9) and CRNMB (1.7; 95%-CI 1.2-2.3 vs 2.4; 95%-CI 1.8-3.2) were lower with NOACs, although non-significant, respectively (Supplementary tables S1 & S2). This could be an explanation for the non-significantly 33% higher major bleeding rate in the Netherlands, although event rates were too low for a reliable adjustment for possible confounders.

STRENGTHS AND LIMITATIONS

A strength of this study is that all patients were newly diagnosed with AF, so differences in patient experience with OAC use were minimal. Moreover, we compared the largest NL and BE AF cohorts to date. However, the comparison was underpowered to detect small differences in absolute adverse event rates. Also, confounding could have played an important role concerning event rates, although no event rates were significantly different when comparing NL to BE.

CONCLUSION

In GARFIELD-AF, despite similar characteristics, patients were treated differently in NL and BE with predominantly VKA vs NOAC and a higher target INR range in NL, respectively. Although the rate of major bleeding was 33% higher in NL, variations in bleeding, mortality and stroke/TE rates were not statistically significant.

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CHAPTER 7

When to withhold oral anticoagulation in atrial fibrillation: an overview of frequent clinical discussion topics

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ABSTRACT

Stroke prevention with oral anticoagulants in patients with atrial fibrillation predisposes for bleeding. As a result, in select patient groups anticoagulation is withheld because of a perceived unfavourable risk-benefit ratio. Reasons for withholding anticoagulation can vary greatly between clinicians, often leading to discussion in daily clinical practice on the best approach. To guide clinical decision making, we have reviewed available evidence on the most frequently reported reasons of withholding anticoagulation: previous bleeding, frailty and age, and an overall high bleeding risk.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with heart failure, mortality and ischemic stroke.[1] Stroke prevention with anticoagulants predisposes AF-patients for bleeding. As a result, in select patient groups anticoagulation is withheld because of a perceived unfavourable risk-benefit ratio.[2-4] However, these choices cannot always be justified based on available evidence.

With an aging population, AF is becoming even more prevalent. Decision making concerning withholding or (re-)initiating anticoagulation is a growing challenge for physicians.[5] In parallel, AF patients are likely to have more comorbidities, and consequently are at higher risk of both stroke and bleeding.[6,7] Increasingly common factors such as previous bleeding, frailty and an overall high bleeding risk are amongst the most frequently reported reasons of withholding anticoagulation.[2,8]

In this review, evidence and gaps in current knowledge of the benefits and risks of anticoagulation in AF are discussed, with a focus on high bleeding risk, previous bleeding and frailty.

ANTICOAGULATION AND HIGH BLEEDING RISK

Due to an increase in comorbidities, patients with AF will more often be at an increased bleeding risk. Decision making regarding anticoagulation can be particularly challenging in these patients, especially when both stroke and bleeding risk are high.[2,9] Oral anticoagulants (OAC) used for stroke prevention in AF are vitamin K antagonists (VKA), such as warfarin, or the non-vitamin K oral anticoagulants (NOAC) dabigatran, rivaroxaban, apixaban and edoxaban.[1] As described below, available evidence suggests the clinical benefit of anticoagulation is higher than is often perceived.

In patients with a CHA_2DS_2-VASc stroke risk score of ≥ 2 (male) or ≥ 3 (female), anticoagulation is indicated by current AF-guidelines, and it should be considered in patients with a CHA_2DS_2-VASc of 1 (male) or 2 (female).[1,10] In the GARFIELD-AF registry, 30% of patients with CHA_2DS_2-VASc ≥ 2 were not treated with oral anticoagulation (OAC).[2] The strongest predictors for withholding OAC were concomitant antiplatelet therapy (odds ratio (OR) 15.0 [95% confidence interval (CI) 14.1 - 15.8]) and a history of bleeding (OR 2.5 [95% CI 2.2 - 3.0]).[2] Compared to patients on OAC, patients withheld from OAC had an increased risk of all-cause mortality (5.3% vs 3.9%, $p < 0.001$), ischemic stroke or systemic embolism (1.6% vs 1.1%, $p < 0.001$), but a decreased risk of major bleeding (0.5% vs 0.8%, $p < 0.001$). Data from the NCDR PINNACLE, a prospective United States based registry focusing on quality-improvement, showed an even higher proportion of 42% of

patients with CHA_2DS_2-VASc ≥ 2 not treated with OAC.[11] In a multivariable model, lower CHA_2DS_2-VASc scores and higher HAS-BLED scores were both associated with OAC non-prescription.[11,12] Similar observations were derived from German insurance databases, where 40.5% to 48.7% of AF-patients were classified as 'definite OAC under-use'.[13]

A Spanish, prospective, observational study in 1361 AF patients with stable anticoagulation control with VKA observed an annual cessation rate of 1.54%/year.[14] In 80% of them, OAC was stopped because of a major bleeding or at the healthcare providers' discretion. Cox regression analysis showed that the occurrence of major bleeding, heart failure, cancer or renal impairment during follow-up were all independently associated with early OAC cessation. The authors conclude that many factors associated with bleeding also predispose to OAC cessation. OAC cessation, however, was associated with an increase in ischemic stroke (Hazard Ratio (HR) 1.85 [95% CI 1.17 - 2.94]) and all-cause mortality (HR 1.30 [95% CI 1.02 - 1.67]).

In a Dutch retrospective study, 45 out of 89 patients (51%) with a history of AF and admitted with a first ischemic stroke, were insufficiently anticoagulated prior to their stroke.[15] Taken into consideration the increased occurrence of intracranial haemorrhage (ICH) as a result of increased OAC use, strict adherence to AF-guidelines could have prevented an estimated 20 out of 89 (22%) ischemic strokes. In the Registry of the Canadian Stroke Network, 90% of the 597 patients admitted with ischemic stroke and known AF with increased stroke risk, were not therapeutically anticoagulated, or not anticoagulated at all.[16] These data demonstrate the perceived difficulties of real-world anticoagulation management, and the importance of good anticoagulation control. Thus, it is of utmost importance to know in which high risk patient OAC can still safely be prescribed.

To reduce AF-related events, more frequent monitoring of high bleeding risk patients for presence of lower haemoglobin levels and/or active (minor) bleeding, changes in renal function, therapy adherence, and modifiable stroke and/or bleeding risk factors, such as hypertension or alcohol abuse, is likely to result in safer OAC use.[1] The use of accurate bleeding prediction models could diminish under- or overtreatment with OAC in AF. Unfortunately, bleeding prediction has been shown difficult. Over the years, multiple bleeding risk scores, such as the HAS-BLED, ATRIA, GARFIELD-AF risk tool or $HEMORR_2HAGES$, have been developed to help clinical decision making.[12,17-19] However, these risk scores have only moderate predictive accuracy, especially in the elderly.[20] Further complicating matters is the fact that an increased bleeding risk is correlated with an increased stroke risk, since strong bleeding risk factors such as increasing age, vascular disease or prior stroke are the most important risk factors for ischemic stroke.[21-23]

In an effort to improve the prediction of bleeding, the ABC-bleeding risk score (Age, Biomarkers (high-sensitive troponin T, GDF-15, and haemoglobin), Clinical history) has been developed, which had a only slightly higher c-statistic (0.68 [95% CI 0.66 - 0.70]) than the HAS-BLED (0.61 [95% CI 0.59 - 0.63]) or the ORBIT score (0.65 [95% CI 0.62 - 0.67]).[24,25] Since the ABC-bleeding risk scores requires the assessment of GDF-15, a cytokine which is upregulated in conditions of systemic inflammation or oxidative stress, the score is currently not implemented in daily clinical practice.[26] An interesting aspect of GDF-15 is that increased levels are not associated with an increased risk of stroke, while it is strongly predictive of bleeding.[27] It will be interesting to see if GDF-15, and perhaps other biomarkers, can guide clinicians with decision making on anticoagulation (re-)initiation.

MANAGEMENT OF PATIENTS WITH A HIGH BLEEDING RISK

Several studies have focused on the question whether AF-patients with a high bleeding risk are better off when OAC is withheld. However, based on current literature, anticoagulation is especially important in patients at a very high stroke risk, regardless of HAS-BLED scores.

To assess the benefit of OAC in AF, a Net Clinical Benefit (NCB) using the method of Singer et al is often calculated: NCB = (ischemic stroke$_{\text{off OAC}}$ – ischemic stroke$_{\text{on OAC}}$) - 1.5 * (intracranial haemorrhage rate$_{\text{on OAC}}$ – intracranial haemorrhage$_{\text{off OAC}}$), in which the factor -1.5 is to compensate for the often greater clinical impact of intracranial bleeding.[28] A NCB > 0 indicates that the benefit of less ischemic stroke with OAC outweighs the risk of ICH. A NCB for warfarin was calculated for each CHA_2DS_2-VASc score in a large Swedish study of 182,678 patients with AF.[29] For CHA_2DS_2-VASc 0 (i.e. male without risk factor), there was no net clinical benefit of warfarin treatment (NCB 0.0 [95% CI -0.1 - 0.1]). In patients with CHA_2DS_2-VASc ≥ 1, a positive NCB was observed. The NCB was highest in the patients at the highest risk of stroke, regardless of HAS-BLED scores. Similar results were seen in a large Danish study, where VKA (with or without aspirin) versus no antithrombotic treatment had a positive NCB in patients with a CHA_2DS_2-VASc ≥ 2.[30] The NCB with VKA was greater in patients with HAS-BLED ≥ 3 versus HAS-BLED < 3 on VKA (NCB 2.21 [95% CI 1.93 - 2.50] versus NCB 1.19 [95% CI 1.07 - 1.32]), and VKA + aspirin (NCB 1.97 [95% CI 1.62 - 2.32] versus 0.81 [95% CI 0.56 - 1.07]), respectively.[30] High bleeding risk and high ischemic stroke risk are positively correlated. In individuals with a high bleeding risk, the risk reduction of ischemic stroke with OAC supersedes the small increase in risk of ICH.[30] In a different Danish study, the NCB was calculated for warfarin, dabigatran, rivaroxaban and apixaban versus no anticoagulation.[31] A positive NCB was observed in both VKA or NOAC treated patients

with CHA_2DS_2-VASc ≥ 2. The NCB was even greater in the subgroup of patients with HAS-BLED ≥ 3, irrespective of treatment with VKA or NOAC.

However, there are some limitations to these studies. Confounding by indication could have played an important role in these analyses, as patients on different anticoagulation strategies may differ in terms of stroke and bleeding risk, possibly overestimating NCB counts.[29,30,32] Furthermore, non-intracranial major or non-major clinically relevant bleeding are not a part of the used NCB formula, although they often play an important role in clinical decision making. However, despite these limitations, the evidence for prescribing OAC despite high bleeding risk remains strong.

The treatment of high-risk patients should not only focus on the antithrombotic strategy, but also on reducing the risk of bleeding. A flow chart to help reduce bleeding risk is shown in Table 1. Although many important bleeding risk factors are non-modifiable, treatment should focus on currently known modifiable risk factors for bleeding, including hypertension, labile INR, concomitant drug-use, including over the counter drugs like nonsteroidal anti-inflammatory drugs (NSAID), and alcohol abuse.[1] A systolic blood pressure of > 140 mmHg is associated with an increased bleeding risk, and adequate blood pressure control is therefore recommended to reduce bleeding risk.[1,33] In patients with labile INR, switching to a NOAC should be considered.[1] The concomitant use of antiplatelet drugs, NSAIDs and drugs inhibiting OAC metabolism can strongly increase bleeding risk, and therefore their use should be avoided if possible.[34-39] Drugs affecting metabolism and increasing bleeding risk in NOACs are primarily P-gp and CYP3A4 inhibitors, and in VKA primarily CYP2C9 and CYP3A4 inhibitors.[40] Alcohol abuse (i.e. ≥ 8 units/week) shows conflicting results regarding bleeding risk.[12,21,41] However, suspected heavy drinking is an important reason for clinicians to withhold OAC.[2] Since alcohol abuse is also associated with an increased risk of stroke in AF patients and medication non-adherence, addressing a patients' alcohol usage is nonetheless an important element of the management of AF patients.[21,33,42] However, there is no substantial evidence to withhold OAC in alcohol abusers without significant hepatic impairment.

In patients at risk for gastro-intestinal (GI) bleeding, proton pump inhibitors (PPI) can be prescribed to reduce bleeding risk. In a retrospective cohort study in Medicare beneficiaries treated with either apixaban, rivaroxaban, dabigatran or warfarin, PPI co-therapy was associated with a lower risk of hospitalization for upper GI-bleeding.[43,44] Only in patients categorized in the lowest GI-bleeding risk decile, no protective effect of PPI therapy was observed.[44]

Table 1 Flow chart to help reduce bleeding risk in high-risk AF patients

1.	**Estimate benefit of OAC**	
	Assess stroke risk (e.g. CHA_2DS_2-VASc)	
	Identify known bleeding risk factors (e.g. anaemia, age, previous bleeding, impaired renal function, etc.)	
2.	**Treatment plan**	
	Treat modifiable risk factors:	
	Hypertension	Aim for < 140 mmHg systolic blood pressure if tolerated
	Heavy alcohol use (≥ 8 units/week)	Discourage use of alcohol
	Labile INR (Time in Therapeutic Range (TTR) < 60%)	Consider switch to NOAC In case of VKA preference: more frequent monitoring switch to longer acting VKA
	NSAIDs, strong P-gp inhibitors, or antiplatelet therapy.	Avoid these medications if possible. Consider switch to an alternative treatment. In case of antiplatelet therapy, consider switch from VKA to NOAC.
	Consider co-treatment with PPI, in:	
	History of GI-bleeding or ulcer	
	Malignancy	
	Concomitant antiplatelet therapy or NSAIDs	
3.	**Monitoring plan**	
	Assess haemoglobin levels and renal function at least yearly	
	Stimulate and monitor therapy adherence	
	Actively ask for (minor) bleeding	

AF Atrial fibrillation; *OAC* Oral anticoagulation; *INR* International normalized ratio; *VKA* Vitamin K Antagonist; *NOAC* Non-VKA oral anticoagulant; *NSAID* Non-steroidal anti-inflammatory drug; *PPI* proton pump inhibitor.

Current guidelines recommend that in patients with an elevated GI-bleeding risk PPI should be considered, specifically in patients with a history of GI-bleeding or ulcer, malignancy, or concomitant antiplatelet therapy.[9]

Combined use of antiplatelet drugs and anticoagulants strongly increases bleeding risk, and is a frequently observed reason for withholding OAC.[2,11,38,39] In comparison to VKA monotherapy, single antiplatelet therapy in addition to VKA or NOAC had a HR for major bleeding of 1.82 (95% CI 1.76 - 1.89) and 1.28 (95% CI 1.13 - 1.44), respectively.[39] Concomitant dual antiplatelet therapy with a NOAC or VKA was associated with a 1.2-3.9-fold and 2.4-5.4-fold higher risk of major bleeding, respectively.[39] In a meta-analysis only including patients on low-dose aspirin from the pivotal NOAC trials, rates of stroke or systemic embolism were lower with NOACs (HR 0.78 [95% CI 0.67 - 0.91]), in comparison to VKAs.[45] The rates of major bleeding were similar (HR 0.83 [95% CI 0.69 - 1.01]). The rates of ICH were lower (HR 0.38 [95% CI 0.26 - 0.56]). The results from these studies suggest NOACs may be both safer and more effective than VKAs in patients on concomitant antiplatelet therapy. There have only been head-to-head studies between NOAC or VKA and concomitant antiplatelet use in patients after a recent percutaneous coronary intervention (PCI). The WOEST, PIONEER-AF PCI, RE-DUAL PCI and AUGUSTUS trials all showed less bleeding with dual therapy (NOAC or VKA with a $P2Y_{12}$ inhibitor) compared to triple therapy (dual therapy plus aspirin), with no significant difference in efficacy.[46-49] However, these individual trials were not powered for the efficacy endpoints. A meta-analysis of the WOEST, PIONEER-AF PCI and RE-DUAL PCI trials suggests the incidence of ischemic events with dual therapy versus triple therapy is equally low.[50] The current guidelines provide a good overview and recommend an individualized approach of triple therapy duration based on bleeding and atherothrombotic risk with the aim to keep triple therapy duration as short as possible.[9] The optimal antithrombotic regimen beyond 1 year remains undefined in these patients, but will also importantly depend on risks factors for bleeding.

Although the far majority of AF-patients with increased stroke risk will benefit from OAC, the risks can outweigh the benefits in some patients (e.g. patients with a non-treatable cause of (recurrent) major bleeding).[9] In these patients, a left atrial appendage (LAA) occluding device or surgical LAA occlusion may be considered according to current guidelines (class of recommendation IIb, level of evidence C).[1] The ASAP study included AF-patients with $CHADS_2 \geq 1$ and a contraindication for OAC (in 93%: history or tendency of bleeding), in which a LAA occluding device (Watchman) was implanted.[51] After implantation, patients received 6 months of clopidogrel or ticlopidine, and lifelong aspirin. Ischemic stroke rate (1.7%/year) was significantly lower than expected based on the predicted stroke risk of the cohort (7.3%/year). The EWOLUTION trial was a nonrandomized, prospective cohort study

in which 1020 patients with a Watchman device were enrolled.[52] In this study, 72.2% of patients had a reported contraindication for OAC. The observed ischemic stroke rate was 1.3 (95% CI 0.8 - 1.9) per 100 patient-years, which was 83% lower than predicted based on historical data using the CHA_2DS_2-VASc score. In patients with a previous major bleeding specifically, the risk reduction was similar at 85% (observed risk: 1.2 [95% CI 0.4 - 2.5]). Unfortunately, there are no randomized data available on LAA occlusion in patients with a contraindication for OAC. However, based on available evidence, LAA occlusion seems to be a safe and effective strategy in patients with a contraindication for OAC.[53]

(RE-)INITIATION OF ANTICOAGULATION AFTER BLEEDING

One of the most frequently reported reasons to withhold anticoagulation is a history of bleeding, especially a history of ICH.[2,3,14,54] Nevertheless, available data indicate a benefit of OAC resumption in patients with AF and a prior major bleeding.

Recently, a meta-analysis was published comprising 5685 AF patients that experienced a major bleeding.[55] In comparison with the withholding of OAC after the index bleeding, OAC restarters had a 46% relative risk reduction of any thromboembolic event, and a 10.8% absolute risk reduction for all-cause mortality.[55] Restarting OAC was associated with an increased risk of a recurrent major bleeding (OR 1.85), although no increased risk of recurrence of the index bleeding event (i.e. ICH or GI-bleeding) was observed. Net clinical benefit analysis, including thromboembolic events, major bleeding and all-cause mortality, demonstrated that restarting OAC was associated with a clinical advantage (NCB 0.11 [95% CI 0.09 - 0.14]).[55] An important limitation, however, is that all included studies were observational, and selection bias in these studies is possible.[56] Furthermore, only one study included patients with a history of 'any major bleeding', whereas the other 6 studies solely focused on either ICH or GI-bleeding. Therefore, these results should be interpreted with caution.

A retrospective analysis of insurance data showed a lower combined risk of ischemic stroke and all-cause mortality with resumption of warfarin (HR 0.76 [95% CI 0.59 - 0.97]) or dabigatran (HR 0.66 [95% CI 0.44 - 0.99]).[57] In comparison to no re-initiation, warfarin resumption had an increased risk of major bleeding (HR 1.56 [95% CI 1.10 - 2.22]), whereas dabigatran resumption was not significantly associated with major bleeding (HR 0.65 [95% CI 0.32 - 1.33]). The risk-benefit ratio was therefore higher for dabigatran than for warfarin. Careful interpretation of these results are warranted, as differences in time to resumption, dosing (75mg dose was initiated in 9.6% of dabigatran users), switching, and discontinuation

between warfarin or dabigatran treated patients could have strongly influenced outcomes.[56]

In patients with a history of ICH and AF, an increasing body of evidence shows the benefits of OAC resumption. However, there is substantial controversy regarding the optimal time period for re-initiation.[58-60] A pooled analysis of the retrospective AF studies of Kuramatsu et al and Nielsen et al showed that OAC restarters had a lower rate of any thromboembolic event (HR 0.45 [95% CI 0.26 - 0.78]), and that OAC resumption was not significantly associated with recurrent major bleeding (HR 1.65 [95% CI 0.97 - 2.79]).[55,61,62] In a model with any thromboembolic event, major bleeding and all-cause mortality, OAC resumption after ICH resulted in a positive NCB.[55] A meta-analysis from 8 studies with a retrospective design comprised of 5306 patients hospitalized for anticoagulation-associated ICH for any indication.[63] The re-initiation of OAC resulted in a lower risk of thromboembolic events (Relative Risk (RR) 0.34 [95% CI 0.25 - 0.45]), without an increase in recurrent ICH (RR 1.01 [95% CI 0.58 - 1.77]).[63] Not only a lower risk of thromboembolism has been observed, but also an improvement in functional recovery of OAC resumption in ICH survivors. A pooled analysis of 3 prospective studies in 941 AF patients showed that anticoagulation resumption was associated with improved functional recovery at 1-year post ICH (OR 1.89 [95% CI 1.32 - 2.70]).[64] Although there is good evidence in favour of VKA resumption from observational studies, data on NOAC resumption after recent ICH are very limited.[65,66] Data from randomized controlled trials are not available. APACHE-AF is an ongoing trial focusing on the safety and efficacy of full-dose apixaban versus antiplatelet drugs or no antithrombotic therapy after recent ICH in AF.[67] SoSTART is an ongoing trial with a similar design, but the choice of OAC is left to the physician: dabigatran, rivaroxaban, apixaban, edoxaban, warfarin, phenindione or acenocoumarol.[68]

Overall, (re-)initiation of OAC in AF-patients after a major bleeding seems to be beneficial. However, it is unclear what the optimal moment for (re-)starting OAC therapy is. In a retrospective assessment of insurance data, 1329 patients with AF, a major GI-bleeding, and an interruption of warfarin for 48 hours were included. [69] Warfarin restarters had a reduced risk of thromboembolism (HR 0.71 [95% CI 0.54 - 0.93]) and all-cause mortality (HR 0.67 [95% CI 0.56 - 0.81]), compared to non-restarters. Both groups had a comparable risk of recurrent GI-bleeding. Compared to restarting warfarin after 30 days after GI-bleeding, an early restart within 7, 7 - 15, 15 - 21, or 21 - 30 days was not associated with a decreased thromboembolic risk. In contrast, restarting warfarin within 7, 7 - 15, or 15 - 21 days was associated with a decreased all-cause mortality risk. Careful interpretation of these results is warranted, as it is likely that the different groups analysed had different risks of rebleeding and thromboembolism, given the high probability of selection bias.

Moreover, in this study, restarting warfarin within 7 days was associated with an increased risk of recurrent GI-bleeding, compared to restarting after 30 days.[69] A retrospective study using administrative and clinical databases showed that a restart of warfarin, which was after a median of 4 days (95% CI 2 - 9), was not related with a recurrence of GI-bleeding.[70] However, when a restart within 1 - 7 days was compared with > 7 days, the rate of recurrent GI-bleeding was increased significantly (12.4% and 6.23%, respectively).[70] In a prospective study of 197 patients hospitalized for GI-bleeding, it was observed that warfarin resumption after a median of 5 days resulted in lower thromboembolic events (HR 0.12 [95% CI 0.006 - 0.81]), without increasing the risk of GI-bleeding recurrence (HR 2.17 [95% CI 0.86 - 6.67]).[71,72] All-cause mortality within 90 days after hospital discharge was similar between restarters and non-restarters (HR 0.63 [95% CI 0.22 - 1.89]).Therefore, it has previously been suggested that warfarin resumption can be considered as early as 7 - 14 days after GI-bleeding.[73] Since data is lacking on the timing of NOAC resumption after GI-bleeding, the authors advised to apply data for warfarin resumption with caution, because of the faster therapeutic onset of NOACs.[73]

In patients with ICH, 'early resumption' (within 2 weeks) of OAC therapy in patients with a high risk of thromboembolism, and 'late resumption' (after 4 weeks) in patients with a high risk of ICH, has been suggested.[60] The most recent European Heart Rhythm Association (EHRA) guidelines recommend that OAC may be restarted after 4 - 8 weeks after ICH, if the risk of thromboembolism is high and the risk of recurrent ICH is low.[9] In general, the optimal timing of resumption after ICH is still largely unknown, and is dependent on many factors. OAC should not be restarted in patients with cerebral amyloid angiopathy, because of the high recurrent ICH risk.[9] In other situations, decision making is more difficult and should therefore be decided in a multidisciplinary team.[1,60] For example, lobar bleeding, cerebral microbleeds, a non-traumatic origin, cerebral aneurysm or lacunar infarcts are associated with an increased risk of recurrent ICH, while a deep cortical bleed has a relatively low recurrence risk.[60] As data are limited, further research from preferably randomized controlled trials is essential.

ANTICOAGULATION AND FRAILTY

Frailty has been defined as a syndrome of increased aging-associated vulnerability, resulting in a compromised ability to cope with stressors.[74] With aging of the population, the incidence of both frailty and AF increases drastically, and is likely to result in an increased incidence of ischemic stroke.[9] It is however problematic that multiple reports have shown a 50% lower prescription rate in frail AF-patients, compared to non-frail patients.[75,76] In a questionnaire distributed amongst treating

physicians of AF-patients from nursing homes in France, recurrent falls (47%) and cognitive impairment (22%) were the most common reasons for withholding OAC.[4] Other studies also found an (excessive) fall risk as an important reason for OAC non-prescription.[8,77] However, an increasing body of evidence suggests that oral anticoagulation should not be withheld based on frailty solely.

A recent prospective study in hospitalized, elderly AF patients in Spain showed that amongst patients with anticoagulation, the incidence of ischemic stroke (2.7% versus 3.2%, p = 0.79) and major bleeding (7.5% versus 8.1%, p = 0.84) were similar between frail and non-frail patients at 1-year follow-up, respectively.[78]

Fall risk is an important parameter of frailty. A history of falls or an increased fall risk is associated with all-cause mortality, ischemic stroke and bleeding.[79-81] However, conflicting results have been published on the risk of the most feared complication of anticoagulation in patients with frailty: (traumatic) ICH.[79-82] In a retrospective study in AF patients anticoagulated with warfarin, the incidence rate per 100 patient-years of traumatic ICH was 2.0 (95% CI 1.3 - 3.1)) in high fall risk AF patients, and 0.34 (95% CI 0.27 - 0.45) in other patients.[82] In a post-hoc analysis of the ARISTOTLE trial, a history of fall(s) was associated with an increased ICH risk (HR 1.96 [95% CI 1.06 - 3.61]).[80] However, in the ENGAGE-AF TIMI-48 trial and in the Loire Valley AF Project, the presence or absence of fall risk or a history of fall(s), did not increase the incidence of ICH.[79,81] The reason for these contradictory results are uncertain. Nevertheless, using a Markov model, it was estimated that patients with AF taking warfarin have to fall more than 295 times in one year for the risks of warfarin to outweigh its benefits.[83] Also, for both edoxaban and apixaban the relative safety and efficacy profile compared with warfarin were consistent in high fall risk patients.[80,81] Fall risk alone should therefore not be a reason to withhold anticoagulation.[9]

Dementia is another often cited reason for OAC non-prescription in AF.[4] However, like fall risk, dementia should not be a general contraindication for OAC.[9] Anticoagulation initiation and monitoring in dementia can be challenging, as therapy adherence and a patients' ability to make decisions are often suboptimal.[9] Nonetheless, OAC treatment is correlated with lower ischemic stroke and all-cause mortality rates in these patients.[84] Moreover, AF is linked to dementia and cognitive decline, and oral anticoagulation in AF has been associated with lower risk of dementia.[85,86] Anticoagulation treatment is therefore encouraged, but attention to therapy adherence is especially important.

CONCLUSION

Anticoagulation management remains an important discussion topic, especially in an aging AF population with progressively more comorbidities. Often, the perceived unfavourable risk-benefit ratio of anticoagulation is overestimated in these patients. Although a careful assessment of risks and benefits is warranted, the benefits of stroke prevention generally outweigh bleeding risk. This holds true specifically in patients with commonly reported reasons for anticoagulation withholding: previous bleeding, frailty and age, and high bleeding risk (table 2). After major bleeding, the optimal timing of anticoagulation resumption is largely unknown, and often requires multidisciplinary assessment.

Table 2 Summary of recommendations

Discussion topic	Recommendations
High bleeding risk	
	High bleeding risk is often not a contraindication, as stroke risk generally outweighs bleeding risk.
	A detailed recommendation can be found in table 1.
Recent major bleeding	
Overall	OAC resumption after major bleeding seems to be beneficial.
	The optimal timing of resumption is not extensively researched.
GI-bleeding	Resumption of OAC is generally recommended.
	Resumption of OAC can be considered as early as within 7 - 14 days after GI-bleeding.
ICH	Resumption of OAC is often beneficial, but should be decided in a multidisciplinary team as the benefits and risks are dependent on many factors.
	The optimal timing of resumption is unknown. If OAC is resumed, restarting after 4 weeks is deemed safe.
Frailty and age	
Overall	Frailty and age are no general contraindications for OAC.
High fall risk	A high risk of falls, or a history of falls, are no general contraindications for OAC.
Cognitive decline	OAC should not generally be withheld in patients with cognitive decline. Feasibility of OAC treatment in terms of medication adherence should always be checked and monitored.

GI Gastrointestinal; *OAC* Oral anticoagulation; *ICH* Intracranial haemorrhage.

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CHAPTER 8

Summary, discussion and future perspectives

Oral anticoagulants (OAC) are a cornerstone of treatment for patients with atrial fibrillation (AF). These drugs substantially reduce the associated high risk of thrombosis, hereby preventing disabilities, hospitalization and death, but come at the price of an increased bleeding risk.[1-3] The latter can also lead to serious adverse events, with the most feared complication being intracranial bleeding. In randomized controlled trials (RCT), the effectiveness and safety of OAC therapy for stroke prevention in AF has been demonstrated. However, it is important to complement trial data with real-world data as aspects such as guideline adherence including off-label dosing, and therapy adherence can significantly influence the safe and effective use of these drugs in the real-world. Moreover, patients from these trials are selected and strictly monitored, which can limit the generalizability of these results to patients encountered in daily clinical practice. Given the risks involved with (under- or over)treating these patients, this thesis aimed to further elucidate and expand current knowledge on the safety and effectiveness of real-world OAC treatment in patients with AF.[4-7]

In this chapter, the main results of the research described in the previous chapters of this thesis are summarized, discussed and put into future perspective.

EVALUATING REAL-WORLD OAC USE IN AF: THE DUTCH-AF REGISTRY

In **Chapter 2**, the design and rationale of the DUTCH-AF registry is described. This ongoing, observational study aims to investigate the safety and effectiveness of OAC in Dutch patients with newly diagnosed AF, with a focus on anticoagulation adherence. In collaboration with the Netherlands Heart Registration (NHR), DUTCH-AF is also the foundation for a long-term registry program, which aims for a long-term and systematic assessment of patient characteristics and follow-up of AF patients, in order to improve quality-of-care and to facilitate future research. This nationwide registry program is designed to improve quality of AF care in part by making large scale research in AF easier to conduct, with the possibility of registry-based randomized controlled trials. Patients included in the registry agreed that they may be approached for future research. The current collaboration with the NHR allows for central data storage and easy selection of patients potentially suitable for follow-up research. Patient recruitment for randomized controlled trials is normally very time-consuming and therefore expensive. The current AF registry design is aimed to make the inclusion of patients for future studies easier, with the benefit of a reduction in time and cost.

The DUTCH-AF registry is unique in its design and a first for the Netherlands, and was inspired by successful registries such as the SWEDEHEART registry from Sweden.[8] A strong suit of the DUTCH-AF registry is that patients can be enrolled in all care settings throughout the Netherlands, and caregivers were actively approached and encouraged to do so. Due to collaboration with the NHR this registry is future-proof, the data can be used for benchmarking with other participating centres, and cross-talk with other NHR registries is integrated. The latter is not only convenient for benchmarking, but also allows for patient selection for future research using variables collected outside of the AF-registry in e.g. the ablation or heart failure registries.

A disadvantage of the current registry is that collecting data requires effort, since eligible patients have to be identified and data has to be entered manually. Therefore, in this phase only a minimal dataset is requested from centres to reduce workload, while still sufficient to answer the primary research questions of DUTCH-AF. Also, significant progress has been made to implement the existing dataset into Dutch electronic medical records (EMR). This is aimed at simple and uniform data registration which is to be easily extractable from EMRs and directly uploadable in the digital NHR environment, avoiding time-consuming double (manual) registration. Hereby, the DUTCH-AF registry provides all the right building blocks for the nationwide AF registry to continue to build on.

A CHANGING OAC LANDSCAPE

Following the aforementioned advice of the Health Council of the Netherlands, the uptake rate of NOACs has initially been relatively slow in the Netherlands.[9,10] However, data from Dutch pharmacies showed that as of 2016 NOACs have replaced VKAs amongst novel anticoagulant users as the most prescribed anticoagulant.[11] In **Chapter 5**, changes in OAC prescription between 2010 and 2016 are described using data from the Dutch cohort from the worldwide GARFIELD-AF registry. In GARFIELD-AF, over 50,000 patients with newly diagnosed AF and ≥1 risk factor for stroke were enrolled worldwide, of which 1,189 patients were included in the Netherlands. This report shows that, after a slow start, NOACs have replaced VKAs as the anticoagulant of first choice in novel AF as of 2015-2016 in the Netherlands. Although this was the largest Dutch AF cohort to date, it should be noted that the data may not be entirely representative as nearly 95% of patients were included in a hospital setting. In **Chapter 3**, the results of the first 4,500 included patients from the DUTCH-AF registry are described, who were enrolled between July 2018 and November 2020 throughout the Netherlands. This chapter shows that VKA prescription in newly diagnosed AF has further decreased since 2016, from 34.8% of patients in the most recent 2015-2016 cohort of GARFIELD-AF to 7.0% in DUTCH-AF. The data from the nationwide DUTCH-AF registry is likely to be more representative for the Netherlands than GARFIELD-AF, given the high number of participating centres (22 hospitals, 5 anticoagulation clinics and 18 primary care practices) and the significant efforts made to not only enrol patients from hospitals. However, it is important to note that the proportion of VKA users in the DUTCH-AF registry is still likely to be an underestimation of the situation in the Netherlands as patients from primary practice were, despite all efforts, underrepresented. This is shown in a cross-sectional study using data from 39 general practices from the Netherlands in 2020, where 2,357 AF patients were identified.[12] In this study, around 27% of patients were treated with VKAs. However, this data does not show the proportion of patients with newly diagnosed AF in whom VKA treatment was initiated. In 2019, 11,000 patients were newly registered with AF at Dutch FNT affiliated anticoagulation clinics, out of an estimated total of 45,000 patients (24.4%) with AF diagnosed in the Netherlands yearly.[13,14] However, double-registration was possible in the FNT data, and 'newly registered AF' does not directly translate into newly diagnosed AF. Nonetheless, it is clear that OAC treatment in newly diagnosed AF has shifted from primarily treatment with VKAs to NOACs in the past few years as real-world evidence on NOAC safety increased and guidelines have changed.[15-18] However, variation between the type of OAC treatment initiated in newly diagnosed AF between general practices and hospitals is still likely to exist.

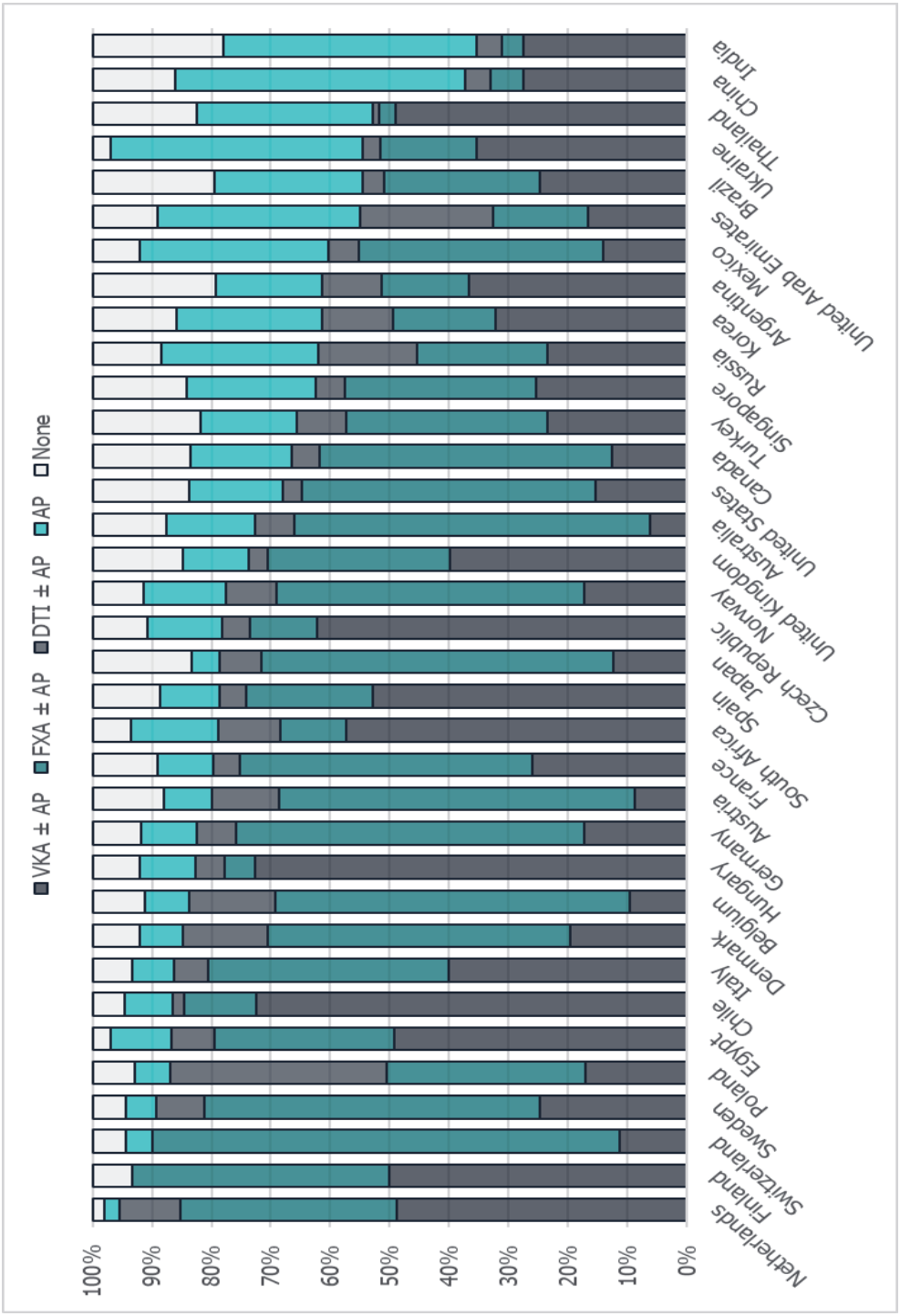
Monitoring these real-world trends remains relevant. Not only for evaluation of current practices, but it is also important that when new anticoagulants, such as

factor XI inhibitors, are introduced a large-scale registry able to evaluate the real-world safety and effectiveness of these novel drugs is already operative.[19] It is evident that the initiation of a large-scale registry such as DUTCH-AF is a time-consuming process, and the evaluation of new anticoagulants is especially needed right when these novel drugs are introduced into daily clinical practice. The continuation of a national AF registry is therefore of continued importance, not only for OAC registration, but also the registration of other factors deemed clinically relevant, such as AF symptoms and the control hereof. A continued AF registry opens the possibilities for easier to perform research on any topic in AF. Besides registry-based randomized controlled trials, a large-scale registry could also give more insight in patients with a relatively 'rare' condition, such as patients on haemodialysis or on the extreme end of the weight spectrum, which are otherwise difficult to capture in RCTs. Also, data from the AF registry can give patients more insight in for instance the (re-)occurrence of symptoms or the effect of treatment choices hereon, which contributes to better shared decision making.

Data from the AF registry can also be used for comparison of our AF care to other countries worldwide. Currently regarding anticoagulation, the GARFIELD-AF registry provides the best data hereon, as it is the largest global newly diagnosed AF cohort to date with completed follow-up and includes a relatively large Dutch cohort. Of all 35 countries which enrolled patients in the two most recent cohorts (cohorts 4 and 5, enrolment years 2014-2016), the Netherlands had the highest proportion of patients treated with anticoagulants (95.5% vs on average 71.2% global) (Figure 1). Moreover, the Netherlands had aside from Finland (0.0%) the lowest proportion of patients on antiplatelet monotherapy (2.6%, vs on average 16.7% global). Overall, in this respect the Netherlands performs well in comparison to other countries worldwide when looking at the recommendations of the current European Society of Cardiology (ESC) guidelines.[16,18]

In addition to the above, the identification of differences in treatment practices on a national scale is undoubtedly also of added value. At the moment, not all regions or levels of care are equally represented in the national AF registry. A registry in which all AF patients throughout the Netherlands are systematically registered could give us more insight in variations in treatment practices, approach to cardiovascular risk management and the (re-)occurrence of symptoms or cardiovascular outcomes. A uniform registry in collaboration with different care providers will increase our insight into the effect of various treatment choices on different types of patients, and could help to provide more patient-tailored approaches and a foundation for a consensus guideline for the uniform treatment of all AF patients in the Netherlands.

Figure 1 Treatment at diagnosis by country for cohort 4 & 5 in GARFIELD-AF



AP Antiplatelet therapy; *DTI* Direct thrombin inhibitor; *FXA* Factor Xa inhibitor; *VKA* vitamin K antagonist.

SAFETY OF A CHANGING OAC LANDSCAPE

In comparison to VKAs, all four NOACs pooled have shown an overall 20% reduction in stroke/systemic embolism (SE), 10% in mortality and 50% in intracranial bleeding in the landmark NOAC trials on AF.[20] Moreover, current real-world evidence on the safety and effectiveness of NOAC treatment in AF is strong, but as certain issues on for instance therapy adherence or observed differences in safety between different NOACs remain, continued research is needed to see where the real-world safety of these drugs can be improved even further.[15,21,22] It is therefore of importance to investigate the shift in OAC landscape over the years and its relationship to in- or decreases in thromboembolism, bleeding and mortality rates. Evaluating and learning from these past choices is important, as research aiming to discover and evaluate new anticoagulants will continue and, when approved by the EMA, will confront us with a similar scenario and choices as with the introduction of the NOACs.[19,23]

In **Chapter 6**, differences in anticoagulation treatment strategies in newly diagnosed AF and its effect on thrombosis, bleeding and mortality were studied in 1,186 Dutch and 1,705 Belgian patients enrolled in the GARFIELD-AF registry. This study provides us with a unique insight, since the Netherlands and Belgium are neighbouring countries with relatively comparable patient characteristics, while OAC management strategies in terms of NOAC uptake and target level of International Normalized Ratio (INR) intensity for VKA users differed significantly. In the Netherlands, 'non-valvular' AF patients on VKA therapy were treated with a target INR range of 2.5-3.5 until 2016, while internationally a target INR range of 2.0-3.0 was and is used. Since the rate of ischemic stroke increases rapidly with INR levels <2.0, it was hypothesized that targeting a higher INR range would result in less INR measurements <2.0 and thus a lower risk of ischemic stroke.[24-26] Consequently, this would result in an increased net clinical benefit, as bleeding risk appears to remain quite similar with INR range 3.0-3.5.[24-26] However, there has never been hard evidence for this theory, and as of 2016, Dutch target INR ranges were lowered to comply with international guidelines.

Indeed, targeting a higher INR range resulted in a lower proportion of patients with INR <2.0 (13.1% and 32.1%) in the Netherlands vs Belgium, while the proportion of patients with INR ≥3.0 was higher (35.0% and 19.7%), respectively. As expected with an overall 0.5 point higher target INR range, mean (± standard deviation) INR was 2.9±1.0 in the Netherlands vs 2.4±1.0 in Belgium. Despite these differences, unadjusted hazard ratios (HR) of all-cause mortality (HR 0.86, 95%-confidence interval (CI) 0.65-1.15), ischemic stroke/thromboembolism (HR 1.14, 95%-CI 0.62-2.11) and major bleeding (HR 1.33, 95%-CI 0.89-1.99) were not significantly different between the Netherlands and Belgium. However, these results should be

interpreted with caution, as adjustment for possible confounders was not possible due to the low number of events, and confidence intervals are wide. Possibly the most important confounder was the significant difference in the rate of NOAC uptake between countries. Although NOACs were approved a year later in Belgium (2012), the NOAC uptake rate was much faster in comparison to the Netherlands. In 2012, already 51.1% of Belgian AF patients in GARFIELD-AF were treated with a NOAC, compared to 0.4% in the Netherlands. In the last year of enrolment (2016), the difference had reduced significantly with 79.3% vs 66.3% of patients treated with NOACs in Belgium and the Netherlands, respectively. When comparing crude rates, the rate of major bleeding per 100 patient-years was non-significantly lower with NOACs compared with VKAs (HR 1.31, 95%-CI 0.93-1.85 vs HR 2.10, 95%-CI 1.56-2.85). As a reminder, most VKA patients were Dutch and targeted to a higher INR range, which influences results.

Although the largest, prospective AF cohort from the Netherlands and Belgium to that date was analysed, the number of included patients was still too low to provide us with sufficient data to fully address the aforementioned hypothesis. However, it is clear that these differences in OAC treatment strategies can have a clinically significant impact on outcomes as demonstrated by the hazard ratios. It remains therefore important to monitor and evaluate our AF-care. As mentioned before, the ongoing DUTCH-AF registry targets initially 6,000 patients to answer its primary questions, but it was designed to continuously grow with data to provide the necessary statistical power to answer important additional research questions such as these. Moreover, the DUTCH-AF registry provides an important benchmark for future studies derived from this registry to compare to.

BLEEDING AND THROMBOSIS RATES

Traditionally, data on bleeding and thrombosis rates in VKA users from the Netherlands, all managed by anticoagulation clinics, are generally well registered. In these anticoagulation clinics patients are monitored at least every six weeks. Concomitant with the INR level monitoring, patients are also periodically interviewed on the occurrence of bleeding and thrombosis events, which are recorded and published in yearly reports.[27] Also, in order to improve the quality of reported data, anticoagulation clinics are encouraged to verify the reported events by checking against data from medical records.[13] This results in fairly high data quality on the occurrence of thrombosis and bleeding in these patients, which is useful for comparison of event rates between anticoagulation clinics, or for aggregated analyses.[28] The FNT annual report from 2019 showed that across all VKA users the rate per 100 patient-years was 0.85 for thromboembolism, 1.42 for major bleeding, and 0.35 for intracranial bleeding.[27] However, there exists no monitoring system for NOACs which could report on adverse event rates on a nationwide scale, although

smaller studies with limited generalizability have been conducted previously in the Netherlands.[29-31] In the XANTUS study, only AF patients on rivaroxaban were included, while in a study from Groningen, the Netherlands, only patients with VKA or dabigatran were investigated.[29,30] Furthermore, a large study was performed in older patients from general practitioner's offices, but only 3% of patients were treated with a NOAC (dabigatran).[31]

In **Chapter 6**, unadjusted event rates per 100 patient-years from two-years follow-up of the GARFIELD-AF registry in the Netherlands and Belgium are shown, which were 3.38 (95%-CI 2.70-4.24) and 3.90 (95%-CI 3.28-4.65) for all-cause mortality, 0.82 (95%-CI 0.51-1.30) and 0.72 (95%-CI 0.48-1.08) for ischemic stroke/SE, and 2.06 (95%-CI 1.54-2.76) and 1.54 (95%-CI 1.16-2.04) for major bleeding, respectively. These data provide a first, nationwide insight in event rates in AF as we await the results from the DUTCH-AF registry.

The observed thromboembolism and bleeding rates were similar to previous Dutch and Belgian studies in AF, but mortality rates vary, which is likely due to different study designs and the enrolled population.[29-31] Compared with the Dutch cohort only, the global GARFIELD-AF data on two-year outcomes showed not-significantly different but numerically slightly higher rates (per 100 patient-years) of all-cause mortality (3.83, 95%-CI 3.71-3.95 vs 3.38, 95%-CI 2.70-4.24) and stroke/SE (1.01, 95%-CI 0.94-1.07 vs 0.82, 95%-CI 0.51-1.30), while major bleeding rate was significantly lower (0.98, 95%-CI 0.92-1.05 vs 2.06, 95%-CI 1.54-2.76) worldwide. These variations in event rates seems to be mainly the result of the large differences in patient characteristics and antithrombotic strategies for AF worldwide, which makes an assessment of ways to improve our current Dutch OAC care based hereon difficult (Figure 1).[32-34]

It seems more useful to compare event rates with other European countries given the use of a uniform AF guideline throughout the continent.[16] The PREFER in AF registry enrolled AF patients from seven European countries between 2012 and 2013.[35] At one year of follow-up, the rate of stroke/thromboembolism per 100 patient-years was 2.4, while the rate of major bleeding was 2.9.[35] The one-year outcomes from the EORP-AF, which included AF patients from 27 European countries between 2013-2017, showed a rate per 100 patient-years of 1.2 for stroke/thromboembolism, 2.3 for major bleeding, and 5.2 for all-cause mortality.[36] In comparison, the Dutch event rates observed in GARFIELD-AF were overall lower or similar compared to European data in other AF studies. However, as patients with longer existing AF were also included in these studies, a direct comparison with GARFIELD-AF is difficult to make, as these patients are often older and have more comorbidities, which increases the rate of adverse events.

With the current national AF registry, we can compare patient characteristics, treatment strategies and event rates throughout the Netherlands. However, we can potentially learn to improve our OAC treatment strategy from other European countries, and vice versa. As mentioned, it is currently however difficult to compare our data directly with other countries in Europe. It would be of great value to broaden our view and to create ongoing European registries, such as for AF, but also for other cardiovascular diseases. Of course, this poses a very difficult challenge given variations in national healthcare systems, political views and regulations as well as costs involved. However, the added benefits of lowering adverse event rates in AF and easier patient selection for clinical trials alone have the potential to greatly reduce costs of AF care and research in the long-run.

ADHERENCE TO GUIDELINE ANTICOAGULATION RECOMMENDATIONS

An important aspect regarding the safe and effective use of OACs is observing real-world practices and comparing these practices with guideline recommendations. Of course, valid arguments can be made to deviate from guideline recommendations in certain patients, but there is often no reason to in the majority of patients. Comparing observed data with guideline recommendations can be very insightful, as previous studies have shown.[4,7,37] A report from the European EORP-AF registry from 2015 showed that under- and overtreatment according to guideline recommendations was present in 17% and 23% of AF patients, respectively.[4] In this report, both under- and overtreatment were associated with an over 60% increase in the combined rate of all-cause mortality and any thromboembolism.[4] Although selection is likely to have influenced these results, this study shows that the risks involved with under- or overtreatment is potentially very substantial. Also, reports from the GLORIA-AF and GARFIELD-AF registries show that guideline inappropriate OAC prescription is common in AF.[38,39] Therefore, it is important to establish guideline adherence for OAC therapy in AF in the Netherlands.

In **Chapter 4**, guideline adherence of OAC therapy was assessed in patients with newly diagnosed AF from the DUTCH-AF registry using the 2016 ESC AF guidelines, which are similar to the recommendations of the updated 2020 guidelines.[16,18] In this paper, we particularly focused on sex differences in OAC treatment, as we hypothesized that guideline recommendations hereon could be prone to error as sex category contributes to the CHA_2DS_2-VASc score but not to the decision on OAC initiation. In the ESC AF guidelines, recommendations are based on stroke risk according to the CHA_2DS_2-VASc score and are categorized as: 1) recommendation for OAC use (class I recommendation; CHA_2DS_2-VASc ≥3 for females or ≥2 for males), 2) OAC should be considered (class IIa recommendation; CHA_2DS_2-VASc 2 for females or 1 for males), or 3) OAC is not recommended (class III recommendation; CHA_2DS_2-VASc 1 for females or 0 for males). In patients with a

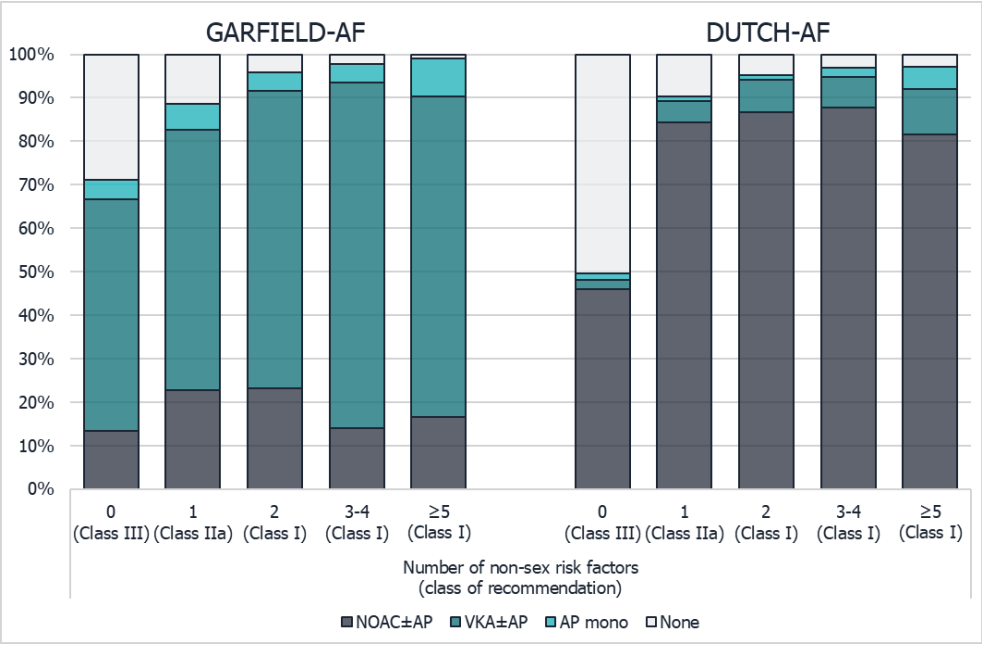
class I recommendation for OAC, the use of oral anticoagulants was high, and similar between females and males (90.9% vs 89.5%, respectively). However, in patients with a class IIa recommendation, males were significantly less often treated with OAC than females (81.2% vs 89.6%, p <0.001, respectively). In this group, males and females differed in age and comorbidities associated with stroke risk, which could possibly have influenced the observed difference. Therefore, in a logistic regression model with OAC as a binary outcome, we adjusted for each stroke risk factor from the CHA_2DS_2-VASc score as well as renal function, which showed that of these covariates only male sex was significantly associated with no OAC treatment (OR 2.1, 95%-CI 1.4-3.2) in patients with a class IIa recommendation. We therefore hypothesized that it is possible that in newly diagnosed AF patients with a class IIa recommendation for OAC, female patients are considered to be at a higher risk of stroke than male patients. It is understandable that physicians associate a numerically higher CHA_2DS_2-VASc score with a higher stroke risk, but this is not always the case concerning sex as a risk factor. Large, real-world studies show that sex only contributes to stroke risk in patients with ≥2 other stroke risk factors, and sex category has therefore previously been dubbed a risk modifier rather than a risk factor.[40,41] For the sole purpose of guiding OAC initiation in AF, a CHA_2DS_2-VA rather than a CHA_2DS_2-VASc score would therefore suffice, and could possibly prevent the observed an unwarranted difference in OAC treatment in males and females with a class IIa recommendation for stroke. The 2020 ESC AF guidelines mention that the CHA_2DS_2-VA score could guide the initial OAC decision, but that not considering sex category would underestimate stroke risk in females with AF.[42] While this statement is true, this chapter shows the potential downside of incorporating sex category into a score primarily used to guide OAC initiation. After incorporation of the CHA_2DS_2-VA score in daily clinical practice, the ongoing AF registry should monitor if the aforementioned hypothesis is true and the observed difference in OAC treatment between sexes disappears. Also, the registry should monitor changes in thrombosis and bleeding rates in these patients with a class IIa recommendation for OAC, if any.

In **Chapter 5**, guideline adherence is described in Dutch patients with newly diagnosed AF from the GARFIELD-AF registry. In this study, the proportion of patients using an anticoagulant was similar to anticoagulant use in the DUTCH-AF registry in patients with a recommendation for OAC use (92.5% vs 90.1%) or for patients in which OAC should be considered (82.6% vs 84.6%), respectively. However, in patients with no recommendation for OAC, anticoagulant use was higher in GARFIELD-AF (66.7% vs 48.1%), relative to DUTCH-AF. The latter is difficult to interpret, as it is presumable that most patients have received OAC for a (planned) cardioversion or catheter ablation, but was not intended for long-term treatment. However, a recent publication of Dutch and Belgian results from the EORP-AF

registry also showed a large proportion of patients despite no indication for OAC treated with OAC, often without a clear underlying explanation.[43] As in DUTCH-AF all OAC changes as well as cardioversions are reported, the DUTCH-AF results should provide us with more insights hereon.

In both studies from **Chapter 4 and 5**, guideline adherence to OAC appears to be largely appropriate, as overall OAC use in AF is high and the use of antiplatelet (AP) monotherapy is low. However, in both the data from the DUTCH-AF registry as well as Dutch data from the GARFIELD-AF study, a trend towards more AP monotherapy use can be seen in patients with the highest risk of stroke (Figure 2).

Figure 2 Antithrombotic treatment according to guideline recommendations



Non-sex stroke risk factors were defined as the CHA_2DS_2-VASc risk factors without 'sex category'. *AP mono* Antiplatelet monotherapy; *NOAC* non-vitamin K oral anticoagulant; *VKA* vitamin K antagonist.

An explanation for this trend could be that AP monotherapy is chosen over OAC because of a fear of bleeding, as stroke and bleeding risk are positively correlated.[44] Previous data from the global cohort of GARFIELD-AF showed that patients using AP monotherapy were more often classified as having a high bleeding risk according to the HAS-BLED score (HAS-BLED ≥3: 20.3% vs 5.3%), compared to patients on OAC monotherapy.[45] Moreover, adjusted predictors of AP monotherapy included age ≥75 years (OR 1.24, 95%-CI 1.20-1.29), a history of bleeding (2.11, 95%-CI 1.79-2.48) and dementia (OR 1.81, 95%-CI 1.47-2.23). However, AP monotherapy should not be used in these patients in an attempt to mitigate bleeding risk, as these agents

are inferior in reducing ischemic stroke risk compared to oral anticoagulants, while major bleeding risk is overall similar.[46-48] Completely withholding antithrombotic therapy in patients with a high risk of stroke should similarly be avoided in general. However, weighing the benefits and disadvantages of OAC in patients with a high risk of adverse events can pose a challenge in daily clinical practice.

Therefore, in **Chapter 7**, available evidence on the risks and benefits of anticoagulant treatment in AF patients with a high bleeding risk, with a history of bleeding or in the frail elderly is reviewed. The net clinical benefit of OAC appears to be highest in patients at the highest risk of bleeding, as these patients are often also at a high risk of stroke.[49-51] Anticoagulation should therefore generally not be withheld, but efforts should be made to lower bleeding risk by targeting modifiable bleeding risk factors such as alcohol use, concomitant use of antiplatelet agents or uncontrolled hypertension.[16,18] Concerning a history of bleeding, in patients with a recent (major) bleeding anticoagulation can be temporarily withheld dependent on the severity of the bleeding, but a permanent discontinuation should generally be avoided.[52,53] Only in selected patients with a high recurrent risk of a severe (intracranial) bleeding, such as in patients with cerebral amyloid angiopathy or with cerebral microbleeds, the resumption of anticoagulation is considered unfavourable.[16,54] In most however, there is a positive net clinical benefit of OAC resumption, although the optimal timing of a restart is often less certain.[16,18,54] Lastly, multiple reports have shown that frail elderly are far less likely to receive OAC than non-frail elderly.[55,56] Examples of commonly cited reasons for withholding OAC are a high fall risk, cognitive impairment and an advanced age.[57] However, available literature suggests that these reasons alone do not justify withholding OAC. There is general consensus that an increased fall risk should not solely be a reason to withhold OAC, as the risk of bleeding due to falls seems very limited, and the risk of stroke in this population is often high.[16,18,58-60] Also in patients with cognitive impairment, OAC should generally not be withheld.[18] In addition, some observational studies have linked OAC use to a decreased risk of dementia.[61,62] As a result, multiple trials are currently ongoing to investigate whether cognitive decline in AF is reduced with OAC treatment.[63-65]

LABEL ADHERENCE OF NOAC DOSING

It is important for the safe and effective use of oral anticoagulants that the real-world dosing of NOACs is in accordance with the Summary of Product Characteristics (SmPC) as formulated by the European Medicines Agency (EMA).[66-69] These are the dosing recommendations which were used in the landmark NOAC trials, and therefore known to be safe and effective in the investigated population.[70-73] With 'off-label' dosing (i.e. the use of an unapproved dose) the treatment effect of the prescribed dose is uncertain, especially when considering medication non-

adherence. If done with the best intentions to reduce the risk of adverse events, this could backfire and result in increased event rates, as far as we know. This is demonstrated by a systematic review which showed that overdosing of NOACs in AF was associated with increased all-cause mortality and worse bleeding events, and underdosing with an increased risk of hospitalization and stroke.[5] However, these data should be interpreted with caution, as this concerns non-randomized data and it is likely that selection has influenced event rates significantly. However, the data clearly demonstrate the potential risks involved in off-label dosing, which could be substantial given off-label NOAC dosing ranges mostly between 25-50% in studies.[5]

Moreover, it is important to understand whether the prescription of an off-label dose was unintentional or intentional. In this way, we know if we should focus our efforts on finding solutions to avoid unintentional dosing errors, or if we should focus research on the reasons behind the off-label dosing, or both. In case of intentional off-label dosing, it could be due to misconceptions for which the goal should be to better inform treating physicians, or it could be that the choice was made based on valid arguments as not every patient is representative of the population enrolled in the large NOAC trials.

In **Chapter 3**, the label adherence of NOAC dosing was assessed in newly diagnosed AF patients from the DUTCH-AF registry. Off-label dosing was assessed by checking for weight, age and renal function using the respective NOAC SmPCs from the EMA.[66-69] In the 3,252 patients analysed, off-label use of NOACs was infrequent, with 2.4% of NOAC users overdosed and 4.2% underdosed. Of patients with a recommendation for a reduced dose NOAC, 22.9% were overdosed. Of patients with a recommendation for a full dose NOAC, 4.6% were underdosed. After multivariable analyses including other stroke risk factors, determinants of overdosing were lower age and lower renal function, and determinants of underdosing were higher age, lower renal function, lower weight, active malignancy, anaemia, and concomitant use of antiplatelets.

The extent of off-label dosing in this study is comparable to previous data on NOAC naïve AF patients from Groningen, the Netherlands (5.4% underdosing vs 4.5% overdosing) and previous Dutch data from GARFIELD-AF (<10% off-label dosing).[74,75] However, off-label dosing appears to occur far less frequently in the Netherlands compared to other countries.[5,6,75-78] The reason why off-label NOAC dosing in the Netherlands is infrequent is not fully understood, but is possibly the result of a combination of factors including a high awareness of the issue. However, there still seems room for improvement. It is important to note, however, that the first NOAC prescription was recorded, and it is possible that the NOAC dose was corrected in the first weeks after diagnosis. A theory may be that a NOAC dose prescribed off-label by a general physician is corrected by a cardiologist as most

patients are referred to a hospital after AF diagnosis. However, this does not seem to be the case as both overdosing (2.1% vs 2.5%) and underdosing (4.0 vs 4.2%) were equally infrequent in patients who were initiated with a NOAC in primary care compared to in-hospital in DUTCH-AF, respectively.

Similar to the results of DUTCH-AF, underdosing occurs more often than overdosing worldwide.[5,6,43,75-78] Although it is not entirely clear why this happens, it is reasonable to assume that physicians prescribing anticoagulants intend to have more of a fear of bleeding rather than a fear of stroke, as is also described in **Chapter 7**.[79-81] However, since bleeding and stroke risk are positively correlated and the net clinical benefit of anticoagulants appears to be highest in patients with the highest risk of stroke and bleeding, prescribing a reduced NOAC dose off-label generally seems unwise, in line with previous observations of increased adverse event rates with off-label dosing.[5,44,50,82] However, as mentioned previously, this concerns non-randomized data, and it remains uncertain whether some patients deemed to be at a high risk of bleeding could benefit of underdosing, or vice versa.[83]

The determinants of underdosing were characteristics from the NOAC dose adjustment criteria, i.e. age, renal function and weight, as well as other factors associated with an increased bleeding risk, i.e. active malignancy, anaemia and concomitant use of antiplatelet agents. Although these results from a predictive model analysis are difficult to translate to causal inferences, these findings might suggest that some physicians reduce NOAC dose in patients deemed to be at an increased risk of bleeding, outside of the dose adjustment criteria. It is important to note, however, that although age, renal function and weight were associated with underdosing, the dose adjustment criteria were not fulfilled in these patients, and reducing NOAC dose was therefore not justified. Intuitively, active malignancy, anaemia and concomitant use of antiplatelet agents seem valid factors for reducing NOAC dose in some patients, but the consequences hereof on the rates of bleeding, stroke and mortality remain uncertain. In the 2020 ESC AF guidelines, there is a class IIb recommendation (i.e. may be considered) to reduce the dose of dabigatran or rivaroxaban outside of the EMA dose adjustment criteria when patients are concomitantly treated with antiplatelet agents after percutaneous coronary intervention.[42] These recommendations are based on results of the RE-DUAL PCI and PIONEER-AF trials, which showed lower bleeding events with this approach.[84,85] However, both trials were underpowered to detect the observed between-group differences in their composite efficacy endpoints, and reducing NOAC dose in these patients should therefore always be done carefully. Therefore, it remains important to further investigate the effect of off-label dosing on adverse events. The ongoing DUTCH-AF registry will give us more insight when follow-up has been completed, as the effect of off-label NOAC dosing in newly diagnosed AF is less well researched.

However, the DUTCH-AF registry does not collect information on underlying reasons for off-label dosing, and follow-up research using a questionnaire intended for Dutch physicians would be needed to explore this issue further. In general, it would be of added value if deviations from guideline recommended doses, preferably automatically detected via an electronic prescription system, are brought to the attention of the prescriber. In this way, unintentional dosing errors can be avoided, and in the case of intentional off-label dosing a reasoning can be provided so we can learn from these decisions.

CONCLUSION

Atrial fibrillation is a prevalent disease which incidence continues to rise, and concomitantly the associated rates of thrombosis, bleeding and a general increased burden on our healthcare system. Therefore, it is imperative that the real-world AF anticoagulation treatment follows the most recent guideline recommendations and advances in literature, in an effort to minimize the rate of adverse events. Before this thesis, the quality of contemporary anticoagulation management in Dutch patients with AF was a largely unexplored area. With the results of the GARFIELD-AF registry and the first results of the DUTCH-AF registry, this thesis has provided a first, nationwide insight into Dutch anticoagulation management in AF. Key points of this thesis were the assessment of the extent and determinants of off-label NOAC dosing, the extent of anticoagulation guideline non-adherence and contemporary rates of thrombosis, bleeding and mortality in Dutch AF patients. Also, with DUTCH-AF the foundation for a long-term nationwide AF registry has been created, which will continue to provide us with novel insights into risk factors and (anticoagulation) management in AF. Hereby, we continue to elucidate and expand our knowledge on the implementation, safety and effectiveness of real-world AF treatment, with the aim to identify where further potential improvements in AF care can be made.

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CHAPTER 9

Nederlandse samenvatting

Atriumfibrilleren (AF) is de meest voorkomende hartritmestoornis en komt met name voor bij ouderen. Gezien de toenemende vergrijzing is de verwachting dat het aantal mensen met AF zal blijven toenemen. Dit is problematisch, want AF is geassocieerd met een sterk verhoogd risico op trombose (d.w.z. vorming van een bloedprop), wat ernstige lichamelijke gevolgen kan hebben en kan leiden tot ziekenhuisopnames of in het ernstigste geval de dood. Behandeling met antistollingsmedicijnen (ook wel foutief bekend als 'bloedverdunner') is zeer effectief om dit tromboserisico te verlagen, maar verhoogt daarentegen het bloedingsrisico sterk. Dit laatste kan ook ernstige gevolgen hebben, waarbij het optreden van een hersenbloeding het meest gevreesd wordt. In grote, gerandomiseerde onderzoeken zijn de veiligheid en effectiviteit van antistollingsmedicijnen al eerder aangetoond. Het is echter belangrijk om deze gegevens aan te vullen met data uit de dagelijkse praktijk, aangezien zaken als het opvolgen van richtlijnen of therapietrouw van medicatiegebruik de veiligheid en effectiviteit van deze antistollingsmedicijnen behoorlijk kan beïnvloeden. Ook kan het lastig zijn om de resultaten van gerandomiseerde onderzoeken te vertalen naar de dagelijkse praktijk, aangezien de patiënten die in deze studies deelnamen sterk geselecteerd waren en nauw in de gaten gehouden werden. Hierdoor is niet iedere patiënt even goed vertegenwoordigd in deze studies en is de therapietrouw in deze studies waarschijnlijk hoger dan dat realistisch is voor de alledaagse patiënt. Aangezien er risico's zitten aan het (onder)behandelen van patiënten met antistollingsmedicijnen is het van belang om het dagelijks gebruik van deze medicijnen beter in kaart te brengen. Dit heeft als doel om de veiligheid en effectiviteit van antistollingsmedicijnen bij patiënten met AF verder te verbeteren.

In dit proefschrift is onderzoek beschreven naar de kwaliteit van antistollingsgebruik in de dagelijkse praktijk bij patiënten met AF. In dit hoofdstuk worden de belangrijkste resultaten uit dit proefschrift in het Nederlands samengevat weergegeven.

In **Hoofdstuk 2** wordt het ontwerp en de gedachte achter de landelijke DUTCH-AF studie weergegeven. Deze studie heeft als doel om de veiligheid en effectiviteit van antistollingsgebruik bij patiënten die recent zijn gediagnosticeerd met AF in kaart te brengen. Hierbij focust de DUTCH-AF studie zich met name op de therapietrouw (neemt de patiënt de medicijnen wel in?) en therapiepersistentie (hoe lang gebruikt de patiënt de medicijnen door?) van antistollingsmedicijnen. Daarnaast wordt in deze studie onderzocht of de juiste doseringen voorgeschreven worden en wordt er in kaart gebracht wat voorspellers zijn van bloedingen als bijwerking van deze antistollingsmedicijnen. Tevens vormt deze studie in nauwe samenwerking met de Nederlandse Hart Registratie (NHR) de basis van een landelijke AF-kwaliteitsregistratie. De NHR is een organisatie die zich bezighoudt met hoogwaardige kwaliteitsregistraties van onder andere hartoperaties en -interventies, maar sinds 2018 is daar ook de AF-registratie bijgekomen. Door de samenwerking met de NHR blijft de studiedata behouden voor toekomstige onderzoeken en kwaliteitsevaluaties, en kan de huidige data en kennis verder uitgebreid worden. Tevens kan de data gemakkelijk gekoppeld worden met de andere kwaliteitsregistraties binnen de NHR, wat tevens toekomstig onderzoek bevordert. Ook is DUTCH-AF zo ontworpen dat studiedeelnemers in de toekomst eenvoudig benaderd mogen en kunnen worden om vervolgonderzoek mogelijk te maken. Op deze manier kan op een gemakkelijke manier een grote groep patiënten sneller benaderd worden, waardoor toekomstig onderzoek binnen patiënten met AF goedkoper en gemakkelijker wordt.

In **Hoofdstuk 3** worden de eerste resultaten van de DUTCH-AF studie gepresenteerd. De patiëntkarakteristieken van de eerste 4500 geïncludeerde patiënten worden beschreven, waarbij gekeken werd of antistollingsmedicijnen wel juist gedoseerd worden op basis van de Europese aanbevelingen. Waar voorheen AF patiënten behandeld werden met vitamine K antagonisten (VKA), worden tegenwoordig steeds meer patiënten behandeld met non-vitamine K orale anticoagulantia (NOAC). De NOAC's hebben als voordeel dat er sprake is van een (grotendeels) vaste dosering, er geen controle via trombosediensten nodig is, en dat uit onderzoek is gebleken dat ze minstens net zo goed en veilig zijn als VKA's met het bijkomend voordeel dat er minder hersenbloedingen optreden. Voor het doseren van NOAC's zijn criteria opgesteld door het Europees Medicijn Agentschap, welke gebaseerd zijn op de gerandomiseerde studies waarin deze medicijnen onderzocht zijn. Het is belangrijk dat deze criteria goed gevolgd worden in de dagelijkse praktijk, gezien 'off-label' (d.w.z. gebruik van een dosis waarvoor deze niet geregistreerd is) gebruik van NOAC's in verschillende eerdere studies geassocieerd is met het optreden van meer beroertes, bloedingen en/of ziekenhuisopnames. Uit de resultaten van DUTCH-AF blijkt dat zowel over- als onderdoseren van NOAC's (2.4% en 4.2% van de NOAC gebruikers, respectievelijk) in Nederland weinig voorkomt,

zeker in vergelijking met andere landen. Onafhankelijke voorspellers voor overdoseren waren een slechtere nierfunctie en een lagere leeftijd. Onafhankelijke voorspellers voor onderdoseren waren een hogere leeftijd, een slechtere nierfunctie, een lager gewicht, de aanwezigheid van bloedarmoede, kanker, en gebruik van antiplaatjestherapie. De voorspellers leeftijd, nierfunctie en gewicht zijn niet onverwacht, gezien deze ook in de NOAC dosisaanpassingscriteria gebruikt worden om te bepalen welke NOAC dosis een patiënt zou moeten krijgen. Echter, deze patiënten voldeden ondanks hun leeftijd, gewicht en nierfunctie niet aan deze criteria, en dus zijn de criteria hier niet goed toegepast. Ook bloedarmoede, actieve kanker en gebruik van antiplaatjestherapie zijn niet onverwacht als voorspellers van onderdoseren, aangezien deze factoren geassocieerd zijn met een verhoogd bloedingsrisico. Het tegen de dosisaanpassingscriteria in verlagen van de NOAC dosis bij deze factoren is echter niet goed onderzocht, en zou ook averechts kunnen uitpakken met een toegenomen risico op trombose. Momenteel is DUTCH-AF nog bezig met de follow-up fase, maar zodra deze is afgerond zal DUTCH-AF meer licht kunnen laten schijnen op het vóórkomen van bloedingen, trombose en sterfte bij Nederlandse AF patiënten die onder- of overgedoseerd worden.

In **Hoofdstuk 4** worden tevens resultaten van de DUTCH-AF studie beschreven, ditmaal met de focus of de richtlijnen over de indicatie van antistollingsmedicijnen bij AF goed worden opgevolgd. Om te bepalen of een patiënt antistollingsmedicijnen voorgeschreven zou moeten krijgen bij AF wordt doorgaans de CHA_2DS_2-VASc risicoscore gebruikt. Deze score bestaat uit factoren als suikerziekte, hoge bloeddruk of vrouwelijk geslacht welke elk 1 of 2 punten in de score oplevert; hoe hoger de score hoe hoger het ingeschatte risico op een beroerte. Huidige richtlijnen bevelen aan om bij vrouwen met een score van 3 of hoger, en bij mannen met een score van 2 of hoger, antistollingsmedicijnen voor te schrijven. Bij vrouwen met een score van 2 of mannen met een score van 1 zou het overwogen moeten worden (in principe wél voorschrijven), en bij vrouwen met een score van 1 of mannen met een score van 0 is er geen lange termijn indicatie voor antistollingsmedicijnen. In DUTCH-AF zagen we een significant verschil in de mate waarin antistollingsmedicijnen tussen vrouwen en mannen waren voorgeschreven in de categorie waarbij antistollingsmedicijnen overwogen moeten worden. In deze categorie kreeg 89.6% van de vrouwen en 81.2% van de mannen antistollingsmedicijnen voorgeschreven, terwijl zowel de mannen als vrouwen een even sterke indicatie hadden voor deze medicijnen. Ook wanneer er gecorrigeerd werd voor andere risicofactoren voor beroerte bleef dit verschil bestaan. Hiermee lijkt het erop dat artsen vrouwen met een CHA_2DS_2-VASc score van 2 als hoger risico inschatten dan mannen met een CHA_2DS_2-VASc score van 1, dit terwijl eerdere onderzoeken lieten zien dat beiden een vergelijkbaar risico hebben om een beroerte te krijgen. Wij bevelen daarom in dit hoofdstuk aan om de CHA_2DS_2-VA score (minus

'Sc', 'sex category') te gebruiken voor het bepalen van de antistollingsindicatie. Dit raden we enerzijds aan omdat geslacht geen rol speelt in de beslissing om wel of niet antistollingsmedicijnen te starten, en anderzijds omdat hiermee mogelijk een ongerechtvaardigd verschil in antistollingsgebruik tussen mannen en vrouwen voorkomen kan worden.

In **Hoofdstuk 5** worden de resultaten van de wereldwijde GARFIELD-AF studie beschreven. Deze studie had als doel om trends in het gebruik van antistolling bij patiënten met een recente diagnose van AF te onderzoeken, en om te onderzoeken of de richtlijnen over de indicatie van antistollingsmedicijnen bij AF goed worden opgevolgd. De 1189 in Nederland geïncludeerde patiënten vormden het grootste cohort van Nederlandse AF patiënten die tot dan toe, vóór DUTCH-AF, omschreven waren. Deze studie laat voor het eerst de transitie van het Nederlandse antistollingslandschap van een met name op VKA naar een op NOAC-gebaseerde AF-zorg zien. Opvallend hierbij is dat de initiële transitie gedurende de jaren 2011-2014 langzaam verliep, maar dat na deze periode NOAC's snel omarmd werden voor de behandeling van AF in deze studie. Tevens valt op dat antistollingsgebruik in Nederland bij AF hoog is; het hoogste van alle 35 onderzochte landen. Het ingezette antitrombotische beleid verloopt hiermee grotendeels volgens de richtlijnen, maar een klein deel van de patiënten kreeg ondanks een antistollingsindicatie toch geen antistolling of alleen antiplaatjestherapie voorgeschreven. Redenen hiervoor waren helaas vaak niet te achterhalen, maar van de te achterhalen argumenten kwamen 'laag risico op beroerte' en 'bloedingsrisico' het vaakst voor.

In **Hoofdstuk 6** worden de 2-jaarsuitkomsten van het Nederlandse en Belgische cohort van de GARFIELD-AF registratie beschreven. Ondanks de overeenkomsten tussen deze twee landen is er in de afgelopen jaren een verschillende aanpak geweest wat betreft het antistollingsbeleid bij AF-patiënten. Het eerste verschil is dat tot januari 2016 Nederlandse patiënten die een VKA gebruikten behandeld waren met een hogere streef 'International Normalized Ratio' (INR, een maat voor de stollingstijd van bloed) dan in België (streefwaarde INR 2,5-3,5 versus 2,0-3,0, respectievelijk). Sinds 2016 zijn de INR-streefwaarden in Nederland echter verlaagd om te voldoen aan huidige internationale richtlijnen. Het tweede verschil is dat NOAC's veel sneller geïmplementeerd werden in de België dan in Nederland, waarbij in GARFIELD-AF in 2012 al meer dan 50% van de Belgische patiënten een NOAC gebruikten, tegenover 3% van de Nederlandse patiënten. Het is onbekend wat de impact van dergelijke verschillen in antistollingsbeleid zijn op de incidentie van bloedingen en beroertes. Omdat de patiëntkarakteristieken tussen deze twee landen vrij vergelijkbaar zijn, bood de GARFIELD-AF registratie een unieke kans om dit beter in beeld te brengen. In totaal waren er 2891 patiënten met een recente diagnose van AF geïncludeerd in België en Nederland tussen 2010 en 2016. Alhoewel er in

Nederland 33% meer ernstige bloedingen werden gezien dan in België, waren de verschillen in bloedingen, sterfte en herseninfarct/trombose niet significant verschillend tussen beide landen. Het was echter niet goed mogelijk om te bepalen wat de impact van de eerder genoemde verschillen los van elkaar was op deze cijfers. Tevens waren er te weinig patiënten geïncludeerd om betrouwbaar aan te kunnen tonen of de gevonden verschillen op toeval berusten, ondanks dat dit het grootste cohort AF-patiënten in zowel Nederland als België betrof. Ondanks deze tekortkomingen biedt deze studie een eerste inzicht in de uitkomsten van de tot dan toe grootste groep AF-patiënten in Nederland en België, en onderstreept deze studie het belang van een goed opgezette, landelijke AF-registratie.

In **Hoofdstuk 7** is een overzicht beschreven van de huidige literatuur over de veiligheid en effectiviteit van het wel of niet voorschrijven van antistolling bij specifiek patiëntgroepen waarbij in de praktijk veel discussie over de toegevoegde waarde van antistolling bij AF bestaat. We hebben in dit hoofdstuk specifiek gekeken naar patiënten met een hoog ingeschat bloedingsrisico of een doorgemaakte ernstige bloeding, en naar kwetsbare ouderen. Bij deze patiëntgroepen is het van belang om een weloverwogen keuze te maken op basis van de meest recente onderzoeksresultaten, aangezien deze patiënten vaak zowel een hoog bloedings- als beroerterisico hebben. Over het algemeen lijkt het voorschrijven van antistolling voordelig te zijn, aangezien het risico op een herseninfarct bij deze patiëntcategorieën vaak een stuk hoger ligt dan het risico op een (hersen)bloeding. Het is hierbij met name van belang dat gepoogd wordt om het bloedingsrisico zo laag mogelijk te maken. Het lijkt in de regel niet verstandig te zijn om hiervoor antistolling te onthouden, maar om het bloedingsrisico te verlagen door modificeerbare risicofactoren zoals hypertensie of overmatig alcoholgebruik aan te pakken.

CONCLUSIE

Atriumfibrilleren is een veelvoorkomende aandoening, waar het vóórkomen ervan door de vergrijzing alleen maar verder zal toenemen. De verwachtte toename aan trombose en bloedingen maakt het noodzakelijk dat de antistollingsbehandeling van AF in de praktijk de meest recente aanbevelingen van de richtlijnen en de vooruitgang in de literatuur volgt, in een poging om deze aantallen zo laag mogelijk te houden. Vóór dit proefschrift was de kwaliteit van de hedendaagse antistollingsbehandeling bij Nederlandse patiënten met AF een grotendeels onbekend gebied. Met de resultaten van de GARFIELD-AF studie en de eerste resultaten van de DUTCH-AF studie heeft dit proefschrift een eerste, landelijk inzicht verschaft in de Nederlandse antistollingsbehandeling bij AF. Kernpunten van dit proefschrift waren het onderzoeken van de omvang en determinanten van off-label NOAC doseren, de omvang van het niet naleven van antistollingsrichtlijnen alsmede het hedendaagse optreden van trombose, bloedingen en sterfte bij Nederlandse AF patiënten. Ook is met DUTCH-AF de basis gelegd voor een langlopend, landelijk AF-register dat ons nieuwe inzichten zal blijven verschaffen over de behandeling van AF. Hiermee blijven we onze kennis over de veiligheid en effectiviteit van (antistollings)behandeling in de praktijk verbeteren, met als doel om te achterhalen waar mogelijke verbeteringen in de (antistollings)zorg kunnen worden aangebracht.

Appendix I

Impact paragraph

In this thesis, real-world concerns on issues potentially affecting the safe and effective use of oral anticoagulants (OAC) were explored, i.e. anticoagulation guideline adherence and off-label NOAC dosing in patients with newly diagnosed atrial fibrillation (AF). Investigating these concerns is of importance, as inadequate usage of OACs can potentially increase thrombosis or bleeding risk, both of which can have severe consequences for patients. The most important results of this thesis have been summarized and discussed in chapters 10 and 11. A further elaboration on the scientific and societal impact is discussed below.

Perhaps the most important achievement of this work was the creation and successful growth of a nationwide AF-registry, which combines efforts of the DUTCH-AF research team with the Netherlands Heart Registration (NHR). In this registry, data is gathered on patients with newly diagnosed AF with the aim to further explore concerns on the safe and effective use of OACs, such as medication persistence and adherence of NOACs. A major advantage of the combination of research with the quality registry program of the NHR is that the data is stored in a secure and futureproof environment and can continue to be supplemented with new data (i.e. from new patients, or more variables collected from these patients) even after the current study has finished. This opens research possibilities for future study groups, who can, with the approval of the AF Steering Committee and the Scientific Council of the NHR, use the collected data for their own analyses. This feature is very important, as this reduces time and costs involved with research, such as the process of gaining informed consent or collecting data. In this way, the data collected within the DUTCH-AF registry is not only accessible for the DUTCH-AF researchers, but is also accessible to anyone in the Netherlands with a decent research proposal. Moreover, this registry is unique in its design in that enrolled patients agree that they may be contacted when a future AF-related research proposal is formulated. This creates the possibility of collecting additional data, or to create a registry-based randomized controlled trial. As randomized controlled trials are often struggling with high costs and a slow enrolment process, the current AF registry was designed to make this process easier and cheaper. This is of great importance for the continuous improvement of the quality of AF care in the Netherlands, as well as internationally.

The collaboration with the NHR also provides the possibility to compare collected data from one participating centre with other participating centres. Even in a small country such as the Netherlands, treatment practices can vary significantly between hospitals, as different treatment approaches are often possible in the AF guidelines. The NHR platform creates the possibility for a participating centre to gain full insight into their own data, but can also compare their data with other (pseudonymized) centres for benchmarking. As atrial fibrillation is the most common sustained arrhythmia with over 45.000 newly diagnosed patients in the Netherlands every year,

any improvement in quality of AF care can potentially have a great impact.[1] The results of the DUTCH-AF registry will also be shared with individual, participating centres, where they can compare their centre specific results with the aggregated data of other participating centres.

The data from the DUTCH-AF registry is also shared with AF patients. Besides providing AF patients with current insights, data is also shared with the aim to gain their insights in how to improve the current nationwide registry program and to learn what patients instead of medical doctors want to know about atrial fibrillation. This is now primarily achieved via Harteraad, a Dutch federation for patients with cardiovascular disease. Moreover, the DUTCH-AF study group, the NHR and the Dutch Heart Foundation ("Hartstichting") have collaborated and published results of the AF registry, intended for medical doctors of non-participating centres as well as the general public.

Finally, the returned data is of increasing quality if an increasing number of caregivers collect data for the national AF-registry. Therefore, the DUTCH-AF study group and the NHR encourage all caregivers who treat patients with AF to join the registry, including anticoagulation clinics and primary practices. Besides sharing results and information on the national registry through scientific journals and congresses, physicians were also informed through newsletters, press release, social media and by word of mouth. Moreover, dozens of anticoagulation clinics, hospitals and primary care practices were actively approached to join the registry. Of course, enrolling patients and data-entry is time-consuming, so significant advances have been made to reduce efforts. Currently data entry through a case report form (CRF) is required, but the possibility has been created for participating centres to directly upload their data in a secure environment managed by the NHR. In this way, manual data entry could be reduced, and automatic data extraction is encouraged. Moreover, significant progress has been made to implement the dataset from the DUTCH-AF registry into commonly used Electronic Medical Records (EMR), with the aim to reduce double data-entry and to facilitate automatic data extraction.

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II

Appendix III

Curriculum Vitae

Jaap Seelig werd geboren op 15 december 1992 in Drunen, Noord-Brabant. Na het behalen van zijn VWO diploma aan het Stedelijk Gymnasium te 's-Hertogenbosch begon hij in 2011 met de studie geneeskunde aan de Radboud Universiteit Nijmegen.

De interesse voor de cardiologie was al vroeg tijdens de studie gewekt, waarbij hij in 2014 begon met een onderzoeksstage op het gebied van antistolling bij atriumfibrilleren aan het Radboudumc, Nijmegen. Na het afronden van de studie geneeskunde in oktober 2017, startte hij als arts-assistent cardiologie in het Rijnstate, Arnhem.

Per mei 2018 startte hij vervolgens met zijn promotietraject aan het Cardiovascular Research Institute Maastricht, Universiteit Maastricht, waarbij hij voornamelijk werkzaam was op de afdeling cardioresearch in Rijnstate, Arnhem. Per november 2019 werd de AF-poli opgericht in het Rijnstate en werd hij deel van het behandelteam. In november 2020 heeft hij vervolgens de overstap gemaakt naar het Radboudumc om daar te gaan werken als arts-assistent cardiologie. Per april 2021 is hij in het Radboudumc vervolgens aan de slag gegaan als trialarts.

Per december 2021 is hij vervolgens met de opleiding tot cardioloog begonnen aan het Radboudumc, beginnende met de vooropleiding interne geneeskunde in het Rijnstate, Arnhem.

III

Appendix IV

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