Balancing risks in thromboembolic disease

Emmy Martine Trinks-Roerdink

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COLOPHON

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BALANCING RISKS IN THROMBOEMBOLIC DISEASE

AFWEGEN VAN RISICO'S
BIJ TROMBO-EMBOLISCHE AANDOENINGEN

(met een samenvatting in het Nederlands)

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1

INTRODUCTION

CASE

Mrs. Verburg is a 70-year-old woman with a longstanding history of hypertension. For a few weeks, she has been experiencing fatigue and shortness of breath even at limited exertion. She is no longer able to enjoy her daily twenty-minute biking trip to visit her grandchildren, and she decides to consult her general practitioner (GP).
On physical examination, her blood pressure is 148/92 mmHg, and she has an irregular pulse of around 110 beats per minute (bpm) and 124 bpm on auscultation (pulse deficit of 14 bpm). The GP decides to make an electrocardiogram (ECG) on which atrial fibrillation (AF) is diagnosed. In hindsight, Mrs. Verburg remembers that she had a kind of irregular pounding of the heart from time to time, notably when biking or doing the household. After a telephone consultation with the cardiologist Mrs. Verburg was prescribed the direct oral anticoagulation (DOAC) apixaban 2dd 5 mg (body mass index 28.4 kg/m^2, recent eGFR >60 ml/kg/ 1.73m^2, and CHA_2DS_2-VASc score 3), and 2dd 25 mg metoprolol succinate slow release to slow down her heart rhythm. Subsequently, she is scheduled to undergo electro-cardioversion (ECV) after 4 weeks of DOAC treatment to try to restore her heart rhythm to sinus rhythm, given her fatigue and reduced exercise tolerance. The ECV is successful and sinus rhythm is restored, and after a workup by the cardiologist including echocardiography, she is referred back to the GP for further AF monitoring, including (i) the anticoagulation monitoring, (ii) regular checks for the detection of heart failure symptoms, and (iii) blood pressure management. For six months she had no complaints and was able to resume all her activities. However, after this period she consults the GP again but now for blood in the stool. The GP refers her for colonoscopy, and unfortunately, a malignant tumor is detected in the colon for which she needs to undergo surgery followed by chemotherapy. During the following weeks, she visits the GP multiple times for recurrent nose bleeding. Upon physical examination, the heart rhythm is irregular again suspicious for a relapse of her AF which is confirmed with a 12-lead ECG, however, now at an acceptable heart rate of around 90 beats per minute. Initially, the GP and Mrs. Verburg discuss the nose bleedings and decide to wait and see. Unfortunately, however, the nose bleedings

come unexpectedly and last sometimes up to an hour, which make her feel uncertain, forcing her to stay at home. After inspection of the nose, the GP concludes it concerns a high located bleeding spot because the loci Kiesselbachi on both sides at the nose entrance seem fine. The GP contemplates interrupting anticoagulation in order to help stop the nose bleedings, however, she realizes this is a difficult decision because it would increase the risk of ischemic stroke, the more so because not only AF, but also ongoing treatment for an active malignancy increases the risk of ischemic stroke and other thromboembolism. Thus, the GP and Mrs. Verburg decide in shared decision to continue anticoagulation, nonetheless, hoping that the frequent nose bleeds are not a warning signal for imminent major bleeding elsewhere.

THROMBOEMBOLIC DISEASE

In thromboembolic disease, a blood clot is formed, which can travel through the bloodstream, lodge in a blood vessel, and thus lead to an interruption of blood flow. Thrombus formation is the result of activation of the coagulation cascade. Formerly, the coagulation cascade was explained by an (i) intrinsic, (ii) extrinsic, and (iii) finally a common pathway of intrinsic and extrinsic (notably thrombin activation). It is nowadays often differently explained by an initiation, amplification, and propagation phase. See Figure 1 for an overview of the coagulation cascade according to these three phases.[1] When thromboembolism occurs in the venous system, this is called venous thromboembolism (VTE). The most common manifestations of VTE are deep venous thrombosis (DVT) and pulmonary embolism (PE). DVT is most often located in the lower extremities. When the thrombus dislodges and travels to the lungs, this is called pulmonary embolism (PE). The incidence rate of VTE is around 1-2 per 1000 person-years.[2,3] VTE is not only associated with increased mortality risk, but also with increased hospitalization risk, and long-term complications such as chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome.[4,5] Another manifestation of thrombosis is arterial thromboembolism, in which a blood clot obstructs an artery and causes tissue ischemia. An important risk factor for arterial thromboembolism, notably in the brain, is AF; a common and important heart rhythm disorder occurring in approximately 2-3% of the population, but with a much higher prevalence rate in the elderly (up to 18% in those aged above 85 years).[6,7] In the presence of AF, the risk of ischemic stroke is increased on average about three to five-fold, and the risk of mortality two-fold.[8–10] It is evident that the risks associated with thromboembolic disease ask for prompt diagnosis and adequate treatment of AF.

ANTICOAGULANTS

Anticoagulation is the cornerstone in thromboembolic prevention (mainly of ischemic stroke) in patients with AF, but also in the management of those with VTE and for primary prevention of VTE, e.g., during up to one month after orthopedic knee surgery. Anticoagulants are very effective in reducing the risk of stroke in patients with AF; in the landmark trials in the last ten years of the 20th century and first years of the 21st century on average

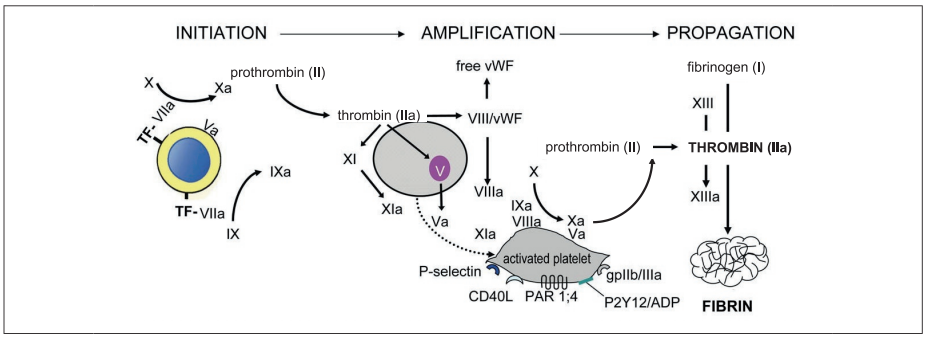

FIGURE 1 Overview of the coagulation cascade. In three phases different coagulation factors are sequentially activated, eventually resulting in the formation of fibrin (the major component of a thrombus). vWF = von Willebrand factor; TF = tissue factor.

This image was published in the following article: de Caterina R et al. General mechanisms of coagulation and targets of anticoagulants (Section I): Position paper of the ESC Working Group on Thrombosis – Task Force on anticoagulants in heart disease. Thromb Haemost. 2013 Feb 28;109(4):569–79. ©Georg Thieme Verlag KG (reprinted with permission).

a 67% reduction in ischemic stroke was seen with vitamin K antagonists (VKA) compared to placebo, which was clearly much higher than a 21% reduction in ischemic stroke in patients managed with aspirin.[11,12] Since 2011 direct oral anticoagulants (DOAC) may also be considered after RCTs showed a comparable or somewhat even better effect on the prevention of ischemic stroke, and on average less major bleeding, notably cerebral bleeds in those who participated in the trials.[11] Both VKA and DOAC inhibit the coagulation cascade but both in different ways. VKAs inhibit vitamin K (via inhibition of the enzyme vitamin K epoxide reductase, VKOR), which is necessary for activation of the coagulation factors II, VII, IX , X, protein C, and protein S.[1] The DOAC dabigatran directly inhibits the formation of factor IIa, and the DOACs rivaroxaban, apixaban, and edoxaban directly inhibit the formation of factor Xa. See Figure 1. Currently, in most patients with AF a DOAC is preferred above a VKA, except e.g., in patients with valvular AF (i.e., patients with moderate/severe mitral stenosis, and patients with mechanic heart valves)[13] in which a DOAC is contra-indicated. Evidence on DOAC safety is also less certain in some subgroups of patients, notably frail elderly or those with severe renal insufficiency.[14,15] Similarly, in all VTE patients, treatment with a VKA or DOAC is indicated, sometimes after initial lead-in treatment with low molecular heparins (LMWH). Both VKA and DOAC are then effective in preventing recurrent VTE and VTE-related death.[16] VTE patients are treated with anticoagulants for a minimum of 3 months, yet extended therapy can be considered to prevent a late recurrence depending on the speculated underlying recurrence risk. Hereto, multiple models have been developed and evaluated to predict recurrence risk in patients with unprovoked VTE.[17] More recently, a prediction model that could help in the prediction of both recurrent VTE and bleeding was developed which thus can be used to predict both the harms and benefits of extended anticoagulation therapy.[18]

Although anticoagulants are effective in the prevention and treatment of thromboembolic disease, the downside is the increased risk of bleeding. The incidence rate of ma-

jor bleeding in VTE patients on extended anticoagulation therapy is around 1.7 per 100 person-years in patients on VKA and 1.1 per 100 person-years in patients on DOAC.[19] The incidence rate of major bleeding in the landmark trials (comparing DOAC vs. VKA for AF patients) was between 2-4% per year for DOACs, and the incidence rate of intracranial bleeding was between 0.1-0.5% per year.[20–23] However, these trials handled strict inclusion and exclusion criteria resulting in a selected population with likely an *a priori* lower risk of bleeding. Indirect evidence comes from observational studies in unselected AF patients reporting on average much higher, yet also more heterogeneous incidence rates of major bleeding varying between 2.7 and even 16.0 per 100 person-years. Importantly, though, incidence rates of the most invalidating or fatal intracranial bleedings also vary, yet to a lesser extent, ranging between 0.05 and 1.1 per 100 person-years.[24] This wide range of reported bleeding events exemplifies that estimating bleeding risk is difficult and probably for a large part dependent on i) the bleeding definition used, ii) underlying patient characteristics, and iii) whether or not rigorous methods were used to capture all relevant bleeding episodes. This also underpins the difficulty clinicians face daily in balancing thrombosis and bleeding risk in individual patients.

BALANCING RISKS

Since both thromboembolic and bleeding events can have severe consequences, the risks of on the one hand preventing thromboembolism should be carefully weighed against bleeding events due to anticoagulants. To carefully decide on the best treatment option, physicians can use a *risk score* or *risk model* to estimate the risk of thromboembolic events and the risk of bleeding risk associated with anticoagulation. For estimating the bleeding risk in patients with AF or VTE, various models have been developed, yet few have been validated.[25] These scores and models can help to identify patients at increased risk for bleeding. However, many of these models are developed and validated for use in either AF or VTE patients on anticoagulants. However, in certain subgroups, the risks can be higher or lower than the calculated individual risk from the models. Notably, patients with cancer are known to have both an increased thromboembolic and bleeding risk, which also differs between cancers and anti-cancer treatments.[26] Finally, many prediction models are developed not using state-of-the-art methodology, often leading to overly optimistic predictions, and thus should not be used, or with great precaution.[27]

Balancing risks also plays an important role when *diagnosing* a thromboembolic disease. That is, finding a balance between the risks of over- and underdiagnosis. For example, in the case of VTE, there is the risk of underdiagnosis; VTE symptoms can be non-specific, and therefore delay in the diagnosis and even misdiagnosis of VTE can occur. On the other hand, there is the risk of overdiagnosis; patients who eventually show to have just subsegmental PE or no PE at all. These patients have been – in hindsight – unnecessarily referred to and undergone CT-pulmonary angiography (CTPA). E.g., in patients younger than 40 years suspected of PE and referred for CTPA, no clots were found in 42% of patients.[28] This is a high number given the fact that CTPA by itself is also not

without risks (i.e., risk of nephropathy and radiation-induced cancer).[29,30] Therefore, physicians face the difficult challenge to weigh the risk of under- and overdiagnosis when assessing a patient suspected of VTE.

Also, in patients with AF, there is a risk of overdiagnosis and underdiagnosis. AF is by nature a slowly progressive and in the beginning a paroxysmal condition; this may result in AF cases left undetected, particularly if symptoms are subtle, non-specific, and episodic in presentation. Such *underdetection* of AF may result in ischemic stroke being the first presentation of clinically manifest AF. Therefore, some advocate screening for AF detection to facilitate early diagnosis and anticoagulant treatment of AF in order to reduce the risk of devastating ischemic strokes, although only one study found a small net benefit of AF screening so far.[31] A large meta-analysis showed that AF screening in patients $\geq$65 years identifies AF in 1.44% of screened patients. In most of the included studies screening was performed by a single-lead ECG or 12-lead ECG (in some studies preceded by pulse palpitation) and in two studies a modified blood pressure device was used. This meta-analysis showed that these patients with AF detected through screening are at increased stroke risk, and for most of them, anticoagulants are indicated.[32] However, two opportunistic AF screening studies performed in Dutch primary care practices, in which AF screening was compared to usual care, did not find an increased detection rate of AF.[33,34] In an observational study using Dutch primary care data, a prevalence of AF of 1.4% in 2017 was found [35], which might also indicate that the same number of AF cases are already detected by providing usual care (at least in Dutch primary care), including e.g. pulse palpitation during blood pressure examination.

Apart from the potential benefits of earlier AF detection, there is increasing evidence that screening may also result in uncovering short episodes of AF, that carry a low risk of stroke, thus not necessitating anticoagulation therapy.[36] Although the definition used for what classifies as a 'short episode' varies across studies, treating all these patients with anticoagulation thus may be considered 'overdiagnosis' of AF. When atrial high-rate episodes $\geq$24 hours detected on a device (i.e., pacemaker), are confirmed AF episodes, this is called subclinical AF.[13] According to the guideline of the European society of cardiology, anticoagulants should be considered in patients with subclinical AF and a high CHA_2DS_2-VASc score.[13] Two randomized controlled trials on the benefit of AF screening show conflicting results. The STROKESTOP study found a small net benefit of AF screening (on the composite of ischemic stroke, hemorrhagic stroke, systemic embolism, major bleeding, and all-cause mortality).[31] However, the LOOP study did not find a significant reduction in the outcome of ischemic stroke and systemic embolism, yet more major bleeding was seen in the screening group (though not statistically significant).[37] In other words, AF screening might result in a small benefit by prevention of thromboembolic events, although it might also cause more harm by an increase in bleeding. More evidence on the net benefits of AF screening is urgently needed.

Balancing risks is thus an important topic for clinicians, certainly within the field of (suspected) thromboembolic disease, with potentially large effects on diagnosis, prognosis, and treatment of patients.

The clinical case described at the beginning of this introduction illustrates the challenge of balancing risks in a patient at risk for thromboembolic disease. First, when the patient is diagnosed with AF, the risks of stroke and bleeding need to be assessed to determine whether anticoagulation is indicated. The CHA_2DS_2-VASc score can be used to assess the stroke risk, and in this case, anticoagulation is indeed indicated (CHA_2DS_2-VASc score 3).[13] Next, during the period that the patient is diagnosed with cancer and receives chemotherapy the bleeding risk is increased. Because of nose bleeding, the GP contemplates temporarily interrupting the treatment with anticoagulants, however, this would increase substantially the risk of ischemic stroke. Importantly, we know that the risk of thromboembolic stroke, but also VTE, is also increased in patients with a recent cancer diagnosis. Cancer is a well-known risk factor leading to (periods of) a hypercoagulation state.[38] Nevertheless, in most clinical situations in which anticoagulation is considered necessary, the risk of thromboembolic events outweighs the risk of bleeding.[13,39] Yet, there are also situations in which the bleeding risk will outweigh the risk of thromboembolic events; e.g., when there are absolute contra-indications for anticoagulation such as a recent intracranial bleed, severe thrombocytopenia, or severe anemia.[13] Also in clinical situations without absolute contra-indication there can be doubt about whether the advantages of anticoagulant treatments outweigh its disadvantages. If Mrs. Verburg would not have had hypertension (CHA_2DS_2-VASc 2 in a woman based on her age between 65–75 years), the risk reduction in ischemic stroke would likely be too small for benefit of anticoagulation in case she did not have also colon cancer (which also increases the risk of thromboembolic events). To make it even more complicated, the risk of thromboembolic events but also the risk of bleeding changes over time depending on changes in the CHA_2DS_2-VASc score, but also on the development of (potentially intermittent) renal insufficiency or cancer in different stages of its treatment. Therefore, decisions on (dis)continuation of anticoagulation should be reconsidered on a regular basis. Of course, knowledge of how to weigh the risks associated with thromboembolic disease and its treatment is necessary for adequate communication with the patient and to come to shared decision-making.

AIMS OF THIS THESIS

The general aim of this thesis is to study the challenges related to balancing risks in patients with thromboembolic disease, and more specifically to:

i. Gain insight into the prevalence and determinants of diagnostic delay in patients with PE.

ii. Improve prediction of bleeding risk in patients with cancer while on anticoagulant treatment.

iii. Explore heterogeneity in the effect of integrated AF care in the primary care setting in order to find out who profits most (and least) from integrated AF care.

iv. Gain insight into sex differences in patients with early AF.

OUTLINE OF THIS THESIS

Diagnostic delay in patients with PE is common, yet the prevalence and extent of this delay have not been reviewed systematically. In **Chapter 2**, the results of a systematic review and meta-analysis on diagnostic delay in patients with PE are described. In this review, we describe how often delay occurs and what the important determinants of diagnostic delay are in patients with PE.

As in the case of Mrs. Verburg, cancer patients have an increased risk of thromboembolism, but unfortunately also of bleeding, and this latter risk is even higher if treated with anticoagulants. Currently, there is no validated bleeding risk model to estimate the bleeding risk in patients with cancer. In **Chapter 3**, the results of a prognostic observational study are presented on the bleeding risk in patients with cancer who are using anticoagulants for AF or VTE. Existing bleeding risk models were first externally validated in a primary care routine care registration and an updated competing risk model was internally validated using state-of-the-art methodology.

In **Chapter 4**, the results of a predictive *heterogeneity treatment effect (HTE)* analysis of the ALL-IN trial are presented. The ALL-IN trial was a cluster-randomized study performed among 1240 AF patients primarily managed in primary care.[40,41] It assessed integrated AF care versus usual care. Integrated AF care reduced all-cause mortality significantly. However, as is common in RCTs, only a single point estimate with 95% confidence interval is presented while this is the average effect. The aim of this study is to explore who profits most (and least) from integrated AF care in a primary care setting.

The increasing prevalence of AF and its associated morbidity and mortality asks for optimal AF management. Observational data can be used to evaluate how patients are managed in everyday clinical practice. In **Chapter 5**, the design of the DUTCH-AF study is described. This is a national registry of over 6000 newly diagnosed AF patients. The aims are to evaluate the safety and effectiveness of anticoagulation treatment and to facilitate registry-based randomized trials in the long-term.

In many cardiovascular diseases, differences in patient characteristics and outcomes between men and women are described, however, such data are scarce for patients with atrial fibrillation. In **Chapter 6**, the characteristics of women and men with early AF included in the DUTCH-AF study are described as well as differences in the one-year clinically relevant outcomes between the sexes.

Finally, in **Chapter 7**, the General discussion, the main findings of this thesis are summarized and discussed. Moreover, gaps of knowledge regarding bleeding risk in patients using anticoagulants for the prevention or treatment of thromboembolic disease will be discussed.

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AUTHORSHIP STATEMENT

The idea and set-up of the introduction were mine; I conducted the literature search and wrote the introduction. During the whole process, I asked for and implemented input and feedback from my supervisory team.

2

A SYSTEMATIC REVIEW AND META-ANALYSIS OF DIAGNOSTIC DELAY IN PULMONARY EMBOLISM

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Key Messages

- In this systematic review and meta-analysis with an extensive scope of all existing relevant studies on delay in diagnosing pulmonary embolism (PE), the mean diagnostic delay was almost one week and in a quarter of patients the delay was even longer.
- This emphasises the importance of increasing awareness on PE and educating patients and physicians on how to recognise PE.

ABSTRACT

Background Diagnostic delay in patients with pulmonary embolism (PE) is typical, yet the proportion of patients with PE that experienced delay and for how many days is less well described, nor are determinants for such delay.

Objectives This study aimed to assess the prevalence and extent of delay in diagnosing PE.

Methods A systematic literature search was performed to identify articles reporting delays in diagnosing PE. The primary outcome was mean delay (in days) or a percentage of patients with diagnostic delay (defined as PE diagnosis more than seven days after symptom onset). The secondary outcome was determinants of delay. Random-effect meta-analyses were applied to calculate a pooled estimate for mean delay and to explore heterogeneity in subgroups.

Results The literature search yielded 10,933 studies, of which 24 were included in the final analysis. The pooled estimate of the mean diagnostic delay based on 12 studies was 6.3 days (95% prediction interval 2.5 to 15.8). The percentage of patients having more than seven days of delay varied between 18% and 38%. All studies assessing the determinants of coughing (n=3), chronic lung disease (n=6) and heart failure (n=8) found a positive association with diagnostic delay. Similarly, all studies assessing recent surgery (n=7) and hypotension (n=6), as well as most studies assessing chest pain (n=8), found a negative association with diagnostic delay of PE.

Conclusion Patients may have symptoms for almost one week before PE is diagnosed and in about a quarter of patients, the diagnostic delay is even longer.

Keywords Pulmonary embolism; venous thromboembolism; delay; diagnosis; systematic review; meta-analysis.

INTRODUCTION

Pulmonary embolism (PE) is the most serious condition within the spectrum of venous thromboembolic (VTE) conditions, given its associated high mortality rate, as well as its related morbidity and frequent hospitalisation [1,2]. Prompt and early recognition of PE is thus paramount. Clinical prediction rules – such as the Wells criteria, Geneva rule or YEARS algorithm – can assist physicians in diagnosing PE in suspected patients [3-5]. However, these rules are useful only when the physician has a clinical suspicion of PE. It can be extremely challenging to diagnose PE on time because symptoms of PE can differ widely in severity, and are often non-specific [6,7]. In some patients ultimately diagnosed with PE, the suspicion either never arose or occurred only after multiple consultations. For example, the so-called 'classical' PE-triad of chest pain, dyspnoea, and haemoptysis occurs in less than 10% of patients [8].

Insight into the proportion of patients with PE that experienced delay and determinants associated with delay may help to increase awareness among physicians and patients, and thereby help to reduce diagnostic delay. This is especially meaningful for general practitioners (GPs) since patients with symptoms of PE often seek medical advice from their GP first. No previous study has systematically assessed the prevalence and extent of delay in diagnosing PE. Therefore, the purpose of this study was to systematically review the literature on studies reporting on delay in diagnosing PE. The primary objective was to assess the proportion of patients with PE that experienced diagnostic delay and the extent of this delay. A secondary objective was to identify determinants associated with a delayed diagnosis of PE.

METHODS

Search strategy

On 31 August 2021, we performed a literature search in Medline and Embase databases without date limits or language restrictions. The key terms in the search consisted of 'pulmonary embolism' and synonyms, combined with 'diagnostic delay', 'time to diagnosis', 'misdiagnosis' and alternative terms (See Appendix 1 for the full search syntax). Two reviewers (RvM and EMTR) screened the abstracts independently and selected original studies, describing any form of delay in the diagnostic management of PE. Subsequently, both reviewers independently selected full-text articles. In case of no consensus between these two researchers selecting a full-text article, a third researcher (GJG) was asked to screen the article in question, and a consensus was reached by discussion. We performed a cross-reference check for all included articles.

Definitions and study selection

For this study, 'diagnostic delay' was defined as the time between the onset of symptoms (as reported by patients and described in the original publication) until confirmation of

the diagnosis of PE. The primary objective was to quantify the presence of 'diagnostic delay', expressed as either a mean or median delay, or as a percentage of patients with diagnostic delay more than seven days. The secondary objective was to quantify determinants for such delay. Studies conducted in general practices, emergency departments and hospital wards were considered for this review. We excluded systematic reviews, case reports, and articles describing the outcome in a particular population, e.g. paediatric populations, only post-operative patients or pregnant women. Also, articles that only considered 'logistic delay', for example, the time between admission and confirmation of the diagnosis with imaging, were excluded from our review since our primary aim was to obtain a pooled point estimate of the total diagnostic delay. Finally, if there was no definition of delay mentioned or if we could not derive the definition of delay, the article was excluded.

Risk of bias and applicability assessment

No validated risk of bias tool was available for observational cross-sectional studies when we performed this review. Therefore, two reviewers independently assessed the risk of bias with modified criteria based on the QUADAS-2 tool [9]. We scored the risk of bias as high, low or unclear, within the following three domains: selection of study population (to assess generalisability and selection bias), validity of diagnostic testing (to assess information bias) and assessment of delay (to assess recall and information bias). Moreover we scored the applicability of studies to primary care. Studies performed in general practice or studies in which the GP referred patients are considered very applicable to primary care. Studies in which a part of the included patients were referred by their GP are considered likely applicable to primary care. Studies in which patients were included from emergency departments are considered as possibly applicable. Studies in which patients were included from hospital wards are deemed not applicable to primary care. If it was unclear from which setting patients were included, we considered the applicability to primary care as unclear. See Appendix 2 for the modified risk of bias and applicability tool used, including further clarification of these domains.

Data extraction and data analysis

The data were extracted using a standardised data extraction form. In addition to the primary objective to assess diagnostic delay of PE, we also collected data concerning our secondary objective, i.e. determinants for delay. Both determinants tested in univariable analysis and determinants tested in multivariable analysis were considered. We created an overview of clinically relevant determinants studied more than once and described whether a (significant) positive or negative association was found in the individual studies.

We performed a meta-analysis with studies that reported a mean delay since most studies reported a mean delay and not a median delay. Studies only reporting a median delay were excluded from this meta-analysis. We have sought contact with authors of studies only reporting a mean delay to obtain the median delay as well but unfortunately,

we received no response. We log-transformed the data because we assumed that the mean delay of the individual studies was not normally distributed. Random-effects meta-analysis was applied to calculate a pooled estimate with a 95% confidence interval and prediction interval for the mean diagnostic delay (defined in days). The prediction interval represents the range of estimates for the mean delay that can be found in future studies with a similar study design and thus can be considered as a measure of heterogeneity across studies [10]. Next, we performed meta-analyses to explain the heterogeneity in the following subgroups: studies that included only patients in the emergency department, studies with a low risk of bias due to misclassification, studies with the same definition of delay (time from onset of symptoms to diagnosis) and studies with prospective and retrospective data collection. Statistical analyses were performed in R version 3.4.1.

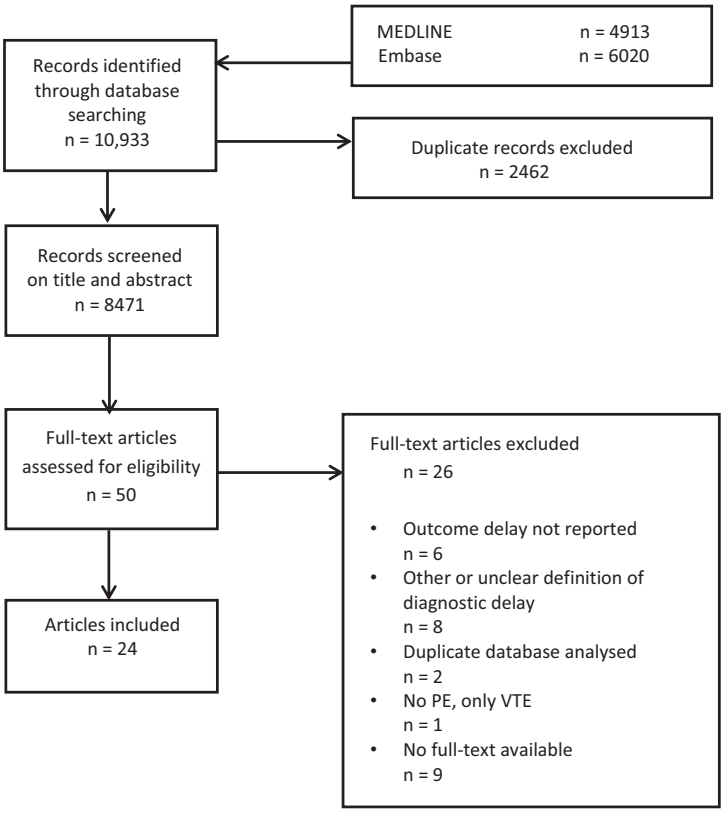

FIGURE 1 Flow-chart article selection

TABLE 1 Studies that assessed diagnostic delay in patients with pulmonary embolism

Study *Name first author + year of publication*	*n* *Patients with PE*	Patient characteristics *Mean age + SD (years)*	Female (%)	Setting inclusion *Emergency department (ED), during hospital admission (HA), general practice (GP)*	Design of data collection	Definition delay *Moment of start counting delay – moment of stop counting delay*	Mean delay *Mean (days) + standard deviation*	Delay > 7 days *Percentage of patients in this category*	Other categories of delay
Ageno 2008 [11]	542	59.8	57.4	HA + ED	Prospective	Symptoms – diagnosis			<5 days: 64% 5–10 days: 20% >10 days: 16%
Alonso-Martínez 2004 [12]	106	72 ± 11	46.2	HA	Prospective	Symptoms – hospital admission	10 ± 12		
Alonso-Martínez 2010 [23]	375	Median 75 IQR 15	49.6	HA	Prospective	Symptoms – diagnosis	Median 6 IQR 12		>6 days: 50% >14 days: 25% >21 days: 10%
Aranda 2021 [28]	150	61.2 ± 18	51.3	HA	Prospective	Symptoms – diagnosis		26%	
Aydoğdu 2013 [29]	53	65 ± 17	54.7	ED	Prospective	Symptoms – diagnosis	6.8 ± 7.7	38%	>1 day: 93%
Berghaus 2011 [30]	248	64.2 ± 16.4	60.5	HA	Retrospective	Symptoms – diagnosis	2.5 ± 1.9		
Bulbul 2009 [31]	178	60.4 ± 16.8	53.9	HA + ED	Retrospective	Symptoms – diagnosis	9.3 ± 11.6		
Bulbul 2011 [32]	156	64.1 ± 15.9	62.2	ED	Prospective	Symptoms – diagnosis	7.93 ± 10.05		
Chan 2020 [33]	302	[a]	[b]	HA	Retrospective	Symptoms – diagnosis		24%	
den Exter 2013 [34]	849	52 ± 18/56 ± 18[c]	58.2[d]	HA + ED	Prospective	Symptoms – diagnosis		19%	
Elliott 2005 [13]	344	61.3 ± 16.4	57.3	HA	Retrospective	Symptoms – diagnosis	4.8 ± 20.2	17%	>25 days: 5%
Goyard 2018 [14]	514	Median 65 IQR28	51.2	HA	Prospective	Symptoms – diagnosis	Median 3 IQR 8	27%	>3 days: 47%
Hendriksen 2017 [15]	128	56 ± 15/62 ± 18[e]	53.1	GP	Retrospective	First GP contact – diagnosis		26%	
Ilvan 2015 [16]	100	58.31 ± 15.13	46	ED	Retrospective	Symptoms – diagnosis	11.9 ± 22.6	28%	
Jenab 2014 [17]	195	59.2 ± 17.1	42.1	ED	Prospective	Symptoms – presentation hospital	5.6 ± 7.9		<1 day: 31% <3 days: 57% >1 month: 1%
Jiménez Castro 2007 [18]	397	69	55.4	ED	Prospective	Symptoms – diagnosis	Median 7	18%	>25 days: 6%
Kayhan 2012 [19]	189	57.95 ± 16.36	55.0	HA	Retrospective	Symptoms – diagnosis		37%	
Menéndez 1998 [20]	102	64 range 21–88	54.9	HA + ED	Retrospective	Symptoms – diagnosis	Median 4 range 3–11		
Ozlem 2016 [21]	11	71.5 ± 7.9	72.7	ED	Retrospective	Symptoms – ED admission	10.6 range 3–30		
Ozsu 2011 [22]	408	62.12 ± 16.2	57.4	HA + ED	Retrospective	Symptoms – diagnosis	6.9 ± 8.5	28%	
Pasha 2014 [24]	113	56 ± 17	46.9	HA + ED	Retrospective	Symptoms – presentation hospital	5.7 ± 9.2	18%	>1 month: 4%
Rahimi-Rad 2013 [25]	88	54.46 ± 17.27[f]	43.6[g]	HA + ED	Prospective	Symptoms – treatment	3.05 ± 6.42		
Walen 2016 [26]	261	60.6 ± 16.9	47.9	ED	Retrospective	Symptoms – diagnosis	8.6 ± 25.5	24%	>1 month: 6%
Zycińska 2013 [27]	53			HA	Retrospective	Symptoms – diagnosis	5		

[a]115 patients (38.1%) <65 years, 152 patients (50.3%) 65–84 years and 35 patients (11.6%) ≥85 years.
[b]77 female patients (67.0%) <65 years, 100 female patients (65.8%) 65–84 years and 25 female patients (71.4%) ≥85 years.
[c]Complaints < 7 days: 52 ± 18, complaints >7 days: 56 ± 18 (suspected PE patients).
[d]Suspected female PE patients.
[e]56 ± 15 (no diagnostic delay) 62 ± 18 (diagnostic delay).
[f]Baseline characteristics of 353 patients with PE, PE/DVT or DVT.
[g]43.6% female patients in a group of 353 patients with DVT, PE and DVT + PE patients.

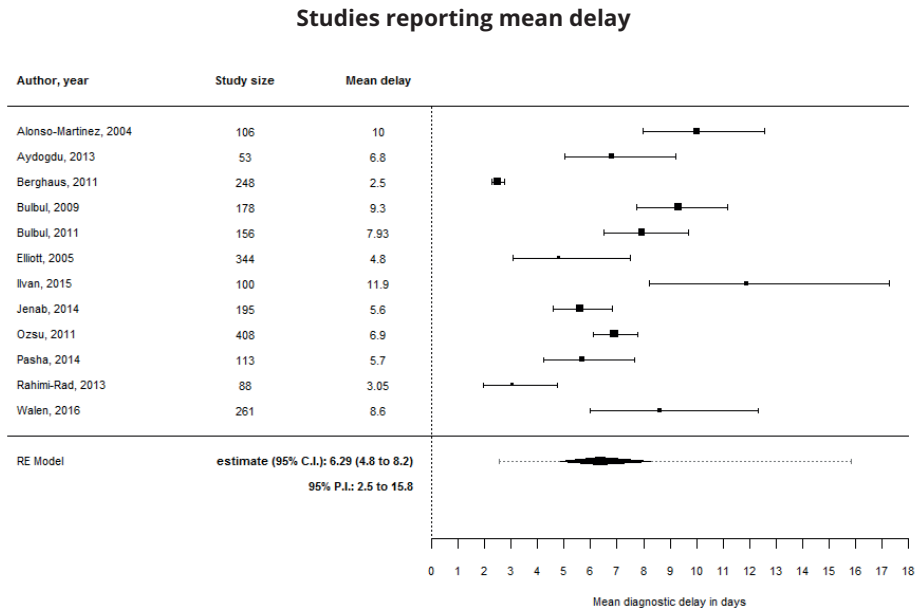

FIGURE 2 Meta-analysis of studies reporting mean delay

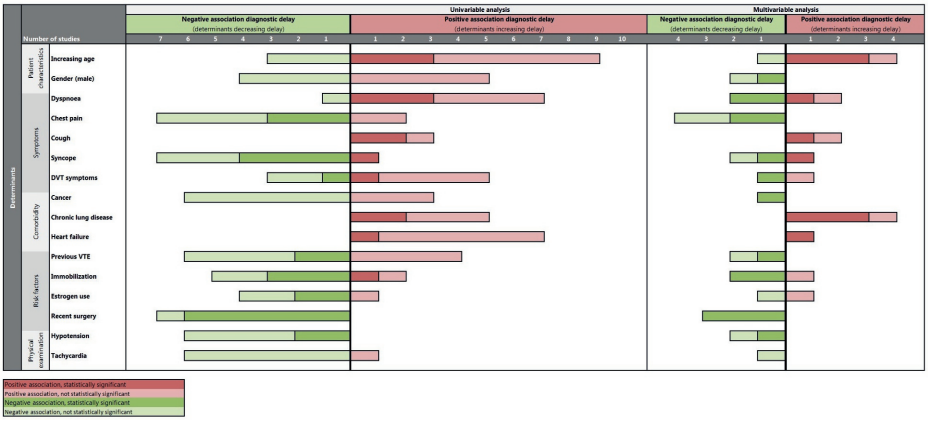

FIGURE 3 Determinants associated with diagnostic delay

RESULTS

The literature search yielded a total of 10,933 studies. After screening on title and abstract, we identified 50 articles, which we assessed for eligibility. Twenty-four articles met our in-and exclusion criteria [11-34]. For an overview of the literature search and article selection, see Figure 1. The 24 studies were published between 1998 and 2021. Data were collected retrospectively in 13 studies and collected prospectively in 11 studies. The included studies were performed in different settings, namely: primary care practices (n=1), emergency departments (n=7), hospital wards (n=9) or combinations (n=7). The characteristics of the included studies are presented in Table 1. The risk of bias regarding the domains of patient selection and valid diagnosis was assessed as 'low' in most studies. The risk of bias due to misclassification (assessment of delay) was assessed as 'high' in 10 studies, mostly because of retrospective data collection. Two studies were assessed as very applicable to primary care, five studies as likely applicable, five studies as possibly applicable, six studies as not applicable and for six studies the applicability to primary care was unclear. See Appendix 3 for the risk of bias and applicability assessment.

Diagnostic delay

In total, 12 studies presented a mean delay with standard deviation. Figure 2 shows the forest plot of all 12 studies reporting a mean delay in diagnosing PE. The reported mean delay ranged from 2.5 to 11.9 days. The pooled point estimate of the mean delay was 6.3 days (95% CI 4.8 to 8.2) with a wide prediction interval (95% PI 2.5 to 15.8 days). The mean delay in studies performed in emergency departments was 7.7 days (95% PI 4.6 to 12.8). In our further predefined subgroup analyses (i.e. analyses of only studies with a low risk of bias, with a uniform definition of delay, or only using either prospective or retrospective data collection) the prediction intervals remained wide, indicating residual and unexplained heterogeneity. Sixteen studies reported a percentage of patients with diagnostic delay. Thirteen of these fifteen studies categorised delay beyond seven days. More than seven days of delay varied between 18% and 38%. The primary outcomes are presented in Table 1.

Determinants associated with delay

Fourteen studies assessed determinants potentially associated with diagnostic delay. Figure 3 summarises these determinants and the positive or negative association with diagnostic delay found in the individual studies (See Appendix 4 for the complete overview). For many of the explored determinants, findings were inconclusive and sometimes conflicting across different studies. Nevertheless, from a narrative synthesis, we identified several determinants positively and negatively associated with diagnostic delay based on univariable and/or multivariable analyses, albeit not all statistically significant (Figure 3, Appendix 4). First, all of the three studies analysing coughing symptoms, all of the six studies analysing chronic lung disease and all of the eight studies analysing heart failure found a positive association of these determinants with diagnostic delay. Second, all of

the seven studies analysing recent surgery and all of the six studies analysing hypotension found a negative association of these determinants with diagnostic delay. Finally, seven out of nine studies analysing chest pain and six out of seven studies analysing tachycardia found a negative association with diagnostic delay.

DISCUSSION

Main findings

This systematic review shows that delay in diagnosing PE is common, with a pooled point estimate of a mean diagnostic delay of almost one week, albeit with a wide prediction interval indicating considerable heterogeneity between studies. About a quarter of patients had more than seven days of delay. Existing data suggest that patients with chronic cardiopulmonary co-morbidity or symptoms of coughing are at greater risk for delay. Yet, these observations were made only out of narrative synthesis from the included studies as formal meta-regression on determinants for delay was considered inappropriate due to differences in determinant definition and analytical techniques used.

Strengths and limitations

To the best of our knowledge, this is the first study to systematically describe the full scope and extent of delay in diagnosing PE. We performed a complete literature search without date or language restrictions and could provide an extensive scope of all existing relevant studies. Thereby, we were able to summarise the existing body of evidence on this important topic, hoping to provide some 'base evidence' for future studies embarking on this topic, allowing to compare findings from these new studies with the inferences found in our review. Furthermore, we pooled the mean delay using random-effect meta-analyses and explored heterogeneity. Some limitations, however, need to be taken into account. First, the mean diagnostic delay in days is probably not normally distributed, so providing a pooled estimate of the median delay would have been preferable. However, most studies only reported a mean delay with a standard deviation and therefore, we had to use the mean delay to calculate a pooled estimate. Second, in some of the included studies, delay was not clearly defined, necessitating us to use a proxy instead. The definition of delay also differed between the studies. Most of the included studies analysed the time from the onset of symptoms until the definitive confirmative diagnosis of PE. However, some studies reported the time from onset of symptoms until hospital admission, emergency department admission, or the start of treatment. For future diagnostic studies on PE, we would recommend reporting on diagnostic delay uniformly. We would suggest reporting the time between symptom onset (patient-reported) and confirmation of the PE diagnosis, and preferably also the time between symptom onset and the moment that the patient seeks medical attention to distinguish between patients and physicians delay. Third, the methodology of the included studies differed, for example, in determining the duration of diagnostic delay. In some studies, patients were interviewed after a confirmative diagnosis, which could introduce recall bias, which is difficult (or even

impossible) to adjust for. Finally, probably as an overall consequence of these above-described limitations, the between-study heterogeneity was considerable. An essential cause of heterogeneity was that patients were included from different settings (hospital wards, emergency departments and primary care). In our review both studies categorised as very applicable to primary care, found a similar percentage of patients delay of more than seven days (24% and 26%). However, since both patient and physician delays and the clinical implications of delay will be largely dependent on the setting of inclusion, this should be considered when interpreting our results.

Clinical implications

In our review, we focussed primarily on the prevalence and extent of diagnostic delay of PE. Although not the purpose of our study, we could hypothesise on possible explanations for the diagnostic delay of approximately a week. First and foremost, it might be that PE-symptoms are often not timely recognised by the physician and/or the patient. As mentioned before, symptoms of PE are often non-specific and can vary in severity. Consequently, it can be challenging to differentiate PE from alternative diagnoses, leading to a delay in the diagnostic process. This is supported by the fact that we found that delay seemed to occur more frequently in patients with comorbidities. Moreover, the decreasing prevalence of proven PE in suspected patients in diagnostic studies might suggest that physicians do think of PE quite often but still are struggling to correctly and timely identify PE in the right patients [35,36]. This emphasises the importance of increasing awareness of PE and educating physicians and patients on how to recognise PE, e.g. during (albeit not exclusively) events like World Thrombosis Day [37].

Second, another explanation for the diagnostic delay we found might be that PE is not an acute disease per se in *all* PE patients. With an average duration of symptoms almost a week before diagnosis, PE might rather be a subacute condition with slower onset of unfolding symptoms in a subset of patients, leading to a 'delayed', or perhaps better framed as a protracted and evolving, presentation. Should this be true, it could be that the delay in diagnosis *might* be associated with less negative clinical consequences in the patients with such a milder clinical trajectory. In that respect, it could well be that delay happens more often in patients with sub-segmental PE than in patients with lobular or more central PE's. Both possible explanations could also be valid simultaneously. Yet, given that PE can also have profound (long-term) implications, more research is urgently needed to gain insight into the outcomes of patients with and without a delayed diagnosis.

We could not study the clinical consequences of diagnostic delay since only a few of the included studies reported on clinical outcomes, such as recurrent PE or mortality. For instance, none of the included studies reported on clinical outcomes such as chronic thromboembolic pulmonary hypertension (CTEPH) or post-embolic syndrome. However, we know from the sparsely existing literature on post-embolic syndromes that a delayed diagnosis might be a risk factor for developing CTEPH [38].

CONCLUSION

Delay in diagnosing PE is common. Patients may have symptoms for almost one week before PE is diagnosed; in about a quarter of patients the diagnostic delay is even longer.

Author contributions EMTR, RvM, and GJG were involved in the study's design. EMTR and RvM performed the systematic search, screened articles on the title and abstract, and selected articles based on full-text assessment. GJG was involved in case of disagreement about article selection and a consensus was reached by discussion. EMTR and RvM performed the data extraction and data analysis. EMTR, RvM, FHR, and GJG were involved in drafting and revising the article. EMTR, RvM, FHR, and GJG approved the article's final version.

Disclosure statement The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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AUTHORSHIP STATEMENT

Rosanne van Maanen and I are joint first authors and equally contributed to defining the research question, performing the systematic literature search, conducting the data analysis, writing the manuscript, and implementing the contribution and feedback of the co-authors and external reviewers up to the final publication.

APPENDIX 1 Search: review diagnostic delay pulmonary embolism

PUBMED

(((((((Pulmonary Embolism*[tiab]) **OR** (Pulmonary Infarct* [tiab]) **OR** (Pulmonary Embolism[Mesh]) **OR** (pulmonary thromboembolism* [tiab])))))) **OR** "Venous Thromboembolism"[Mesh])) **OR** ((lung embol*[Title/Abstract] **OR** lung infarct*[Title/Abstract]))

AND

((((diagnos*[Title/Abstract]) **AND** (late[Title/Abstract] **OR** delay*[Title/Abstract] **OR** missed[Title/Abstract] **OR** missing[Title/Abstract] **OR** error*[Title/Abstract] **OR** inappropriate*[Title/Abstract] **OR** time[Title/Abstract] **OR** timing[Title/Abstract] **OR** timely[Title/Abstract])))) **OR** (("Delayed Diagnosis"[Mesh]) **OR** "Diagnostic Errors"[Mesh])) **OR** (misdiagnos*[tiab] **OR** undiagnos*[tiab])

EMBASE

'pulmonary embolism*':ti,ab,kw **OR** 'pulmonary infarct*':ti,ab,kw **OR** 'lung embolism*':ti,ab,kw **OR** 'pulmonary thromboembolism*':ti,ab,kw **OR** 'venous thromboembolism*':ti,ab,kw **OR** 'lung infarction*':ti,ab,kw **OR** 'lung embolism'/exp

AND

('diagnos*':ti,ab,kw **AND** ('late':ti,ab,kw **OR** 'delay':ti,ab,kw **OR** 'missing':ti,ab,kw **OR** 'missed':ti,ab,kw **OR** 'error':ti,ab,kw **OR** 'inappropiate*':ti,ab,kw **OR** 'time':ti,ab,kw **OR** 'timely':ti,ab,kw **OR** 'timing':ti,ab,kw))
OR ('delayed diagnos*':ti,ab,kw **OR** 'delayed diagnosis'/exp **OR** 'diagnostic error*':ti,ab,kw **OR** 'diagnostic error'/exp **OR** 'misdiagnos*':ti,ab,kw **OR** 'undiagnos*':ti,ab,kw)

APPENDIX 2 Risk of bias & applicability (based on QUADAS-2 tool)

Risk of bias assessment			
Domain	**Patient selection**	**Valid diagnosis**	**Assessment of delay**
Description	Describe methods of patient selection: Describe included patients?	Describe the test used for final diagnosis.	Describe the method of assessment of delay.
Signalling questions	Was a consecutive or random sample of patients enrolled?	Was a CT-scan, V/Q-scan, perfusion scan or ultrasound proven DVT with PE symptoms performed?	- What was the study type? - Risk of recall bias? - Was the delay reported by patients/ doctor/ both? - Was the health record of the patient used?
	Did the study avoid inappropriate exclusions?*		
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the test used for diagnosis have introduced bias?	Could the assessment of delay have introduced bias?

Applicability to primary care				
Signalling question	Are the included patients in the original studies comparable to patients in primary care?			
Very applicable: Patients included in primary care OR Patients referred by a general practitioner	Likely applicable: Patients partly included in primary care or outpatient clinic	Possibly applicable: Patients included in emergency departments	Not applicable: Patients included in hospital wards during admission	Unclear: Not clearly explained where and how patients are included

* >5% exclusion due to lost to follow-up was classified as 'high' risk of bias

APPENDIX 3 Risk of bias & Applicability

Study	Risk of bias			Applicability to primary care
	Patient selection	Valid diagnosis	Assessment of delay	
Ageno 2008	Low	Low	Low	Likely
Alonso-Martinez 2004	Low	Low	Unclear	Not
Alonso-Martinez 2010	Low	Low	Unclear	Not
Aranda 2021	High	Low	Unclear	Not
Aydogdu 2013	Low	Low	Unclear	Possibly
Berghaus 2011	Low	Low	High	Not
Bulbul 2009	Low	Low	High	Unclear
Bulbul 2011	High	Low	Low	Unclear
Chan 2020	Low	Low	High	Not
Den Exter 2013	Low	Low	Unclear	Likely
Elliott 2005	Unclear	Low	Unclear	Unclear
Goyard 2018	Low	Low	Low	Unclear
Hendriksen 2017	Low	Low	High	Very
Ilvan 2015	Low	Low	High	Possibly
Jenab 2014	Low	Low	Low	Possibly
Jimenez 2007	Low	Low	Unclear	Possibly
Kayhan 2012	Low	Low	High	Not
Menéndez 1998	High	Low	High	Unclear
Ozlem 2016	High	Low	High	Possibly
Ozsu 2011	High	Low	High	Likely
Pasha 2014	Low	Low	Low	Likely
Rahimi-Rad 2013	Low	Low	Unclear	Unclear
Walen 2016	High	Low	High	Very
Zycinska 2013	Low	Unclear	Unclear	Likely

APPENDIX 4 Factors associated with diagnostic delay

		Patient characteristics		Symptoms					Comorbidity				Risk factors					Physical examination	
		Gender (male)	Age	Dyspnoea	Chest pain	Cough	DVT (symptoms)	Syncope	Cancer	Chronic lung disease	Heart Failure	Prior Pulmonary Infection	Previous VTE	Smoking	Immobilization	Recent surgery	Oestrogen use	Hypotension	Tachycardia
		Univariable analysis																	
Ageno	2008	= (-)	= (-)	= (+)	= (-)			= (-)	= (-)				= (-)						
Alonso-Mar.	2010		+		= (-)			-					-						
Bulbul	2009	= (+)	= (-)	= (-)	= (-)	+	= (-)											-	= (-)
Bulbul	2011		= (+)	= (+)	= (+)		= (+)	-						= (+)		-		-	
Den Exter	2013	= (+)	+						= (-)	+	+		= (+)		-	-	-		
Goyard	2018	= (-)	= (+)	+	= (-)		= (+)	-	= (-)	= (+)	= (+)		-		-	-	= (+)	= (-)	= (-)
Hendriksen	2017	= (-)	+	= (+)	-	+	-	= (-)	= (+)	+	= (+)	+	= (+)	= (-)	= (-)	= (-)	= (-)		= (-)
Jenab	2014	= (+)	= (+)	+	-		+	= (-)	= (+)		= (+)		= (-)	= (+)	-	-	-	= (-)	= (-)
Jimenez	2007	= (+)	(-)	= (+)	= (+)		= (+)	+	= (+)	= (+)	= (+)		= (+)		= (-)	-		= (-)	= (-)
Ozsu	2011		= (+)				= (+)	-	= (-)		= (+)		= (-)		+	-	= (+)	= (-)	= (+)
Pasha	2014	= (-)	= (+)						= (-)	= (+)	= (+)		= (-)		= (+)				
Walen	2016	= (+)	= (+)	+	-	= (+)	= (-)		= (-)				= (+)						= (-)
		Multivariable analysis																	
Bulbul	2009				= (-)	+												-	
Chan	2020		+	-				+		+	+								
Den Exter	2013		+							+					-	-			
Goyard	2018	= (-)	= (+)	+	= (-)		= (+)	-		= (+)			-		-	-	= (-)	= (-)	= (-)
Hendriksen	2017	-	+	-	-					+		+							
Kayhan	2012		= (-)											-					
Ozsu	2011							= (-)	-				= (-)		= (+)	-	= (+)		
Walen	2016			= (+)	-	= (+)	-												

+ Positive association with delay
- Negative association with delay
= No statistically significant association with delay

3

EXTERNAL VALIDATION AND UPDATING OF PREDICTION MODELS OF BLEEDING RISK IN CANCER PATIENTS RECEIVING ANTICOAGULANTS

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ABSTRACT

Objective Cancer patients are at increased bleeding risk, and anticoagulants increase this risk even more. Yet, validated bleeding risk models for prediction of bleeding risk in cancer patients are lacking. The aim of this study is to predict bleeding risk in anticoagulated cancer patients.

Methods We performed a study using the routine health care database of the Julius General Practitioners' Network. Five bleeding risk models were selected for external validation. Patients with a new cancer episode during anticoagulant treatment or those initiating anticoagulation during active cancer were included. The outcome was the composite of major bleeding and clinically relevant non-major (CRNM) bleeding. Next, we internally validated an updated bleeding risk model accounting for the competing risk of death.

Results The validation cohort consisted of 1304 cancer patients, mean age 74.0±10.9 years, 52.2% males. In total 215 (16.5%) patients developed a first major or CRNM bleeding during a mean follow-up of 1.5 years (incidence rate: 11.0 per 100 person-years (95% CI 9.6-12.5)). The C-statistics of all selected bleeding risk models were low, around 0.56. Internal validation of an updated model accounting for death as competing risk showed a slightly improved C-statistic of 0.61 (95% CI 0.54-0.70). Upon updating, only age and a history of bleeding appeared to contribute to the prediction of bleeding risk.

Conclusions Existing bleeding risk models cannot accurately differentiate bleeding risk between patients. Future studies may use our updated model as a starting point for further development of bleeding risk models in cancer patients.

Key words venous thromboembolism, atrial fibrillation, neoplasms, risk assessment, validation study

Key messages

What is already known on this topic
Bleeding risk is increased in patients with cancer, yet validated models for the prediction of bleeding risk in cancer patients are lacking.

What this study adds
External validation of existing bleeding risk models was performed in routine primary healthcare data. These models cannot accurately predict bleeding in cancer patients. Upon updating, only age and history of bleeding contributed to the prediction of bleeding risk.

How this study might affect research practice or policy
Only age and a history of bleeding were shown to have incremental predictive value and could be considered in future prediction models for bleeding in cancer patients at risk for thromboembolic complications.

INTRODUCTION

Cancer patients using anticoagulants for treatment of venous thromboembolism (VTE) or prevention of stroke in atrial fibrillation (AF) are at increased risk of thrombosis due to the hypercoagulability state of cancer itself as well as caused by its treatment.[1] However, these patients are also at an increased risk of bleeding.[2] For example, cancer patients may need to undergo chemotherapy which often causes thrombocytopenia, drug interactions, periods of reduced renal function, and suboptimal nutritional status, which all may increase bleeding risk. Invasive procedures such as surgery, intravenous access lines, and biopsies also carry an increased bleeding risk, notably in anticoagulated patients.[2] Finally, the malignant tumor itself may also cause spontaneous bleeding, for example gastrointestinal-, lung- or brain tumors.[3–5] Hence, even though often clearly indicated, anticoagulant therapy in cancer patients with VTE or AF is a complicated clinical endeavor, notably during certain periods of the disease, warranting constantly a vigorous balance between bleeding and thrombosis risk.

It is therefore important to identify cancer patients with an increased risk of bleeding. While *on average* patients may have a net benefit of anticoagulation, for *individualized* treatment decisions a bleeding risk assessment can aid in shared decision-making.[6] A bleeding risk model could be used to monitor the bleeding risk during anticoagulant treatment and to identify individual moments of increased bleeding risk where monitoring or perhaps temporarily reduced dosing may be warranted. Moreover, in patients with advanced cancer and a limited life expectancy, the bleeding risk can outweigh the thrombosis risk reduction, and stopping anticoagulant treatment may perhaps be the preferred option. Knowledge of what then defines and differentiates bleeding risk between patients is paramount.

To assess the risk of bleeding, various risk prediction models have been developed for patients with VTE or AF. These bleeding risk models include various common predictors, e.g., age, comorbidities, and the concurrent use of medication such as antiplatelet drugs. Some models also include cancer as a predictor to account for the increased bleeding risk in these patients. However, none of the published bleeding risk models has ever been evaluated in a cohort of cancer patients using healthcare data from primary care including clinically relevant non-major (CRNM) bleeding complications occurring outside the hospital. Therefore, we aimed to externally validate commonly used bleeding risk models in cancer patients in the primary care setting. We will update and internally validate the best-performing bleeding risk model for use in this vulnerable population.

METHODS

Selection and appraisal of existing bleeding risk models

A priori we selected five existing bleeding risk models based on their common use and the availability of predictors in routine primary healthcare. We selected models developed to predict bleeding in either AF and/or VTE patients receiving anticoagulants. The

selected models were: HAS-BLED, ATRIA, ORBIT, VTE-bleed, and the AF-bleed.[7–11] The VTE-bleed was developed specifically for the prediction of bleeding in VTE patients, the HAS-BLED, ORBIT, and ATRIA for the prediction of bleeding in AF patients. The AF-bleed is an adaptation of the VTE-bleed for the prediction of bleeding in AF patients. The risk of bias was assessed using the PROBAST tool.

Source of the external validation cohort

To validate each bleeding risk model, we used a retrospective, observational cohort from the Julius General Practitioners' Network (JGPN). The JGPN database contains longitudinal routine health care data of more than 450,000 individuals from the 90s of the last century onward, de-identified extracted from the electronic medical files of general practitioners in the vicinity of Utrecht in the Netherlands.[12,13] People included in the JGPN database represent the Dutch population, except for nursing home residents who are not represented in this database.

In- and exclusion criteria for the external validation cohort

From May 2000 until January 2022 all patients with a new cancer episode during anticoagulant treatment either with a vitamin K antagonist (VKA), a direct oral anticoagulant (DOAC), low molecular weight heparin (LMWH), or heparin indicated for either the treatment of VTE or stroke prevention in AF – were included. We only selected patients with a new cancer diagnosis to limit the validation cohort to patients with active cancer. Patients with all types of cancer were eligible for inclusion, except for patients with basal cell carcinoma of the skin. Both patients already using anticoagulants, that is, *before* the cancer diagnosis (most often for AF), and patients who initiated anticoagulant treatment no longer than six months *after* the index cancer diagnosis were eligible for inclusion. For patient selection, we used the ICPC codes (International Classification of Primary Care) for AF, VTE, and any type of cancer excluding basal cell carcinoma, and ATC (Anatomical Therapeutic Chemical) codes for anticoagulants.[14] For an overview, see Supplement 1.

Data collection

For patients already using anticoagulants before the cancer diagnosis, data collection started on the date of the cancer diagnosis (i.e., the index date). For patients with active cancer who initiated anticoagulants within six months after the cancer diagnosis, the index date is the date of the first prescription of the anticoagulant. We used a maximum of three years of follow-up data, after which the disease episode of *active* cancer was considered dissolved. Because the theoretical end date of a drug prescription often does not correspond with the actual end of anticoagulant treatment (due to, for instance, stockpiling or medication non-compliance), we used a "grace" period of 14 days to extend the anticoagulant treatment period after the date of the last prescription to adjust for this, an approach often applied in the field of bleeding risk analyses.[15] ICPC codes and ATC codes used for predictors and bleeding outcomes are listed in Supplement 1.

Outcome definition

The outcome of this study was the composite of major and CRNM bleeding defined as all bleeding events which at least led to face-to-face evaluation by a healthcare professional, based on the ISTH criteria.[16] For data on bleeding, both coded data and free text data were used. For every face-to-face contact registered under any bleeding-, cancer-, VTE- or AF-related ICPC, the free text of the consultation was evaluated to verify that the patient in fact had a (new) bleeding event and to assess the location and type of bleeding. Outcome events were assessed without knowledge of the predictor information.

Predictor definition

Where possible we aimed to use the same definition for each predictor as described in the original validation study of each included risk model. If the exact information was not available, we used the best available approximation. See Supplement 2 for an overview of the predictor definitions used in our study. The absence or presence of predictors was assessed without knowledge of the outcome. In absence of an ICPC code or ATC code, the predictor was considered absent. Missing data on predictors was not imputed to reflect daily practice.

Data analysis

An incidence rate of the number of bleeds per 100 person-years with a 95% confidence interval (CI) for a first CRNM or major bleeding during anticoagulant treatment was calculated. Data analyses were performed in R v 4.0.5.

External validation

To determine the predictive performance of the selected bleeding risk models in our study population, we aimed to assess calibration and discrimination. For discrimination, expressing the proportion in which the bleeding risk model correctly assigns the highest risk to those *with* a bleed in a random pair of patients (one with a bleed and one without a bleed) we calculated the C-statistic with corresponding 95% CI. For calibration, in absence of the *expected* risk compared to the *observed* bleeding risk (O/E ratio) and subsequent calibration plots, we reported the *observed* bleeding risk in each of the risk categories (as a proxy of the *expected* risk) where relevant.

Model updating and internal validation

Three Cox proportional hazards models were fitted. First, a simple baseline model was fitted including only the predictors 'age' and 'sex'. Next, this baseline model was updated by including all predictors included in at least two out of four of the existing bleeding risk models selected for external validation. Finally, we added in a third model as a dichotomous variable the cancer types with a high risk of bleeding (i.e., mucosal tumors and lung tumors) versus all other types of cancer. To account for possible non-linearity of age, a restricted cubic spline with four knots was used. For all three models, Akaike's Information Criterion (AIC) was determined and likelihood ratio tests (LRT) were performed to compare the fit of the models. A final model was selected based on AIC and LRT. To

account for the competing risks of non-bleeding-related death, a cause-specific hazard model was used for internal validation.[17] The model was internally validated using 10-fold cross-validation, and calibration and discrimination were calculated. Finally, as an additional explorative analysis, backward elimination based on AIC was used for model reduction [18], and the predicted bleeding risk associated with the remaining predictors was plotted. Proportional hazard assumptions were visually checked for the final model by plotting scaled Schoenfeld residuals for every predictor.

Ethics

The study was conducted in accordance with the General Data Protection Regulation (GDPR) and other regulations, acts, and guidelines. The Medical Research Ethics Committee (MREC) of the UMC Utrecht confirmed that the Dutch law on Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that official approval of this study by the MREC was not required under Dutch legislation. For this study only de-identified data were used, meaning data cannot be directly traced back to the patient.

RESULTS

Descriptive statistics study population

The validation cohort consisted of 1304 cancer patients, mean age 74.0±10.9 years, 52.2% male. In total, 365 (28%) patients had a VTE diagnosis, 883 (67.7%) an AF diagnosis and 56 (4.3%) patients had both an AF and VTE diagnosis (Table 1). At the index date, 655 (50.2%) patients used a VKA, 361 (27.7%) a DOAC, 285 (21.9%) LMWH, and 3 (0.2%) patients heparin.

Bleeding events in the validation cohort

In total 215 (16.5%) patients had at least one major or CRNM bleeding event during a mean follow-up of 1.5 (SD 1.2) years. The incidence rate for a first major or CRNM bleeding was 11.0 per 100 person-years (95% CI 9.6-12.5). Tables 2 and 3 provide an overview of the bleeding locations and characteristics of patients with and without bleeding, respectively.

External validation of the existing bleeding risk models

See Supplement 3 for the risk of bias assessment of the selected bleeding risk models. In Table 4 the C-statistics with 95% CI for each of the existing bleeding risk models are presented. The C-statistics ranged between 0.55 (95% CI 0.51-0.59) and 0.56 (95% CI 0.52-0.60). Since we were not able to formally assess the calibration of the models, Table 5 shows the distribution of patients and bleeding events across the risk strata of each bleeding risk model. Because all patients in our study have cancer, all patients were categorized in the high-risk category in case of the VTE-bleed. For some bleeding risk models, there was a doubling of the observed bleeding risk in the higher risk categories compared to the lower risk categories, for other bleeding risk models this increase was less pronounced.

TABLE 1 Characteristics of the 1304 patients with cancer and anticoagulant treatment subdivided in patients with VTE, AF, or both

	VTE (N=365)	AF (N=883)	VTE & AF (N=56)	Total (N=1304)
Mean Age in years (SD)	66.8 (12.6)	76.8 (8.6)	77.4 (9.3)	74.0 (10.9)
Male sex (n,%)	171 (46.8)	484 (54.8)	26 (46.4)	681 (52.2)
Type of cancer (n,%)				
Gastro-intestinal	63 (17.3)	158 (17.9)	7 (12.5)	228 (17.5)
Lung	64 (17.5)	122 (13.8)	8 (14.3)	194 (14.9%)
Breast	44 (12.1)	93 (10.5)	8 (14.3)	145 (11.1%)
Prostate	25 (6.8)	65 (7.4)	2 (3.6)	92 (7.1%)
Urogenital	41 (11.2)	114 (12.9)	9 (16.1)	164 (12.6)
Hematologic	31 (8.5)	61 (6.9)	4 (7.1)	96 (7.4)
Skin	25 (6.8)	171 (19.4)	11 (19.6)	207 (15.9)
Other	72 (19.7)	99 (11.2)	7 (12.5)	178 (13.7)
Type of anticoagulant (n,%)				
VKA	100 (27.4)	528 (59.8)	27 (48.2)	655 (50.2)
Heparin	1 (0.3)	2 (0.2)	0	3 (0.2)
LMWH	182 (49.9)	92 (10.4)	11 (19.6)	285 (21.9)
NOAC	82 (22.5)	261 (29.6)	18 (32.1)	361 (27.7)

Model updating and internal validation

Our second model, consisting of the variables age, sex, hypertension, history of bleeding, renal insufficiency, anaemia, and use of antiplatelet drugs performed best. For an elaboration, see Supplement 4. The adjusted C-statistic of the competing risk model after internal validation was 0.61 (95% CI 0.54-0.70). Table 6 demonstrates the hazard ratios, confidence intervals, and internal validation performance measures of the competing risk model. In Figure 1 the calibration plot of the final model is shown. Based on backward selection using model 2, only the predictors 'age' and 'history of bleeding' remained in the model. See Figure 2 for the association between the expected bleeding risk and the predictors 'age' and 'history of bleeding'.

TABLE 2 Bleeding location of major and clinically relevant non-major bleeding for which 215 of the 1304 patients with cancer and anticoagulant treatment contacted the GP during a mean follow up of 1.5 years

	Total (N=215)
	(n,%)
Skin	77 (35.8%)
Urogenital tract	53 (24.7%)
Gastrointestinal tract	27 (12.6%)
Ear/nose/throat	22 (10.2%)
Other	20 (9.3%)
Respiratory tract	10 (4.7%)
Intracranial	6 (2.8%)

TABLE 3 Characteristics of the 1304 patients with cancer and anticoagulation divided into those with and without bleeding event

	Bleeding (N=215)	**No bleeding (N=1089)**	**Overall (N=1304)**
Mean age in years (SD)	75.7 (9.2)	73.7 (11.1)	74.0 (10.9)
Male sex (n,%)	111 (51.6)	570 (52.3)	681 (52.2)
VTE (n,%)	61 (28.4)	360 (33.1)	421 (32.3)
AF (n,%)	163 (75.8)	776 (71.3)	939 (72.0)
History of hypertension (n,%)	132 (61.4)	591 (54.3)	723 (55.4)
History of CVA (n,%)	31 (14.4%)	163 (15.0)	194 (14.9)
History of diabetes (n,%)	42 (19.5)	265 (24.3)	307 (23.5)
History of anemia	22 (10.2)	123 (11.3)	145 (11.1)
History of renal insufficiency (n,%)	31 (14.4)	125 (11.5)	156 (12.0)

TABLE 4 External validation of five bleeding risk models in the total study population; C-statistics with 95% confidence interval

	VTE-bleed	**AF-bleed**	**HAS-BLED**	**ATRIA**	**ORBIT**
C-statistic	0.56	0.56	0.56	0.55	0.56
95% CI	0.52 - 0.60	0.51-0.60	0.52 - 0.60	0.51 – 0.59	0.52 - 0.60

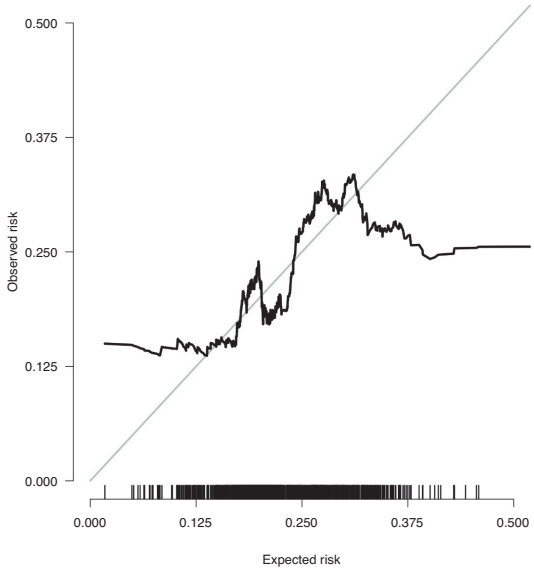

FIGURE 1 Calibration plot final model

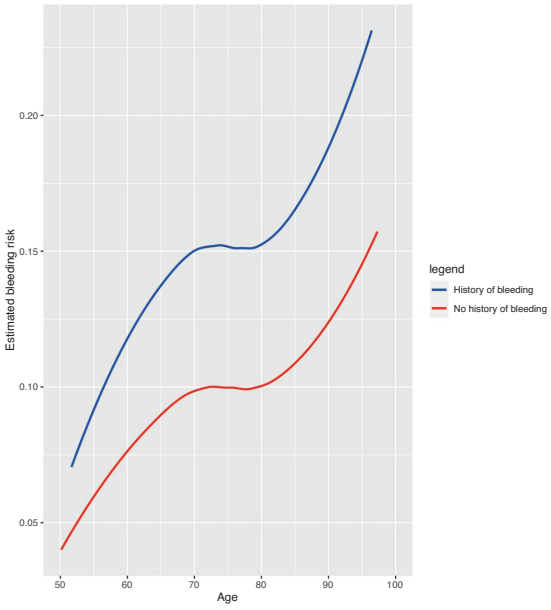

FIGURE 2 Relation between estimated bleeding risk, age and history of bleeding

TABLE 5 Distribution of patients and bleeding events across the risk categories of each bleeding risk model

	VTE-bleed			**AF-bleed**			**HASBLED**			**ATRIA**			**ORBIT**		
Risk category	Distribution of points	n/total	**IR with 95% CI**	Distribution of points	n/total	**IR with 95% CI**	Distribution of points	n/total	**IR with 95% CI**	Distribution of points	n/total	**IR with 95% CI**	Distribution of points	n/total	**IR with 95% CI**
Low	≤1 points	-	-	≤2 points	36/298	8.1 [5.7-11.2]	0 points	10/106	7.6 [3.7-14.0]	0-3 points	81/584	8.9 [7.1-11.1]	≤2 points	130/892	9.4 [7.9-11.2]
Medium	N/A	N/A	N/A	N/A	N/A	N/A	1-2 points	126/837	9.5 [7.9-11.3]	4 points	26/194	8.7 [5.7-12.8]	3 points	48/243	13.6 [10.1-18.1]
High	≥ 2 points	215/1304	11.0 [9.6-12.5]	≥ 3 points	179/1006	11.8 [10.2-13.7]	≥ 3 points	79/361	15.7 [12.4-19.5]	≥ 5 points	108/526	14.3 [11.7-17.3]	≥ 4 points	37/169	16.4 [11.5-22.6]
Total		215/1304	11.0 [9.6-12.5]		215/1304	11.0 [9.6-12.5]		215/1304	11.0 [9.6-12.5]		215/1304	11.0 [9.6-12.5]		215/1304	11.0 [9.6-12.5]

IR= Incidence rate per 100 person-years with 95% confidence interval
N/A=not applicable

n/total = number of bleeding events/ total number of patients in the corresponding risk category

TABLE 6 Internal validation of the competing risk model

	Hazard ratio	95% Confidence interval
Age	1.0	1.0-1.1
Age'	0.9	0.8-1.0
Age"	1.4	0.8-2.5
Sex	0.9	0.7-1.3
Anemia	1.0	0.7-1.4
Renal insufficiency	1.1	0.7-1.6
Antiplatelet use	1.5	0.9-2.5
History of hypertension	1.1	0.9-1.5
History of bleeding	1.5	1.1-2.0
C-statistic	0.61	0.54-0.70
R^2	0.018	
Brier score	0.13	0.12-0.15

A cubic spline with 4 knots was used to account for non-linearity of the variable *age*. The variable *age* is therefore divided in 3 groups depicted as age, age' and age".

DISCUSSION

Our study shows that while bleeding is common in cancer patients receiving anticoagulants (11 per 100 patient years), existing and updated bleeding risk models with commonly available predictor variables were unable to differentiate the risk of bleeding in this population. Only age and a history of bleeding appeared to be relevant to estimate bleeding risk in our primary care dataset.

Comparison with literature

The incidence rate of a first major or CRNM bleeding event in our study was 11.0 per 100 person-years, which was higher than in previous studies in AF [8–11], and in VTE patients (7). Because we selectively focussed on cancer patients and could include CRNM bleedings only seen by the GP and not necessarily by specialists, our incidence rate indeed is much higher. In a recently published study performed in patients with cancer-associated thrombosis who were included in a randomized trial, an incidence of major and CRNM bleeding of 14.2% was found during a follow-up period of 12 months [19], which is more comparable to what we found. Such a high bleeding risk certainly calls for a careful and shared decision on anticoagulant treatment based on an individually predicted bleeding risk.

Performance of existing bleeding risk models including an updated competing risk model

This study showed that predicting bleeding risk in cancer patients is difficult with existing bleeding risk models. The C-statistics of 0.56 for all existing models indicate that in two individual cancer patients on anticoagulant treatment, one experiencing bleeding and the other not, the probability that the patient experiencing the bleeding event receives a higher estimated bleeding risk from available models is 'only' 56%, thus almost similar as to flipping a coin. Model updating using state-of-the-art methodology only slightly improved model performance, yet this still would be considered poor performance against current standards. Moreover, this updated model did not yield sufficient calibration, likely due to insufficient sample size.

Likely other predictors, not included in the valuated prediction models, may be predictive of bleeding in cancer patients. Identifying these predictors and incorporating these in prediction models for bleeding should be the focus of further studies. The recently developed CAT-BLEED model (developed in patients with cancer-associated thrombosis) includes cancer-related factors such as cancer subtypes and associated chemotherapy.[19] Although detailed information on chemotherapy was not available in our dataset, we were not able to confirm that cancer subtypes provide reliable incremental prognostic information with relation to bleeding risk. We did however observe that age and a prior history of bleeding are useful, and these predictors are 'ready at hand'.

Clinical implications and future considerations

For patients with active cancer using anticoagulants, a clinically relevant or major bleed may be an impactful event that perhaps could influence further anticoagulant treatment decisions. Our analyses demonstrate that such bleeding events indeed occur frequently in anticoagulated cancer patients, highlighting the need for shared decision-making with respect to anticoagulant treatment. To support such decisions, e.g. (temporarily) withholding anticoagulation, reducing the dose, or switching between anticoagulants, an accurately predicted risk of bleeding for balancing against the benefits of anticoagulation is an important necessity. There are several steps to be taken to improve prediction in future research. First, to improve the value of *known* predictors, reporting on bleeding risk models and the modeling itself need improvement. All models included in our study had a high risk of bias according to the PROBAST guideline due to the lack of relevant information on e.g. predictor selection or predictor assessment, not handling missing data appropriately, or not accounting for competing risk. This in fact is a more general call for better reporting on bleeding risk models, not only for the subgroup of cancer patients. Second, further research is needed to identify *future* cancer-specific risk factors for bleeding and to include these in bleeding risk models. Ultimately, though, after accurate *prediction*, RCTs are needed that evaluate clinically relevant outcomes when anticoagulation is reduced with the aim to mitigate bleeding risk in high-risk individuals. Thus, not only identifying those who may experience a bleed but also what to employ in order to prevent these bleeds. Finally, future developments in anticoagulants with lower risk of bleeding, such as with factor XIa inhibitors are promising. These drugs are currently tested in phase II and III trials, and they may also reduce bleeding risk in cancer patients as they do in patients without cancer.[20,21]

Strengths and limitations

A strength of this study is that the dataset consisted of a large and representative sample of anticoagulated cancer patients with VTE and/or AF, managed in the community (with data extracted from a longitudinal primary care database), encompassing all cancer patients, also those only seen by the GP for bleeding complications. All clinically relevant bleeding outcomes could be included, also clinically relevant non-major bleeding only reported by patients to the GP, including e.g. so-called 'nuisance' bleeds' (euphemistically), which are not always reported or registered in hospital datasets. Also, clinically

relevant bleeding which occurred in the hospital setting was registered in our database as well, and thus included in our analysis. For model updating, we used state-of-the-art methodology including a cause-specific Cox proportional hazard model, which is a recommended method for analysis of time-to-event data in the presence of competing risk (i.e., non-bleeding related death).[17] Not accounting for competing risks can lead to an overestimation of the bleeding risk, certainly in a population of cancer patients.[22] A limitation of this study is that both misclassification of the outcome and of predictors could have occurred. Regarding the predictors, most predictor definitions used in our validation closely resembled the definitions used in the development studies, however, some minor differences could not be avoided. We relied on data from routine care, and while we were able to assess free text for all patients, a distinction between major and CRNM was not possible. Last, due to a lack of power we were not able to study the predictive performance of the models in subgroups (e.g., for AF and VTE patients separately, type of cancer or type of anticoagulant).

Conclusions

Bleeding in cancer patients could not be accurately predicted using commonly used existing bleeding risk models. Only age and a history of bleeding were shown to have incremental predictive value and should be considered in future prediction models for bleeding in cancer patients at risk for thromboembolic complications.

Patient and public involvement in research Patients were not involved in the design or conduction of this research.

Authorship Details E.M. Trinks-Roerdink, S. van Doorn, G.J. Geersing, F.H. Rutten, and M. van Smeden were involved in the design of the study. EM Trinks-Roerdink, and S van Doorn performed data analysis and wrote the first draft of the manuscript. All authors were involved in the interpretation of the results, revising the manuscript, and approval of the final manuscript.

Conflict of interest statement E.M. Trinks-Roerdink, S. van Doorn and, and M. van Smeden declare no conflict of interest. G.J. Geersing, F.H. Rutten, and M.E.W. Hemels report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer and Daiichi Sankyo. F.A. Klok reports research support from Bayer, BMS, BSCI, MSD, Leo Pharma, Actelion, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe Program. I.C. van Gelder reports consultancy fees from Boston, BMS and Bayer to the institution, unrestricted research grants from the Netherlands Cardiovascular Research Initiative, unrestricted research grant from the European Union's Horizon 2020 research and innovation programme under grant agreement; EHRA-PATHS (945260).

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AUTHORSHIP STATEMENT

I contributed to defining the research question, conducted the data analysis, and wrote the first version of the manuscript. During the whole process, I asked for and implemented input and feedback from the other contributors to this study.

SUPPLEMENT 1 ICPC and ATC codes used for patient selection and used for extraction of outcome and predictor information from the JPGN database

ICPC and ATC codes used for patient selection

ICPC code atrial fibrillation/flutter: K78

ICPC codes venous thromboembolism: K93, K94, K94.01, K94.02

ATC codes anticoagulants: B01AA, B01AE, B01AF, B01AB

ICPC codes malignancy:, A79, B72, B72.01, B72.02, B73, B74, B74.01, D74, D75, D76, D77, D77.01, D77.02, D77.03, D77.04, F74.01, H75.01, K72.01, L71.01, N74, R84, R85, S77, S77.02, S77.03 , S77.04, T71 , U75 , U76, U77, X75, X76, X76.01, X77, X77.01, X77.02, Y77, Y78, Y78.01, Y78.02, Y78.03

ICPC codes used for extraction of outcome information

ICPC codes bleeding events: A10, F75.01, F75.02, U80.01, S16.01, D16, K90.01, K90.02, R06, D14, D15, F75.01, N80.01, N80.02, N80.03, R24, U06, X06, X08, X08.01, X12, X13, W17

ICPC code atrial fibrillation/flutter: K78

ICPC codes venous thromboembolism: K93, K94, K94.01, K94.02

ICPC codes malignancy:, A79, B72, B72.01, B72.02, B73, B74, B74.01, D74, D75, D76, D77, D77.01, D77.02, D77.03, D77.04, F74.01, H75.01, K72.01, L71.01, N74, R84, R85, S77, S77.02, S77.03 , S77.04, T71 , U75 , U76, U77, X75, X76, X76.01, X77, X77.01, X77.02, Y77, Y78, Y78.01, Y78.02, Y78.03

ICPC codes and ATC codes used for extraction of predictor information

ICPC codes malignancy:, A79, B72, B72.01, B72.02, B73, B74, B74.01, D74, D75, D76, D77, D77.01, D77.02, D77.03, D77.04, F74.01, H75.01, K72.01, L71.01, N74, R84, R85, S77, S77.02, S77.03 , S77.04, T71 , U75 , U76, U77, X75, X76, X76.01, X77, X77.01, X77.02, Y77, Y78, Y78.01, Y78.02, Y78.03

ICPC code atrial fibrillation/flutter: K78

ICPC codes venous thromboembolism: K93, K94, K94.01, K94.02

ICPC codes (abnormal) alcohol use: P16, P15, P15.01, P15.02, P15.03, P15.05, P15.06

ICPC codes hypertension: K85, K86, K87

ICPC codes anaemia: B78, B78.01, B78.02, B78.03, B80, B81, B81.01, B81.02, B82

ICPC code reduced kidney function: U99.01

ICPC code liver disease: D97

ICPC codes stroke: K90, K90.00, K90.01, K90.02, K90.03

ICPC codes history of bleeding: A10, F75.01, F75.02, U80.01, S16.01, D16, K90.01, K90.02, R06, D14, D15, F75.01, N80.01, N80.02, N80.03, R24, U06, X06, X08, X08.01, X12, X13, W17

ATC code antiplatelet therapy: B01AC

SUPPLEMENT 2 Overview of the predictor definition used in the current study for each of the bleeding risk models

	VTE-bleed[7]	AF-bleed[18]	HAS-BLED[8]	ATRIA[9]	ORBIT[11]
Age	Age ≥ 60 years	Age ≥ 75 years	Age > 65 years	Age ≥ 75 years	Age ≥ 75 years
Sex	Male with history of hypertension	Male with history of hypertension			
Hypertension			History of hypertension	History of hypertension	
History of bleeding	History of bleeding	History of bleeding	History of bleeding	History of bleeding	History of bleeding
Anemia	ICPC anemia OR Hemoglobin <8 mmol/l in men and <7.5 mmol/l in women around index date (+/- 30 days)	ICPC anemia OR Hemoglobin <8 mmol/l in men and <7.5 mmol/l in women around index date (+/- 30 days)		History of anemia	Hemoglobin <8 mmol/l in men and <7.5 mmol/l in women around index date (+/- 30 days)
Malignancy	New cancer diagnosis	New cancer diagnosis			
Abnormal renal/liver function	eGFR 30-60 ml/min around index date (+/- 30 days)	eGFR 30-60 ml/min around index date (+/- 30 days)	- Bilirubin > 2x upper limit & ASAT/ALAT/AF > 3x upper limit around index date (+/- 30 days) - Creatinine ≥ 200 umol/l around index date (+/- 30 days)	eGFR < 30 ml/min around index date (+/- 30 days)	eGFR < 60 ml/min around index date (+/- 30 days)
Drugs (antiplatelet/NSAID) /alcohol concomitantly			Treatment with antiplatelet around index date (+/- 30 days) / ICPC code alcohol (ab)use		
Stroke			History of stroke		
Labile international normalized ratio			INR <1 or > 4 around index date (+/- 30 days)		
Antiplatelet treatment					Treatment with antiplatelet around index date (+/- 30 days)

SUPPLEMENT 3 Risk of bias assessment of the five evaluated bleeding models

	Domain: Participants	Domain: Predictors	Domain: Outcome	Domain: Data analysis	
Model	Risk of bias introduced by selection of participants	Risk of bias introduced by predictors or their assessment	Risk of bias introduced by the outcome or its determination	Risk of bias introduced by the analysis	Overall judgement
ATRIA	Unclear	Low	Unclear	High	High
HAS-BLED	Low	High	Unclear	High	High
ORBIT	Low	Low	Unclear	High	High
VTE-bleed	Low	Low	Unclear	High	High
AF-bleed	Low	Low	Unclear	High	High

For each selected model, two authors (ETR, SvD) independently assessed the risk of bias using the PROBAST checklist.[23] *All twenty signaling questions in four domains were answered, to derive at an overall judgment of the model's risk of bias (high, low, unclear).*

SUPPLEMENT 4 Elaboration model selection

The AIC of the models were 2721.4 (first model, only including age plus sex), 2719.1 (second model with age, sex, hypertension, history of bleeding, renal insufficiency, anaemia and use of antiplatelet drugs), and 2721.0 (third model with age, sex, history of hypertension, history of bleeding, renal insufficiency, anaemia and use of antiplatelet drugs plus cancer type). The second model performed significantly better than the first model based on LRT ($\chi^2 = 12.3$, df=5, $p<0.031$). The third model did not perform significantly better than the second model ($\chi^2 = 0.2$, df=1, $p\approx0.68$). Based on both AIC and LRT, the second model had the best fit and was internally validated.

4

INTEGRATED CARE IN PATIENTS WITH ATRIAL FIBRILLATION – A PREDICTIVE HETEROGENEOUS TREATMENT EFFECT ANALYSIS OF THE ALL-IN TRIAL

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ABSTRACT

Introduction Integrated care is effective in reducing all-cause mortality in patients with atrial fibrillation (AF) in primary care, though time and resource intensive. The aim was to assess whether integrated care should be directed at all AF patients equally.

Methods The ALL-IN trial (n=1,240 patients, median age 77 years) was a cluster-randomized trial in which primary care practices were randomized to provide either integrated AF care or usual care to AF patients aged 65 years and older. Integrated AF care comprised of (i) anticoagulation monitoring, (ii) quarterly checkups, and (iii) easy-access consultation with cardiologists. For the current analysis, Cox proportional hazard analysis with all CHADS-VASc variables was used to predict all-cause mortality in the ALL-IN trial. The hazard ratio (including a p-value for interaction) and absolute risk reduction were plotted as a function of this predicted mortality risk to explore treatment heterogeneity.

Results Under usual care, the absolute risk of all-cause mortality in the highest-risk quarter was 30.9%, compared to 4.6% in the lowest-risk quarter. On the relative scale, there was no evidence of treatment heterogeneity (p for interaction=0.93). However, there was substantial treatment heterogeneity on the absolute scale: risk reduction in the lowest-risk quarter of risk 3.3% (95% CI -0.4% - 7.0) compared to 12.0% (95% CI 2.3% - 21.6) in the highest-risk quarter.

Conclusion While the relative degree of benefit from integrated AF care is similar in all patients, patients with a high all-cause mortality risk have a greater benefit on an absolute scale and should therefore be prioritized when implementing integrated care.

Key words atrial fibrillation, integrated care, predictive heterogeneous treatment effect, treatment benefit.

INTRODUCTION

The increasing prevalence of atrial fibrillation (AF) and associated morbidity and mortality have heightened the need for optimizing care of AF patients.[1] The latest guidelines on AF management by the European Society of Cardiology (ESC) recommend integrated AF care which should entail stroke prevention, symptom control, and management of comorbidities in a multidisciplinary setting (Class IIa recommendation, level of evidence B).[2] Studies on the clinical effects of integrated AF care have been mainly performed in patients seen in AF clinics, reporting mixed findings. Some studies showed a reduction in adverse events (e.g., a reduction in (cardiovascular) mortality and (cardiovascular) hospital admissions) [3,4], while other studies did not.[5–7] More recently, integrated AF care was studied in Dutch primary care in ALL-IN cluster-randomized trial which demonstrated a large average relative reduction in all-cause mortality by 45% of those in the intervention group compared to usual care.[8] This undisputed benefit notwithstanding, integrated care is a time and resource-intensive intervention. Since the prevalence of AF is expected

to increase further in our aging society, and our healthcare system is already under pressure, careful evaluation of which patients should be prioritized when implementing integrated AF care, is of great importance.

To study differences in treatment effects in randomized trials it is common to perform subgroup analyses on predefined subgroups. However, these conventional subgroup analyses have limitations, including the risk of false negative results from lack of power and the risk of false positive results due to multiplicity. Further, because patients differ on so many variables that may influence the outcome of interest and the degree of benefit, results from one-variable-at-a-time subgroup analysis do not yield patient-centered treatment effect estimates.[9] More recently, a "risk modeling approach" to study heterogeneous treatment effects (HTE) has been recommended to partially address some of the limitations of conventional subgroup analysis. In this approach, a multivariable regression risk model, which takes into account multiple patient characteristics simultaneously, is used to examine how treatment effects vary at different levels of risk for the primary outcome.[9,10] This study aims to assess whether integrated care should be directed at all AF patients equally by performing a predictive HTE analysis among primary care patients participating in the ALL-IN cluster randomized trial.

METHODS

For this study, we followed the recommendations for HTE analysis stated in the *Predictive Approaches to Treatment Heterogeneity* (PATH) statement.[10] The TRIPOD guideline was used as reporting guideline for predictive studies.[11]

ALL-IN trial

In short, the ALL-IN trial was a cluster-randomized trial in which primary care practices were randomized to provide either integrated AF care or usual care to patients aged 65 years and older. Integrated AF care comprised of (i) anticoagulation monitoring in primary care, (ii) quarterly checkups for AF and its related comorbidities with special attention for the development of heart failure, and (iii) easy-access consultation with AF- and anticoagulation specialists. Practices were included between 2015 and 2017 and the follow-up duration was at least two years. The study design and results of the trial have been described in more detail previously.[8,12]

Outcome definition

The outcome of this current study is all-cause mortality. This outcome was chosen since the primary outcome of the main study was also all-cause mortality and because HTE analysis is considered only valuable when an overall effect of an intervention is found.[10] Since the ALL-IN trial found an overall effect regarding its primary outcome all-cause mortality, this outcome was selected for the current analysis.

Model development and internal validation

Although the guideline-recommended CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke, Vascular disease and Sex) score is widely used to predict stroke in patients with AF, no guideline-recommended prediction model exists for predicting all-cause mortality in AF patients that has shown good performance on an external dataset. Therefore, we developed a new prediction model for the outcome all-cause mortality in a dataset external to the ALL-IN trial. This dataset for model development (derivation cohort) contained data from another cluster-randomized trial performed in primary care in the Netherlands, in which automated CHA_2DS_2-VASc decision support for general practitioners regarding treatment with anticoagulants in established patients with AF was studied against usual primary care.[13] The primary outcome of this study was the composite of stroke, TIA, and/or thromboembolism. Data on mortality was also recorded. The inclusion of practices took place between 2013 and 2014 and the follow-up duration of the study was at least two years for every patient. The design and results of this study have been described in more detail previously.[13]

Common, well-studied prognostic factors for stroke in patients with AF collected in the CHA_2DS_2-VASc score were selected *a priori* as candidate predictors for the model developed. A Cox proportional hazard model was fitted to predict the outcome all-cause mortality over the complete follow-up period of approximately two years, accounting for clustering in primary care practices by adding a random effects term for primary care practice to the model. Both data from the intervention and control groups of the derivation cohort were used for model development. All candidate predictors were added to the model at once, and no predictors were removed from the model. Based on an assumed R-squared between 0.1 and 0.2, an event fraction of 0.11 (261 deaths in 2,355 AF patients), a median follow-up of 2.7 years, and 2 years as the time point of interest for the risk predictions using the Riley minimal sample size criteria, the available sample size was considered sufficient for developing a model with eight parameters. To account for possible non-linearity of age a restricted cubic spline with 3 knots was used. The model was internally validated using bootstrapping with 1000 repetitions to correct for optimism. Discrimination was assessed by calculating Uno's c-statistic with 95% CI, which is the recommended approach for the validation of survival data[14], and calibration was assessed by creating a calibration plot.

External validation

The model to predict all-cause mortality was then externally validated in all AF patients participating in the ALL-IN study, both those who received integrated care as well as those who received usual care. The complete follow-up period of two years was used for external validation. To assess the predictive performance of the model in the ALL-IN trial, calibration was determined by creating a calibration plot. Discrimination was assessed by calculating Uno's c-statistic with 95% CI.

Missing data

In both datasets, for predictor variables 'age' and 'sex', there were no missing data, for the remaining predictors indicating disease history or comorbidity, data were considered present in patients in which the electronic file contained evidence of a respective diagnosis, and not present if the electronic file did not report a diagnosis, thus missing data did (strictly speaking) not occur for these data in both datasets.

Descriptive statistics

Descriptive statistics were used to describe the total study population of the ALL-IN study and the intervention and control group separately, with a mean with standard deviation (SD) or median with an interquartile range (IQR) for continuous variables, and proportions for categorical variables.

Analysis of heterogeneous treatment effects

First, a c-for-benefit with 95% CI was calculated. The c-for-benefit is a concordance statistic expressing the probability that from two randomly chosen matched patient pairs with unequal pairwise observed benefit, the pair with greater pairwise observed benefit also has a higher predicted benefit.[15] Any value over 0.5 indicates evidence for treatment heterogeneity. Next, the distribution of the predicted risk of all-cause mortality in the ALL-IN trial was reported by calculating a mean with SD or median with IQR for the total study population, and for the intervention and control group separately. This risk distribution was also graphically assessed. Subsequently, four predefined risk strata were created and treatment effects were reported across these risk strata. To assess the relative effects of the trial, the hazard ratio for the intervention was plotted as a function of the predicted all-cause mortality risk. To assess the absolute effects the absolute risk reduction was plotted as a function of the predicted all-cause mortality risk. Both absolute and relative treatment effects were plotted as a function of the continuous risk. All plots included a smooth curve, using a spline with 4 degrees of freedom. Finally, to test the null hypothesis (i.e., there is no treatment heterogeneity) on a relative scale, the interaction between treatment and predicted risk was tested for significance. All statistical analyses were performed in R version 4.0.3.

TABLE 1 Baseline characteristics of the total ALL-IN study population and intervention and control group separately

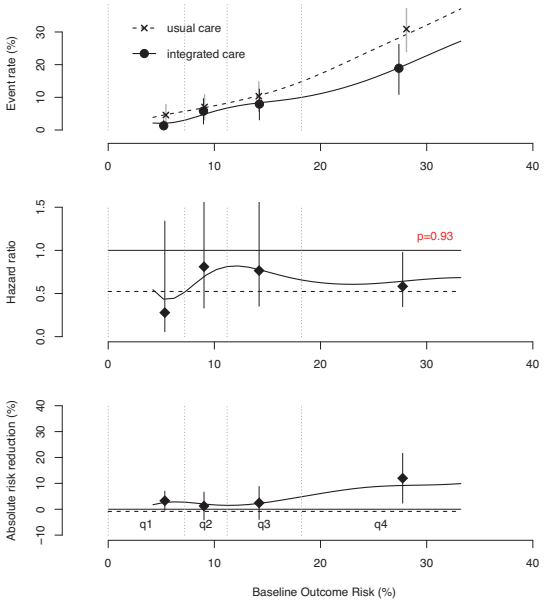
	Total (N=1240)	Intervention group (N=527)	Control group (N=713)
Median age (IQR)	77.0 (11)	76.0 (10)	78.0 (11)
Median CHA_2DS_2-VASC score (IQR)	3.00 (2)	3.00 (1)	3.00 (2)
Female sex	613 (49.4)	239 (45.4)	374 (52.5)
Hypertension	700 (56.5)	311 (59.0)	389 (54.6)
Heart failure	208 (16,8)	72 (13.7)	136 (19.1)
Diabetes	316 (25.5)	131 (24.9)	185 (25.9)
Prior stroke/TIA	179 (14.4)	84 (15.9)	95 (13.3)
Coronary artery disease	213 (17.2)	93 (17.6)	120 (16.8)
Prior myocardial infarction	86 (6.9)	36 (6.8)	50 (7.0)
Peripheral artery disease	84 (6.8)	36 (6.8)	48 (6.7)
Prior venous thromboembolism	55 (4.4)	25 (4.7)	30 (4.2)
Renal insufficiency	169 (13.6)	59 (11.2)	110 (15.4)
COPD	172 (13.9)	73 (13.9)	99 (13.9)
History of cancer	226 (18.2)	95 (18.0)	131 (18.4)

Data are numbers (percentage) unless stated otherwise.

TABLE 2 Development and internal validation of the prediction model

Predictor	Regression coefficient	Standard error
Age	0.0813	0.0231
Age'	0.0024	0.0183
Sex	0.0051	0.1305
Hypertension	-0.2035	0.1305
Diabetes	0.4719	0.1381
Stroke	0.4036	0.1432
Vascular disease	0.1018	0.1368
Heart failure	-0.0236	0.1481
C-statistic after internal validation	0.72	95% CI [0.69;0.75]
R squared	0.093	

A cubic spline with 3 knots was used to account for non-linearity of the variable "age". The variable "age" is therefore divided in 2 groups depicted as age, age'.



The event rate (top), the hazard ratios (middle), and the absolute risk reduction (bottom) are plotted as a function of the baseline outcome risk (i.e., predicted 2-year all-cause mortality risk). The intervention group (integrated AF care) is compared to usual care. The dashed line depicts the average effect (HR 0.55). q1, q2, q3 and q4 are four risk quarters. The vertical lines are 95% confidence intervals.

FIGURE 1 Heterogeneous treatment effects analysis of integrated AF care in primary care setting based on ALL-IN study population

RESULTS

The study population of the ALL-IN trial consists of 1,240 AF patients (median age 77, IQR 11 years, and 49.4% females); 527 patients in the intervention arm, and 713 patients in the control arm. The baseline characteristics of these patients are presented in Table 1. The mean duration of follow-up was 2.0±0.5 years. In total 135 (10.8%) patients died (incidence rate (IR) of all-cause mortality 5.3 [95% CI 4.4-6.2] per 100 person-years). In the intervention group, 39 patients died (7.4%, IR 3.5 [95% CI 2.5-4.7] per 100 person-years), and in the control group 96 patients (13.5%, IR 6.7 [95% CI 5.4-8.2] per 100 person-years).

Development, internal- and external validation of the AF prediction model

The study population for model development consisted of 2,359 AF patients (median age 77, IQR 16 years). See Table 2 for the Cox regression coefficients of the model. The c-index of this model was 0.72 [95% CI 0.69-0.75] at internal validation. See Appendix–Figure A1 for the calibration plot. The c-index of the externally validated model in the ALL-IN study population was 0.72 [95% CI 0.66-0.78]. Appendix–Figure A2 shows the calibration plot of the model in the ALL-IN study, indicating good calibration for the lower predicted probabilities, for which we have the most observations.

Analysis of heterogeneous treatment effects

The c-for-benefit was 0.59 (95% CI 0.54-0.64). The distribution of the predicted risk of all-cause mortality in the ALL-IN study population is presented in Appendix–Figure A3 for the total population, the intervention group, and the control group. At baseline, at the inception of the study cohorts, the median predicted risk of all-cause mortality during approximately two years of follow-up for the total study population was 0.07 (IQR 0.07), for the intervention group 0.06 (IQR 0.06) and for the control group 0.08 (IQR 0.08). Under usual care, the absolute risk of all-cause mortality in the highest-risk quarter was 30.9%, compared to 4.6% in the lowest-risk quarter. Figure 1 shows the event rate, hazard ratio and absolute risk reduction as a function of the predicted all-cause mortality risk, for both the intervention and control group. This figure shows that the event rate is lower for the intervention group compared to the usual care group across all predicted all-cause mortality risk levels. The hazard ratio for the intervention group, compared to the usual care group is constant across all risk levels. The interaction term between the linear predictor and the intervention was not statistically significant (p=0.93). There was substantial effect heterogeneity on the absolute scale: risk difference in the lowest-risk quarter of risk 3.3% (95% CI -0.4% - 7.0) compared to 12.0% (95% CI 2.3% - 21.6) in the highest-risk quarter.

As an illustration, a 71-year-old, male AF patient with a history of diabetes and vascular disease has a predicted two-year all-cause mortality risk of 7%, which corresponds with an HR of 0.52 and an absolute risk reduction of 3% during two years of follow-up, comparing integrated AF care to usual primary care: from 7% to 4%, number needed to treat = 33. An 89-year-old male patient with a history of diabetes, vascular disease, and heart failure has a predicted all-cause mortality risk of 29% in two years, which corresponds with an HR of 0.66 and an absolute risk reduction of 9%: from 29% to 20%, number needed to treat = 11.

DISCUSSION

In this additional analysis of the ALL-IN study in elderly AF patients, we evaluated heterogeneity in the effect of integrated AF care in the primary care setting across all-cause mortality risk levels. We showed that *on a relative scale* all patients, independent of baseline all-cause mortality risk, seem to benefit from integrated AF care. On an absolute scale, however, we show that the benefit of integrated care is substantially lower for low-risk patients. Importantly, patients with a higher predicted risk of all-cause mortality (based on the CHADS-VASc variables) had the greatest absolute risk reduction. Therefore, spending (limited) healthcare resources and time predominantly on integrated care for high-risk patients and applying a more lenient approach to low-risk patients, could be a promising strategy for efficiently managing the increasing healthcare burden associated with the ongoing AF epidemic.

Comparison with existing literature

This is the first study assessing whether the relative and absolute treatment effect of integrated AF care differed for individuals depending on their risk of all-cause mortality. However, there are previous conventional subgroup analyses evaluating integrated AF care. A study evaluating nurse-led AF care in a cardiology outpatient setting showed that the relative beneficial effect of the intervention was consistent over subgroups (e.g., patients with/without hypertension, or with/without heart failure) regarding the reduction of the composite outcome cardiovascular hospital admission or cardiovascular death, with the exception of females.[16] Women receiving usual care had a relatively low event rate compared to men and this could not be explained by the authors other than by chance. In the RACE-IV study, which was performed in a secondary and tertiary care setting, nurse-led AF care did not significantly reduce the risk of cardiovascular hospital admission or death compared to usual care provided by the cardiologist. Yet, an exploratory analysis showed that nurse-led AF care was effective in the subgroup of centers with experience in nurse-led care.[5] This could possibly be explained by higher guideline adherence in experienced centers in the nurse-led care group. Although these conventional subgroup analyses may certainly be informative, their results should be interpreted with some caution. While patients are stratified according to one or two characteristics (e.g., sex and the presence or absence of concurrent heart failure), in reality many more factors affect the (relative or absolute) effect of a treatment intervention. Our study therefore not only explores — for instance — sex as an explanation for differences in treatment benefit but combines this with many other important clinical characteristics.

Interpretation of the findings

In general, an average overall effect (absolute and/or relative risk reduction) is reported in randomized trials. However, for optimal individualized decision-making, personalization of the treatment effect is more informative. Although in this study all AF patients seem to benefit similarly from integrated AF care on a relative scale, the absolute effect was the greatest in patients with a high predicted all-cause mortality risk, this is in patients in whom many CHADS-VASc comorbidities are present. With increasing age, there is an accumulation of risk factors for all-cause mortality, due to aging but also due to interacting comorbidities. Addressing all these comorbidities at once are the exact merits of integrated AF care and the results of our analysis of heterogeneity in treatment effect show that the higher the burden of comorbidities, the greater the effect of integrated AF care.

Clinical implications

Integrated AF care should not only address AF itself but also evaluate early signs (or worsening) of complications of AF, such as heart failure. But also non-cardiovascular, yet associated comorbidities should be evaluated, such as chronic obstructive pulmonary disease or inflammatory disease, as cardiovascular and non-cardiovascular comorbidities often interact. In fact, in the ALL-IN study, the largest effect of the integrated AF care approach was seen on non-cardiovascular mortality.[8] Next, the associated benefit and

burdens should be weighed for individual patients to decide to whom to offer the intervention most intensely in everyday practice. Integrated AF care is not associated with harm and does not carry many burdens for patients, notably when it is organized close to their homes in primary care. It can however be relatively resource and time intensive with the extra training and workload for GPs and practice nurses. As such, prioritizing and intensifying integrated AF care to those with the highest expected absolute effects seems a reasonable approach, certainly in already highly overstretched healthcare settings in our aging societies. Accordingly, we believe this is an important observation warranting further investigation: permanent AF in older, frail individuals certainly is not a stable 'cooled-down' disease. On the contrary, the all-cause mortality risk is high and an integrated cardiovascular care program, such as ALL-IN, has the largest absolute treatment effects precisely in this population. Although we did not develop our model with the intention to predict all-cause mortality in daily practice, it may help to prioritize high-risk patients who might need stringent care, and to select low-risk patients, who might need less stringent care; a more lenient approach focusing perhaps more on self-management.

Strengths and limitations

We used a state-of-the-art method to study heterogeneity of treatment effects, thus averting the disadvantages of conventional subgroup analyses. We were able to predict all-cause mortality based on often used and readily available clinical variables from the CHA_2DS_2-VASc score, with a good predictive performance upon external validation. These strengths notwithstanding, some limitations should be considered. The results of this HTE analysis are dependent on the model used for risk prediction and thus on the selected predictors and outcome. This study focused on the outcome of all-cause mortality, yet other risks, such as the risk of ischemic stroke or the risk of hospital admission are also relevant for individualized decision-making in AF patients. Moreover, HTE analysis can be even more useful when applied in the analysis of individual data of multiple studies (IPD); by pooling results variation in the baseline outcome risk increases, and the statistical power is increased.[10] However, the ALL-IN trial was the first study to evaluate integrated AF care in primary care. Also, due to the cluster-randomization of the ALL-IN trial some imbalances were created between study arms that we did not correct for. However, these differences were minor, not univocally in favor of one study arm, showed no influence in the primary analysis of the ALL-IN trial [8], and, importantly, are taken into account when stratifying the predicted mortality risk. Imbalance at baseline, therefore, will not have influenced our results substantially. Finally, it must be noted, we only considered the primary outcome all-cause mortality, and further research may focus on studying other outcomes.

Conclusion

The relative degree of benefit from integrated care was shown to be similar in all AF patients managed in primary care in cooperative care with the cardiologist. Importantly, on an absolute scale, the benefit was greatest in patients with a high predicted all-cause mortality risk, i.e., in frail older AF patients with multiple positive CHADS-VASc items. These results may be helpful in efficiently organizing integrated AF care, expending limited resources more on high-risk patients and to a lesser extent on low-risk patients.

Ethics statement This is a post-hoc analysis of the ALL-IN trial that received ethical approval of the Medical Ethics Committee.

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Conflict of interest statement E.M. Trinks-Roerdink, C.J. van den Dries, M. van Smeden, D. van Klaveren, and D. Kent declare no conflict of interest. G.J. Geersing, F.H. Rutten, and M.E.W. Hemels report unrestricted institutional grants for performing research in the field of atrial fibrillation from Boehringer-Ingelheim, Bayer Healthcare, BMS Pfizer and Daiichi Sankyo. I.C. van Gelder reports consultancy fees from Boston, BMS and Bayer to the institution, unrestricted research grants from the Netherlands Cardiovascular Research Initiative, unrestricted research grant from the European Union's Horizon 2020 research and innovation programme under grant agreement: EHRA-PATHS (945260). M. Rienstra reports Consultancy fees from Bayer, Microport, InCarda Therapeutics to the institution, an unrestricted research grant from ZonMW and the Dutch Heart Foundation; DECISION project 848090001, unrestricted research grants from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation; RACE V (CVON 2014–9), RED-CVD (CVON2017-11), an unrestricted research grant from Top Sector Life Sciences & Health to the Dutch Heart Foundation (PPP Allowance; CVON-AI (2018B017)), and an unrestricted research grant from the European Union's Horizon 2020 research and innovation programme under grant agreement; EHRA-PATHS (945260). S. van Doorn reports an unrestricted institutional grant for performing research in the field of stroke diagnosis from Stoffels-Hornstra.

Data availability statement The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHORSHIP STATEMENT

I contributed to defining the research question, conducted the data analysis, and wrote the first version of the manuscript. During the whole process, I asked for and implemented input and feedback from the other contributors to this study.

APPENDIX

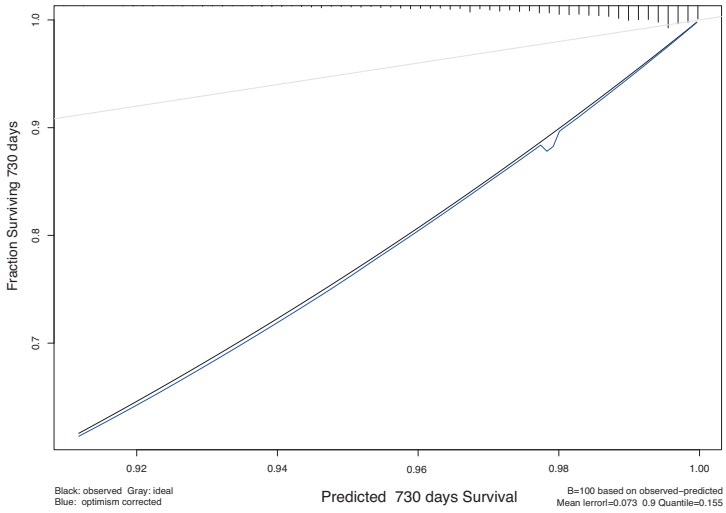

FIGURE A1 Calibration plot of the internal validation of the prediction model

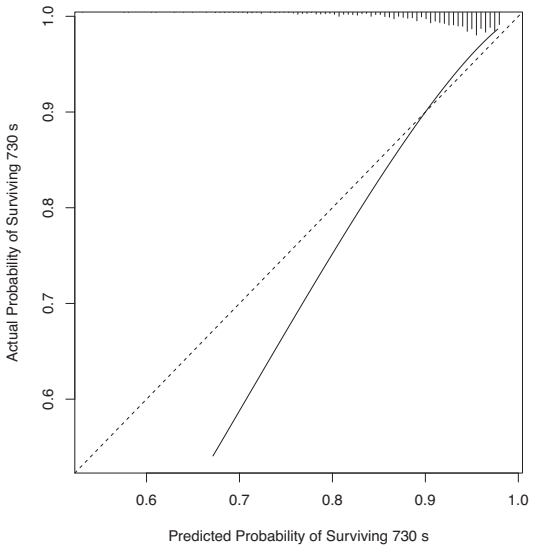

FIGURE A2 Calibration plot external validation of the prediction model

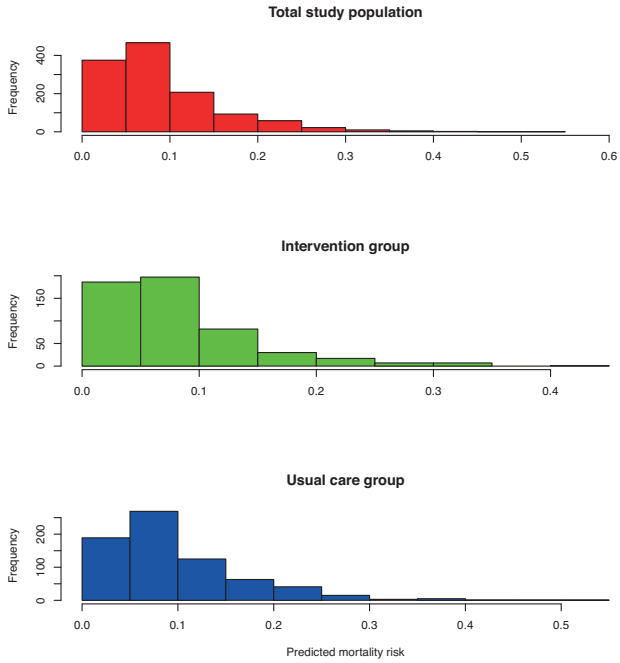

FIGURE A3 Distribution of predicted risk of all-cause mortality in total ALL-IN study population, intervention group and usual care group

5

DESIGN AND RATIONALE OF DUTCH-AF: A PROSPECTIVE NATION-WIDE REGISTRY PROGRAMME 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 and 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 ischaemic 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.

Trial registration number Trial NL7467, NTR7706 (https://www.trialregister.nl/trial/7464).

Strengths and limitations of this study

- The DUTCH-AF registry will provide important insights into the effects of non-adherence and non-persistence of anticoagulation therapy on clinically adverse outcomes such as stroke and major bleeding. Moreover, it will also provide patient characteristics of non-adherent and non-persistent patients that could be targeted for adherence-improving interventions in the future.
- Patients are enrolled from all levels of care across the Netherlands including patients from general practices and thrombosis services, thereby increasing the generalisability of the study results.
- The registry will provide an essential framework for improving quality of care and for patient-centred research, including the opportunity for future registry-based randomised controlled trials or trials within cohort (TWiC) designs.
- Extrapolation and generalisability of this registry could be limited when patients are enrolled from primary or secondary/tertiary care disproportionately.

INTRODUCTION

As a consequence of the increasing prevalence of atrial fibrillation (AF) in our ageing society, its associated adverse events and the overall societal healthcare burden, there is a need for optimisation 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. By collecting these data, DUTCH-AF will provide a base for future research (notably registry-based randomised 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-related 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, 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 oral anticoagulants (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 Netherlands Society of Cardiology (NVVC), the Netherlands 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 (TWiC) design.[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 enrol consecutive patients aged $\geq$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 developing 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% to 40% of all surgeries) and its self-limiting nature (80% revert 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, for example, 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 general practitioner (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), NVVC, 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, minimising selection and allowing for a broad generalisability of findings.

TABLE 1 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'.

AF, atrial fibrillation.

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, European Heart Rhythm Association (EHRA) classification, relevant medical history with items that contribute to the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age $\geq$75, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65-74, Sex category (i.e., female sex)) 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 by telephone interviews. Follow-up data will be complemented with pharmacy dispensing data from the Foundation for Pharmaceutical Statistics (SFK).[24] Box 1 provides an overview of the data collected during baseline and follow-up. Table 1 provides an overview of the causes of secondary AF.[23]

BOX 1. Overview of baseline and follow-up variables

Baseline

Demographics: gender, age and ethnicity

Weight, height and blood pressure

Recent haemoglobin and kidney function

Medical history: all parameters included in CHA_2DS_2-VASc, sleep apnoea, chronic lung disease, malignancy and 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 and 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 and blood pressure

Recent haemoglobin and kidney function

Pattern: paroxysmal, persistent, long-standing persistent and permanent AF

Occurrence of bleeding events:

- Severity: MB, CRNMB
- Location: intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intramuscular, gastrointestinal, urogenital, nasal and pulmonary

Occurrence of ischaemic events: TIA, ischaemic stroke, ATE and MI

Healthcare utilisation: emergency department visits or hospital admission for AF treatment

Side effects to antiarrhythmic treatment

Changes in anticoagulation treatment and CHA_2DS_2-VASc

Prescription data from SFK:

- Dispensing data (type and dosage)
- Concomitant medical therapy

Adherence and persistence
In a subset of patients: MARS-5/BMQ/DGSS questionnaires

ATE, arterial thrombotic event; BMQ, Beliefs about Medicines 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 oral anticoagulants; SFK, Foundation of Pharmaceutical Statistics; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

TABLE 2 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 11-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 Likert 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 to 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 kunne 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 5-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 Likert 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 to 5, where higher scores indicate higher levels of reported adherence.	
1.	I forget to take my anticoagulants Ik vergeet mijn bloedverdunners in te nemen
2.	I modify the doses of my anticoagulants Ik wijzig de dosering van mijn bloedverdunners
3.	I stop taking medications during a certain period Ik stop een tijdje met bloedverdunners te nemen
4.	I decide to miss a dose Ik besluit een dosering over te slaan
5.	I take less than what is prescribed Ik neem minder dan is voorgeschreven
Dutch General Self-efficacy Scale (DGSS)	
The DGSS is a 10-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 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 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 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 Ik vertrouw erop dat ik onverwachte gebeurtenissen doeltreffend aanpak
5.	Thanks to my resourcefulness, I know how to handle unforeseen situations Dankzij mijn vindingrijkheid weet ik hoe ik in onvoorziene situaties moet handelen
6.	I can solve most problems if I invest the necessary effort 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 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 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 Als ik in een benarde situatie zit, weet ik meestal wat ik moet doen
10.	I can usually handle whatever comes my way Wat er ook gebeurt, ik kom er wel uit

Outcomes

The following clinical outcomes will be registered during follow-up: (i) thromboembolic adverse events (i.e., transient ischaemic attack, ischaemic stroke, arterial thrombotic event and myocardial infarction), (ii) bleeding (i.e., major, clinically relevant non-major bleeding (CRNMB) 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 the Statistical Analysis section. 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 Medicines Questionnaire (BMQ), the Medication Adherence Report 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 2 provides an overview of the various items asked in the questionnaires.[27-29,31]

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 pseudonymised and patients are assigned a unique study identifier. Personal data of all included patients will be collected 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% to 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 programme. Linkage of the pharmacy dispensing data with the corresponding study participants will be performed by a trusted third party using pseudonymised data.

Statistical analysis

Research aim 1: association between OAC adherence/persistence, dosage and clinical outcomes

To evaluate adherence and persistence of non-vitamin K oral anticoagulants (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 PDC 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 vitamin K antagonist (VKA), patient adherence to VKA will be expressed through the time in therapeutic range (TTR) of international normalized ratio (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 and 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 thromboembolic 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. ORs with 95% 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/nonpersistence

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 on clinical likeliness to be correlated with NOAC-adherence: age, sex, comorbidity and comedication.[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 receiver operating characteristic (ROC) space) and its calibration, illustrated in a calibration plot (predicted against observed risk).

Research aim 3: validation of bleeding models

All variables of actiVe cancer, male gender with uncontrolled hyperTension, anaEmia, history of BLeeding, agE ≥60 years and rEnal Dysfunction (VTE-BLEED) 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 beta's from the original derivation study. Subsequently, as mentioned previously, 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 the VTE-BLEED model was originally derived to predict bleeding complications in patients with venous thromboembolism, this may occur), simple updating techniques will be applied to optimise 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 beta's for the variables from the original regression model or including novel variables if needed.

Study size

The registry has a target enrolment of 6000 patients with a follow-up of at least 2 years. We expect 5500 NOAC users. Based on a 1 year non-persistence in one-third of the NOAC users, 1815 patients on NOACs will be non-persistent.[36] If we assume a 50% increased risk of ischaemic stroke/systemic embolism in these patients, we can expect on average a 3% yearly risk compared with 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 ischaemic 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 ischaemic 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

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 SC 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 on 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 the quality of care and for patient-centred research, including the opportunity of registry-based randomised controlled trials (RCT). Participating centres can continuously evaluate and benchmark their current practice on guideline implementation and guideline non-adherence. The minimal data set has been designed to minimise registration burden, but will be sufficient for answering important current and future research questions. In the near future, our minimal data set will be implemented in Dutch electronic medical records to minimise double-registration. This will improve the quality of the continuing quality registry, as the data set 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 centralised network structure of the NHR will allow for cross-talk between registries through data linkage and through the adoption of a standardised 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 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, who 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 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 data set of this registry is designed to specifically answer the predefined research aims regarding dosing, adherence and persistence of anticoagulants. To minimise 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 data sheet. 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 minimised 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 generalisability 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 uses 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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AUTHORSHIP STATEMENT

Jaap Seelig, Gordon Chu, and I are joint first authors and equally contributed to defining the research questions, the design, and the methodology, and writing the first draft of the manuscript. During the whole process, we asked for and implemented input and feedback from the other contributors to this study.

SUPPLEMENTARY TABLE 1 Definitions of relevant outcomes as used in the DUTCH-AF registry

Ischemic Stroke	Ischemic stroke is defined as an episode of a focal neurologic deficit as a result of ischemia as diagnosed by a neurologist, lasting > 24 hours.
Transient Ischaemic Attack	An episode of focal neurological deficit of sudden onset, caused by ischemia, as diagnosed by a neurologist, lasting < 24 hours
Myocardial infarction	Definition in accordance with the 4th universal definition myocardial infarction.[50] Elevated cardiac troponin levels with at least one value above the 99th percentile, with at least one of the following: • Symptoms of myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology; • Identification of a coronary thrombus by angiography or autopsy.
Arterial thrombo-embolism	A sudden interruption of arterial perfusion due to a thromboembolic clot obstruction, resulting in ischemia and potentially organ dysfunction and infarction. Cerebral and coronary artery occlusions are registered in the variables 'ischemic stroke' and 'myocardial infarction', and will consequently not be registered as an arterial thromboembolism. Thromboembolism in the aorta, renal, mesenteric, pelvic and extremity arteries, if treated with an interventional procedure (i.e. a catheter-based or open surgical procedure to restore arterial blood flow), are registered as arterial thromboembolism.
Major bleeding	Definition in accordance with the ISTH criteria for major bleeding in non-surgical patients.[25] 1. Fatal bleeding. and/or 2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome. and/or 3. Bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

Non-major clinically relevant bleeding	Definition in accordance with the ISTH criteria for non-major clinically relevant bleeding in non-surgical patients.[26] An acute or subacute clinically overt bleed that does not meet the criteria for a major bleeding but prompts a clinical response, in that it leads to at least one of the following: • A hospital admission for bleeding, or • A physician guided medical or surgical treatment for bleeding, or • A change in antithrombotic therapy (including interruption or discontinuation of study drug).
Minor bleeding	All other overt bleeding not meeting the criteria for major or non-major clinically relevant bleeding.

6

SEX DIFFERENCES AT DIAGNOSIS AND IN ONE-YEAR OUTCOMES IN PATIENTS WITH EARLY ATRIAL FIBRILLATION

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ABSTRACT

Background Little is known about differences in clinical phenotype between men and women with atrial fibrillation (AF). Our aim was to explore phenotypical sex differences at diagnosis and at one-year follow-up, in patients with early AF.

Methods We used data from 5,469 participants of the DUTCH-AF registry; a nationwide prospective registry of patients with early AF or atrial flutter (diagnosis $\leq$ 6 months before inclusion) in the Netherlands, aged $\geq$ 18 years. We describe sex differences in clinical phenotype at diagnosis and at one-year follow-up, including the following outcomes: i) ischemic and bleeding events, ii) all-cause mortality, iii) AF-related hospital admissions, including ablation and cardioversion, and iv) AF progression patterns.

Results At inclusion, women were older than men (median 73 vs. 69 years, p<0.001), had more often paroxysmal AF (66% vs. 55%, p<0.001), and less often persistent AF (27% vs. 37%, p<0.001). They also had hypertension more often (59% vs. 53%, p<0.001), and less often vascular disease (12% vs. 21%, p<0.001, and reported more often symptoms at inclusion and in the month before follow-up; 56% vs. 46%, p<0.001, and 31% vs. 23%, p<0.001, respectively. Women underwent cardioversion and ablation procedures less often than men (14% vs. 21% p<0.001 and 3% vs. 5%, p<0.001, respectively). Moreover, for the combined rhythm control intervention cardioversion and ablation, women also underwent this rhythm control outcome less often than men (unadjusted odds ratio was 0.63 95% CI (0.55-0.73)), regardless of age, and the type of AF (i.e., paroxysmal or persistent AF) at inclusion (adjusted odds ratio 0.77 95% CI (0.62-0.92)). No differences were observed for ischemic and bleeding events, all-cause mortality, or AF progression patterns, but the number of these events was small.

Conclusion Men and women with early AF differ in age, comorbidities, symptoms, and management. These findings are building blocks for individualized sex-specific AF care and research.

INTRODUCTION

In many cardiovascular diseases, there are clear differences between men and women regarding epidemiology, underlying pathophysiology, clinical presentation, management, and outcome.[1] Sex differences in atrial fibrillation (AF) have been less well described. The European Heart Rhythm Association published a consensus paper in 2018 summarizing the existing knowledge on sex differences in cardiac arrhythmias, including AF, to improve the development and implementation of sex-specific guidelines, as well as to synergize research on this topic.[2] Studies focusing on sex differences in AF have shown that women with permanent and persistent AF are older, more often have hypertension, heart failure, and valvular heart disease, and less often coronary heart disease compared to men.[3,4] Moreover, in the large ORBIT-AF registry, women with AF were more symptomatic compared to men, and health-related quality of life was more

often negatively affected.[5] Concurrently, in the RACE-V registry of 202 rather young AF patients with implanted loop recorders progression from paroxysmal to persistent and permanent AF appeared to occur more often in men than in women.[6] In addition, differences between women and men concerning rate and rhythm strategies are described.[7] For example, women are less likely to receive rhythm control compared to men.[8,9] However, a pre-specified subgroup analysis of the EAST-AFNET 4 trial showed an equal benefit of rhythm control for men and women with early AF in reduction of cardiovascular outcomes compared to usual care, with early AF defined as diagnosed $\leq$ 1 year before enrollment.[10,11] Finally, female sex is a risk modifier for stroke, in the presence of other risk factors; the risk of stroke is about 1.5-fold higher in women than in men with the same risk factors.[12] The GARFIELD-AF registry of patients with recently diagnosed ($\leq$ 6 weeks) AF, showed that the adjusted stroke risk in women is higher than in men.[13]

Hence, there is evidence for sex differences in patients with AF, yet, most studies were performed in patients with longstanding (persistent or permanent) AF. This highlights an important knowledge gap, given that important adverse events occur in the first year after AF diagnosis.[14] Moreover, the previously mentioned GARFIELD-AF study focussed mainly on the risk of major events, such as stroke and bleeding, not on sex differences in e.g. AF pattern or AF treatment. Thus, there is a need for more studies on sex differences in patients with early AF because it opens up an avenue to individualized care from the start. In this study, we aimed to explore sex differences in clinical phenotype at diagnosis and at one-year follow-up in patients with early AF who are registered in an ongoing Dutch registry.

METHODS

Study design

This observational study is based on data from the DUTCH-AF registry: a nationwide prospective registry of patients with early AF or atrial flutter in the Netherlands. Inclusion started in July 2018. Data on patient characteristics, anticoagulation treatment, and clinical outcomes were collected during a follow-up period of 2 years. Moreover, data prospectively collected by the Netherlands Heart Network was retrospectively incorporated into DUTCH-AF. Both inclusion and exclusion criteria and the type of data collected were similar and could therefore be used to enrich the DUTCH-AF database. The design of the DUTCH-AF study has been described in more detail previously.[15] All participants provided either written informed consent or consent via an opt-out question. The study is conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice, and local regulatory requirements. The Medical Research Involving Human Research Act (WMO) does not apply to this study. The study is registered at the Netherlands Trial Register (NL7464).

Setting and study participants

Patients $\geq$ 18 years old with a new diagnosis of AF or atrial flutter within the previous 6 months were eligible for inclusion. Exclusion criteria were (i) moderate or severe mitral valve stenosis, (ii) mechanical heart valve(s), (iii) a life expectancy of < 6 months, and (iv) patients in whom AF or atrial flutter was documented within 2 weeks following cardiothoracic surgery. Patients were enrolled from general practices, outpatient anticoagulation clinics, and hospitals.

Data collection and follow-up

Data were primarily collected from electronic healthcare records. Follow-up data were also gathered using telephone interviews with study participants or follow-up questionnaires. Follow-up was scheduled one and two years after inclusion. For the current study, we analyzed the first year of follow-up data. Since follow-up was performed later than scheduled in some patients, for the current study we analyzed at least one year of follow-up data for every patient (unless a patient was lost to follow-up before the follow-up was scheduled).

Study size

In July 2021 the target enrollment of 6000 patients into the DUTCH-AF registry was achieved. A detailed study size calculation was presented in the previously published study design paper.[15] In short, the sample size of 6000 participants was set given the expected total of about 600 patients meeting one of the prespecified major cardiovascular endpoints consisting of ischemic stroke and systemic embolism, major bleeding, and all-cause mortality during two years follow-up. These numbers were considered sufficient to accomplish the three primary research aims of DUTCH-AF: to study (i) the association between anticoagulant adherence/persistence, dosage, and clinical outcomes, (ii) predictors of NOAC non-adherence/non-persistence, and (iii) validate bleeding models.

Data monitoring, and data management

The data used for the current study were checked to ensure completeness and accuracy. However, since data collection is still ongoing and data monitoring is a continuous process, small differences can occur in the data used for the current study and data used for future studies. Data management is overseen by the Netherlands Heart Registration (NHR). For the current study, we excluded participants whose data had not been monitored yet.

Variables

The following baseline characteristics were reported in this study; age, history of hypertension, heart failure, diabetes, vascular disease, stroke/transient ischemic attack (TIA), AF pattern at inclusion (paroxysmal or persistent), AF-related symptoms at inclusion according to the European Heart Rhythm Association (EHRA) classification, secondary causes of AF (e.g., infection, non-cardiothoracic surgery). The choice for anticoagulant treatment at diagnosis was also described for patients with a class I recommendation (i.e., CHA_2DS_2-

VASc score of $\geq$ 3 in women and $\geq$ 2 in men) and a class IIa recommendation (i.e., CHA_2DS_2-VASc score of 2 in women and 1 in men) for long-term anticoagulation. The following outcomes after (at least) one year of follow-up were reported in this study: AF-related symptoms in the month prior to follow-up, again according to the EHRA classification, AF pattern (paroxysmal, persistent, or permanent, or no AF recurrence), number of patients with at least one ischemic event (the composite of transient ischemic attack (TIA), ischemic stroke, arterial thrombotic events, and/or acute myocardial infarction), number of patients with at least one major or clinically relevant non-major (CRNM) bleeding (according to the definition of the International Society on Thrombosis and Hemostasis), number of patients with at least one AF-related hospital admission (e.g., admission for rate control, electrical cardioversion (ECV) or chemical cardioversion (CCV), or ablation), and all-cause mortality.

Statistical methods

Descriptive statistics were used to describe the study population, with a mean with standard deviation (SD) or median with an interquartile range (IQR) for continuous variables, and proportions for categorical variables. Missing data were reported for every variable in the tables. Baseline characteristics and one-year outcomes were compared between men and women. We present p-values for these comparisons to highlight the differences between men and women. Since multiple testing can lead to false-positive results, these p-values should be interpreted with caution.[16] For proportions, we also present the absolute difference in proportions between men and women with a 95% confidence interval (CI). The progression and regression patterns of AF are graphically displayed for both men and women. AF progression was defined as the transition from paroxysmal AF at inclusion to persistent or permanent AF at follow-up. AF regression was defined as the transition from persistent AF at inclusion to paroxysmal, or no AF at follow-up. Finally, to further explore the association between sex and the combined outcome of cardioversion and ablation, we performed a multivariable logistic regression analysis adjusting for age and pattern of AF (i.e., paroxysmal or persistent) at inclusion. Data analyses were performed in R version 4.0.3.

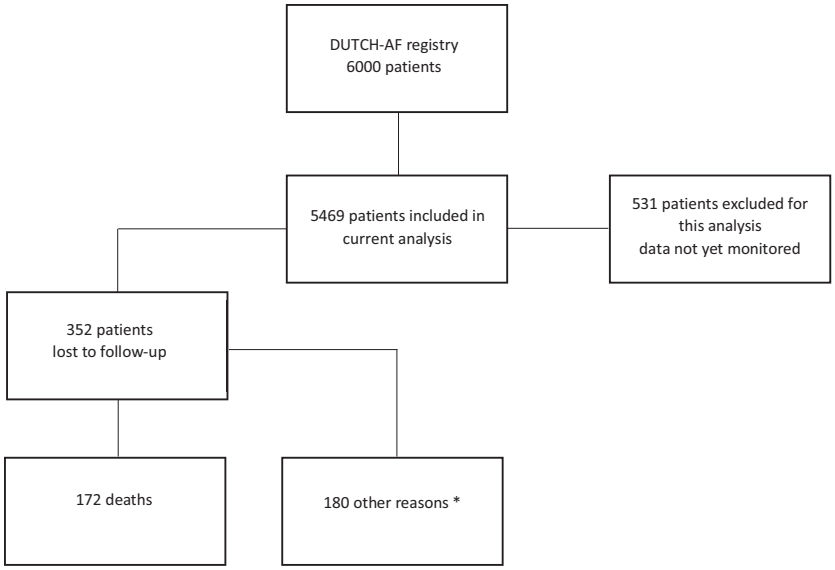
RESULTS

In total 5,469 patients with early AF were analyzed for the current study; 3,231 men (59.1%) and 2,238 (40.9%) women. In total, 352 (6.4%) patients were lost to follow-up; 172 (3.1%) patients died, and 180 (3.3%) patients were lost-to-follow-up for other reasons (Figure 1 study flowchart). The mean time between diagnosis and follow-up was 1.2 ± 0.3 years (for women 1.2 ± 0.4 years, for men 1.2 ± 0.3 years).

Sex differences in baseline characteristics

In Table 1 the baseline characteristics are presented for the total study population, and for men and women separately. Women were older than men (median 73 vs. 69 years, p<0.001), had a higher CHA_2DS_2-VASc score (mean 3.4 vs. 2.2, p<0.001), had more often

hypertension (58.8% vs. 52.6%, p<0.001), but less often vascular disease (11.5% vs. 20.6%, p<0.001). In addition, women had more often paroxysmal AF at inclusion than men (65.6% vs. 54.9%, p<0.001), while men had more often persistent AF (37.0% vs. 27.4%, p<0.001) than women. Women more often reported AF-related symptoms at inclusion compared to men (55.6% vs. 45.6%, p<0.001) and also in the month prior to the follow-up assessment (31.2 vs. 22.5%, p<0.001). See Table 2 for the prescribed anticoagulants at diagnosis for men and women with a class I recommendation and class IIa recommendation for long-term anticoagulation. Direct oral anticoagulant (DOAC) treatment was slightly more often prescribed to women than to men (84.4% vs. 81.5%, p=0.006) for patients with a class I recommendation, and (83.7% vs. 77.1%, p<0.001) for patients with a class IIa recommendation. Men more often received no anticoagulants than women (8.0% vs. 6.4%, p=0.027) for patients with a class I recommendation, and (16.2% vs. 11.4%, p<0.001) for patients with a class IIa recommendation.



*E.g., withdrawal consent, or patient could not be reached for follow-up and no recent follow-up information available in electronic healthcare record.

FIGURE 1 Flow chart of in- and exclusions and status follow-up

TABLE 1 Baseline characteristics for patients with newly diagnosed AF for women and men

	Women (N=2238)	Men (N=3231)	Total (N=5469)	Missings (n,% of total) [b]	Absolute difference in proportions with 95% CI [c]	Two-sided p-value
Median age in years at diagnosis (IQR)	73.0 [12]	69.0 [14]	71.0 (14)			p<0.001
Mean CHA_2DS_2-VASc (sd)	3.4 (1.5)	2.2 (1.6)	2.7 (1.7)	83 (1.5%)		p<0.001
Hypertension (%)	1315 (58.8)	1699 (52.6)	3014 (55.1)	19 (0.3)	0.06 [0.04 - 0.09]	p<0.001
Heart failure (%)	121 (5.4)	194 (6.0)	315 (5.8)	56 (1.0)	0.01 [-0.01 - 0.02]	p=0.349
Diabetes mellitus type 1 or 2 (%)	302 (13.5)	479 (14.8)	781 (14.3)	8 (0.1)	0.01 [-0.01 - 0.03]	p=0.177
Vascular disease [a] (%)	257 (11.5)	665 (20.6)	922 (16.9)	47 (0.9)	0.09 [0.07 - 0.11]	p<0.001
Stroke or TIA (%)	345 (15.4)	473 (14.6)	818 (15.0)	60 (1.1)	0.01 [-0.01 - 0.03]	p=0.414
Median Body Mass Index in kg/m^2 (IQR)	26.8 (7.5)	27.2 (5.6)	27.0 (6.4)	548 (10.0)		p=0.030
Median eGFR (CKD-epi) (IQR)	73.9 (25.7)	77.7 (23.8)	76.3 (24.9)	281 (5.1)		p<0.001
Atrial fibrillation or flutter at diagnosis (%)				907 (16.6)		
Atrial fibrillation	1697 (75.8)	2352 (72.8)	4049 (74.0)		0.03 [0.01 - 0.05]	p=0.013
Atrial flutter	107 (4.8)	246 (7.6)	353 (6.5)		0.03 [0.02 - 0.04]	p<0.001
Both	57 (2.5)	103 (3.2)	160 (2.9)		0.01 [-0.00 - 0.02]	p=0.130
Pattern AF at inclusion (%)				417 (7.6)		
Paroxysmal	1468 (65.6)	1774 (54.9)	3242 (59.3)		0.11 [0.08 - 0.13]	p<0.001
Persistent	613 (27.4)	1197 (37.0)	1810 (33.1)		0.10 [0.07 - 0.12]	p<0.001
AF-related symptoms month previous to inclusion (%)				386 (7.1)		
EHRA I	840 (37.5)	1526 (47.2)	2366 (43.3)		0.10 [0.07 - 0.12]	p<0.001
EHRA II-IV	1245 (55.6)	1472 (45.6)	2717 (49.7)		0.10 [0.07 - 0.13]	p<0.001
Secondary cause of AF (%)	323 (14.4)	446 (13.8)	769 (14.1)	249 (4.6)	0.01 [-0.01 - 0.02]	p=0.530
Setting of diagnosis (%)				35 (0.6)		
General practice	623 (27.8)	994 (30.8)	1617 (29.6)		0.03 [0.01- 0.05]	p=0.017
Hospital/outpatient clinic	1604 (71.7)	2213 (68.5)	3817 (69.8)		0.03 [0.01- 0.06]	p=0.011

[a] Composite of myocardial infarction, coronary artery disease, and peripheral artery disease.
[b] No apparent differences in missing data between women and men were observed.
[c] Absolute difference between women and men in proportions with 95% confidence interval.

TABLE 2 Antithrombotic drugs at diagnosis for men and women with a class I and class IIa recommendation

	Class I recommendation[a]				**Class IIa recommendation**[b]			
	Women (n=1547, 70.0%)	Men (n=1995, 62.8%)	Absolute difference in proportions with 95% CI [c]	Two sided p-value	Women (n=449, 20.3 %)	Men (N=693, 21.8%)	Absolute difference in proportions with 95% CI [c]	Two sided p-value
Antithrombotics (n,%)								
None	99 (6.4%)	159 (8.0%)	0.02 [0.00 - 0.03]	p=0.027	51 (11.4%)	112 (16.2%)	0.05 [0.03 - 0.07]	p<0.001
DOAC +/- APT	1305 (84.4%)	1625 (81.5%)	0.03 [0.01 - 0.05]	p=0.006	376 (83.7%)	534 (77.1%)	0.07 [0.04 - 0.09]	p<0.001
VKA +/- APT	97 (6.3%)	131 (6.6%)	0.00 [-0.01 - 0.02]	p=0.660	19 (4.2%)	24 (3.5%)	0.01 [-0.00- 0.02]	p=0.186
Other[d] +/- APT	12 (0.8%)	19 (1.0%)	0.00 [-0.00 - 0.01]	p=0.449	2 (0.4%)	6 (0.9%)	0.00 [0.00 - 0.01]	p=0.030
mono APT	29 (1.9%)	56 (2.8%)	0.01 [0.00 - 0.02]	p=0.035	0 (0%)	15 (2.2%)	0.02 [0.02- 0.03]	p<0.001
Missing	5 (0.3%)	5 (0.3%)			1 (0.2%)	2 (0.3%)		

A class I and II recommendation could be determined in 2211 women (98.8%) and in 3175 men (98.3%).
DOAC= direct oral anticoagulants, VKA= vitamin k antagonists, APT= antiplatelet therapy

[a] Class I recommendation: women with CHA_2DS_2-VASc score $\geq$3 and men with CHA_2DS_2-VASc score $\geq$2
[b] Class IIa recommendation: women with CHA_2DS_2-VASc score of 2 and men with CHA_2DS_2-VASc score of 1
[c] Absolute difference between females and males in proportions with 95% confidence interval.
[d] e.g., (low molecular weight) heparin

TABLE 3 Number of patients with at least one AF-related hospital admission, including ablation and cardioversion, at follow-up, stratified by AF pattern at inclusion

Type AF at inclusion		Women (N=2238)	Men (N=3231)	Total (N=5469)	Absolute difference in proportions with 95% CI*	Two-sided p-value
Any first AF-related hospital visit or admission (%)		512 (22.9)	955 (29.6)	1467 (26.8)	0.07 [0.04 - 0.09]	p<0.001
	Paroxysmal	290 (13.0)	486 (15.0)	776 (14.2)	0.02 [0.00 - 0.04]	p=0.037
	Persistent	178 (8.0)	386 (11.9)	564 (10.3)	0.04 [0.02 - 0.05]	p<0.001
	Unknown	44 (2.0)	83 (2.6)	127 (2.3)	0.01 [-0.00 - 0.01]	p=0.150
Ablation (%)		67 (3.0)	154 (4.8)	221 (4.0)	0.02 [0.01 - 0.03]	p<0.001
	Paroxysmal	43 (1.9)	81 (2.5)	124 (2.3)	0.01 [-0.00 - 0.01]	p=0.142
	Persistent	21 (0.9)	61 (1.9)	82 (1.5)	0.01 [0.00 - 0.02]	p=0.003
	Unknown	3 (0.1)	12 (0.4)	15 (0.3)	0.00 [0.00 - 0.01]	p=0.038
ECV/CCV (%)		321 (14.3)	678 (20.9)	999 (18.3)	0.07 [0.05 - 0.09]	p<0.001
	Paroxysmal	157 (7.0)	288 (8.9)	445 (8.1)	0.02 [0.00 - 0.03]	p=0.011
	Persistent	137 (6.1)	331 (10.2)	468 (8.6)	0.04 [0.03 - 0.06]	p<0.001
	Unknown	27 (1.2)	59 (1.8)	86 (1.6)	0.01 [-0.00 - 0.01]	p=0.078

* Absolute difference between females and males in proportions with 95% CI.

TABLE 4 Number of patients with at least one ischemic or bleeding event (including CRNM/Major), and mortality after one year of follow-up

	Women (n=2238)	Men (n=3231)	Total (n=5469)	Absolute difference with 95% CI	Two-sided p-value
Ischemic events (%)	53 (2.4)	102 (3.2)	155 (2.8)	0.01 [-0.00- 0.02]	p=0.082
All bleeding events (%)	285 (12.7)	359 (11.1)	644 (11.8)	0.02 [-0.00- 0.03]	p=0.071
CRNM/Major (%)	93 (4.2)	143 (4.4)	236 (4.3)	0.00 [-0.01- 0.01]	p=0.721
All-cause mortality	77 (3.4)	95 (2.9)	172 (3.1%)	0.00 [-0.01- 0.01]	p=0.295

* Univariable comparison between female/male
CRNM: clinically relevant non-major

Sex differences in one-year outcomes

In Table 3 the AF-related hospital admissions (including the ECV/CCV and ablation) are presented; 955 men (29.6%) and 512 women (22.9%) had at least one AF-related hospital admission (p<0.001). There were fewer women with at least one ECV/CCV than men (321 women (14.3%) vs. 678 men (20.9%), p<0.001) and women underwent less often ablation (67 women (3.0%) vs. 154 men (4.8%), p<0.001) than men, regardless of the pattern of AF at inclusion (paroxysmal or persistent). Also, regarding the combined endpoint cardioversion and ablation, women underwent cardioversion or ablation less often than men (unadjusted odds ratio was 0.63 95% CI (0.55-0.73)), regardless of age, and the AF pattern at inclusion (adjusted odds ratio 0.77 95% CI (0.62-0.92)). Regarding the incidence of ischemic and bleeding events, there were no differences between men and women (see Table 4).

Of the men, 1,516 (46.9%) had paroxysmal AF, 362 (11.2%) persistent AF, 517 (16.0%) permanent AF, and 373 (11.5%) had not had a symptomatic AF recurrence since inclusion. Of the women, 1196 (53.4%) had paroxysmal AF, 190 (8.5%) persistent AF, 276 (12.3%) permanent AF, and 233 (10.4%) had not had a symptomatic AF recurrence since inclusion.

In Figure 2 the progression and regression patterns between inclusion and follow-up are graphically presented for women and men. In Table 5 and 6 the AF patterns at inclusion and during follow-up are presented for women and men. No apparent differences in progression and regression patterns between women and men were observed.

TABLE 5 AF progression and regression patterns for women with early AF

		Inclusion			
		Paroxysmal	Persistent	Unknown	Total
Follow-up	Paroxysmal	961 (65.5%)	176 (28.7%)	59 (37.6%)	1196 (53.4%)
	Persistent	49 (3.3%)	118 (19.2%)	23 (14.6%)	190 (8.5%)
	Permanent	49 (3.3%)	211 (34.4%)	16 (10.2%)	276 (12.3%)
	No AF	195 (13.3%)	22 (3.6%)	16 (10.2%)	233 (10.4%)
	Unknown	214 (14.6%)	86 (14.0%)	43 (27.4%)	343 (15.3%)
	Total	1468 (100%)	613 (100%)	157 (100%)	2238 (100%)

* Due to rounding the total is not exactly 100%.

TABLE 6 AF progression and regression patterns for men with early AF

		Inclusion			
		Paroxysmal	Persistent	Unknown	Total
Follow-up	Paroxysmal	1111 (62.6%)	330 (27.6%)	75 (28.8%)	1516 (46.9%)
	Persistent	65 (3.7%)	266 (22.2%)	31 (11.9%)	362 (11.2%)
	Permanent	84 (4.7%)	388 (32.4%)	45 (17.3%)	517 (16.0%)
	No AF	278 (15.7%)	75 (6.3%)	20 (7.7%)	373 (11.5%)
	Unknown	236 (13.3%)	138 (11.5%)	89 (34.2%)	463 (14.3%)
	Total	1774 (100%)	1197 (100%)	260 (100%)	3231 (100%)

* Due to rounding the total is not exactly 100%.

FIGURE 2 AF progression and regression patterns for men and women

DISCUSSION

In this observational study among real-life early AF patients, we detected clinically relevant differences between women and men. Women were older than men (median 73 vs. 69 years) at the moment AF was discovered. Moreover, the AF risk pattern differed between women and men (e.g., more hypertension and less concurrent vascular disease in women), as did the pattern of AF at the moment of inclusion (more paroxysmal AF in women). Interestingly, the AF symptom burden was higher in women at inclusion and follow-up, while men more often underwent cardioversion and ablation procedures. Ischemic events, bleeding events, and all-cause mortality did not differ substantially between women and men nor were there any apparent differences observed in AF progression- or regression patterns.

Comparison with literature

Our results are in some aspects similar to previous studies performed in AF patients with different patterns of AF. Previous studies in patients with permanent and persistent AF also showed that women have more often hypertension, heart failure, and valvular heart disease, and less often coronary heart disease compared to men.[3,4] Also, previous studies mainly performed in patients with longstanding AF reported that women are more symptomatic than men with AF, similar to our findings.[3–5,8] Our findings are also largely in line with the EAST-AFNET 4 trial, in which women with early AF (diagnosis $\leq$ 1 year before enrollment) were older than men, were less often asymptomatic, and had a higher CHA_2DS_2-VASc score than men.[11] In our study, men underwent cardioversion and ablation more often than women despite the fact that women were more often symptomatic (at inclusion *and* at one-year follow-up), even after adjustment for the apparent difference in age and the AF pattern. This finding is intriguing since rhythm control with either cardioversion or ablation is indicated to improve the functional status and health-related quality of life and thus reduce the symptom burden of AF.[17,18] We are not the first to report this finding [8,9], underpinning the robustness of this observation. Indeed, similar results were reported in a previous study based on data from the pan-European EORP-AF study regarding electrical cardioversion.[8] In this study population (n=3119; around a third early AF), men were also more likely to undergo cardioversion than women. Although we can only hypothesize, possibly men are more willing to undergo procedures like cardioversion and ablation than women, or possibly doctors are more inclined to offer such procedures to men than to women. Further studies are definitely needed to clarify this.

In the ORBIT-AF registry with 4293 women (42%) with AF, the adjusted all-cause mortality after a median FU of 2.3 years was lower in women than men, but the stroke risk was higher. The GARFIELD-AF registry with 12,709 women (44%) with early AF also showed that the adjusted stroke risk in women was higher compared to men, yet they did not find a difference in adjusted all-cause mortality between women and men.(13) We, however, were not able to detect any substantial sex differences in the occurrence of ischaemic events, bleeding events, and all-cause mortality, irrespective of the age difference between women and men, albeit it should be stressed here that our follow-up of one year may be too short to already detect differences in these outcomes. Finally, we showed that women with a class I or IIa recommendation received more often DOAC therapy at diagnosis than men with a class I or IIa recommendation. Men with a class I or IIa recommendation received no anticoagulants more often compared to women with a class I or IIa recommendation. These differences between men and women in management with DOAC and management with no anticoagulants are significant, but small and should therefore be interpreted with caution. Our study group previously showed that women with a class II recommendation receive anticoagulants at diagnosis more often than men with a class II recommendation, which might indicate that women are considered by clinicians to be at higher risk for stroke than men when prescribing anticoagulants.[19]

Strengths and limitations

A major strength of this study is that we were able to analyze a large prospective cohort of patients with early AF. Apart from the equal 'starting point' and thus a fair comparison between women and men, this is important because many adverse events occur already in the first year after AF diagnosis. Another strength of the DUTCH-AF registry is that it truly represents a real-life population of AF patients by including patients from cardiology outpatient clinics but also those mainly managed by the general practitioner and outpatient anticoagulation clinics. Moreover, prospective monitoring assured the completeness and accuracy of the data which we believe is very high for an observational study.

Some limitations need to be addressed. First, as in all observational studies, some misclassification cannot be ruled out. Second, more detailed clinical phenotyping in this cohort is lacking because we wanted to minimize the registration burden; e.g. details on echocardiography or non-cardiac medication were not included in the registry. Third, the number of events with regard to mortality, bleeding, and ischemia was still low due to the relatively limited follow-up duration, therefore no definite conclusions can be drawn on sex differences for these outcomes. Finally, given the observational design, explanation of the differences is speculative and hypothesis-generating. Further studies on differences in the pathophysiology of AF between men and women are definitely needed.

Clinical and research implications

Differences appear to exist between women and men, already at the moment of AF diagnosis and in the first year of follow-up. We believe that further research on these sex differences is needed, in order to help improve the knowledge of sex differences in this disease and subsequently help improve the diagnosis and treatment of both sexes by a more individualized sex-tailored approach. Etiologic studies are needed that focus on potential pathophysiologic differences that may help elaborate on plausible biological mechanisms underlying these sex differences in AF. In addition, we believe future clinical trials on AF management should by protocol define how to address the potential interaction of sex on their outcomes.

Conclusion

Men and women with early AF differ in age at diagnosis, but also in risk factors, symptoms, and subsequent management. These findings are building blocks for individualized sex-specific AF care and should prompt further investigation on this topic.

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AUTHORSHIP STATEMENT

I contributed to defining the research question, collection of the data, and management of the data. I conducted the data analysis and wrote the first version of the manuscript. During the whole process, I asked for and implemented input and feedback from the other contributors to this study.

7

GENERAL DISCUSSION

This thesis focuses on balancing risks in patients with thromboembolic disease. First, we will return to the research aims formulated in the introduction of this thesis (Chapter 1) and present the main findings of this thesis. Next, we will continue with the case of Mrs. Verburg presented in the introduction of this thesis. Finally, we will in detail illustrate the dilemma of balancing risks, notably in frail patients with AF, and discuss possible solutions for dealing with this dilemma.

The research aims formulated for this thesis were to:

i. Gain insight into the prevalence and determinants of diagnostic delay in patients with PE.

ii. Improve prediction of bleeding risk in patients with cancer while on anticoagulant treatment.

iii. Explore heterogeneity in the effect of integrated AF care in general practice in order to clarify which individuals profit most (and who profit least) from integrated AF care.

iv. Gain insight into sex differences at diagnosis and in one-year outcomes in patients with early AF.

MAIN FINDINGS OF THIS THESIS

Diagnostic delay can be considered as underdiagnosis together with missed or misclassified disease. Diagnostic delay in patients with PE is common, yet the prevalence and extent of the delay have never been systematically reviewed. We performed a systematic review and meta-analysis to review diagnostic delay in PE. The primary outcome was the mean delay in days. The secondary outcome was determinants of delay. We included 24 studies for the final analysis. The pooled estimate of the mean delay was 6.3 days (95% prediction interval between 2.5 and 15.8 days). The percentage of patients having more than seven days of delay varied between 18% and 38% in studies. Although the results of the studies were mixed and at points conflicting, coughing, chronic lung

disease, and heart failure seemed to be associated with a higher risk of delay. Recent surgery, hypotension, and (in most of the studies) chest pain were associated with a lower risk of delay. Our findings emphasize the importance of increasing awareness of PE by organizing events such as the World Thrombosis Day.[1] Moreover, educate both physicians and laypeople on when to consider PE as possible cause for symptoms such as shortness of breath. Since PE is associated with a high mortality rate as well as with long-term complications such as chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome [2–4], more research is urgently needed to gain insight into differences in the long-term outcomes between patients with and without a delayed diagnosis of PE. (**Chapter 2**)

Cancer patients are at increased risk of bleeding. Periods of increased hypercoagulability alternate with increased bleeding risk both caused by cancer itself or its chemotherapeutic treatments. Cancer patients who use anticoagulants indicated for thromboembolic disease are even more at risk of bleeding. Thus, in cancer patients on anticoagulants, it is very difficult to adequately balance the risks and benefits of anticoagulation during their disease trajectory. We aimed to (i) externally validate existing bleeding risk models and (ii) internally validate an updated model in patients with cancer who used anticoagulants for concurrent VTE and/or AF. Five bleeding risk models (HAS-BLED, ORBIT, ATRIA, VTE-bleed, and AF-bleed) were selected from the literature for validation in a retrospective, observational cohort consisting of routine primary healthcare data. A table with characteristics of these five models can be found in Chapter 3. The outcome was the composite of major and clinically relevant non-major (CRNM) bleedings.
The validation cohort in which we evaluated these five models consisted of 1304 cancer patients, mean age 74.0±10.9 years, 52.2% men. In total 215 (16.5%) patients developed a first major or CRNM bleeding during a mean follow-up of 1.5 years incidence rate; 11.0 per 100 person-years (95% CI 9.6-12.5). The c-statistics of the five selected bleeding risk models were low, around 0.56. A c-statistic of 0.50 is comparable with 'flipping a coin', so these models do not accurately distinguish between patients who will develop bleeding or not. Internal validation of an updated model accounting for death as competing risk showed a slightly improved c-statistic of 0.61 (95% CI 0.54-0.70). Upon updating, only age and a history of bleeding appeared to contribute to the prediction of bleeding. This study thus shows that predicting bleeding risk in cancer patients is very difficult with existing bleeding risk models. Future studies may use our updated model as a starting point for further upgrading of bleeding risk models in cancer patients. If possible, cancer-specific predictors (type of cancer, chemotherapy) may be considered to be added to these models. (**Chapter 3**)

Integrated care is recommended (class IIa, level B recommendation) by the 2020 guideline on atrial fibrillation of the European Society of Cardiology. It should entail (i) stroke prevention, (ii) symptom control, and (iii) management of comorbidities in a multidisciplinary setting.[5] Several studies on integrated AF care have been performed, but the content of the integrated care, and the outcomes that were considered differed between studies

differed which hampers comparing the results, the more so because the comparator group 'usual care' differs among health care settings and also over time. Nevertheless, most studies pointed in the direction of a beneficial effect. See Table 1 for an overview of integrated AF care studies. Most studies were in the hospital or outpatient setting. The ALL-IN trial was performed in general practices. The patients included in the ALL-IN study were older compared to the participants in hospital-based studies, and the intervention had a larger focus on managing comorbidities compared to the other studies. The ALL-IN trial showed that integrated care is effective in reducing all-cause mortality by 45% in patients with AF in primary care.[6] Integrated AF care in the ALL-IN study comprised of (i) anticoagulation monitoring organized in primary care, (ii) quarterly checkups for AF and its related comorbidities paying special attention to the possible development of heart failure, and (iii) easy-access consultation of AF specialists and thrombosis service. Although this study evidently showed that overall integrated primary AF care is beneficial, some individuals may benefit more than others, while others based on certain characteristics may profit less. We aimed to predict the individual treatment benefit of such integrated AF care in an additional analysis of the cluster-randomized ALL-IN trial to better prioritize healthcare resources and efforts for AF patients who are most likely to benefit. Cox proportional hazard analysis with the variables from the CHA_2DS_2-VASc score was used to predict all-cause mortality in the ALL-IN trial. Among 1,240 AF patients included in the ALL-IN trial (median age 77 (IQR 11) years, 49.4% women) the model for predicting short-term all-cause mortality showed a c-statistic of 0.72 [95% CI 0.66-0.78]. Patients receiving usual care had an absolute risk of all-cause mortality of 30.9% in the highest-risk quarter, while this was 4.6% in the lowest-risk quarter. On the relative scale, there was no evidence of treatment heterogeneity (p for interaction=0.93). However, there was substantial treatment heterogeneity on the absolute scale: integrated care reduced the risk of mortality by 3.3% (95% CI -0.4% - 7.0) in the lowest-risk quarter while this was 12.0% (95% CI 2.3% - 21.6) in the highest-risk quarter. This study thus shows that while the relative degree of benefit from integrated care is comparable for different individuals with AF, the absolute benefit is by far the greatest in patients with the highest predicted risk, being older and more frail AF patients. This should serve as an exemplification that in particular in older AF patients with multimorbidity offering an integrated AF approach with multiple control visits yearly, including AF care but also paying attention to comorbid conditions, is highly beneficial. (**Chapter 4**)

The increasing prevalence of AF in our aging society, and its associated adverse events and healthcare burden ask for optimization and where needed tailoring of AF management. Observational data can be used to evaluate how patients are managed in everyday clinical practice. The DUTCH-AF registry primarily aims to determine the clinical impact of non-adherence and non-persistence to anticoagulation therapy and its predictors. In addition, it aims to validate and refine bleeding risk models. In the near future, registry-based randomized controlled trials are planned, using the registry as a starting point for patient recruitment and follow-up. The DUTCH-AF registry is a unique nationwide, prospective registry of patients with newly diagnosed non-valvular AF. Patients are enrolled from

Dutch general practices, thrombosis services, and hospitals. End of 2021 the consortium of researchers managed to include the targeted 6000 patients. A follow-up duration of 2 years is planned. The design of this study is described in **Chapter 5**.

There is evidence of sex differences in AF patients, yet little is known about sex differences in patients with early AF. Since most adverse events occur in the first year after diagnosis, this year is particularly important for studying sex differences because it may open up an avenue to individualized sex-tailored care right from the start. We used data from 5,469 participants of the DUTCH-AF registry (Chapter 5) to describe sex differences at diagnosis and differences in AF management in the first year of follow-up. At inclusion, women were older than men (median 73 vs. 69 years, p<0.001), had more often paroxysmal AF (66% vs. 55%, p<0.001), and less often persistent AF (27% vs. 37%, p<0.001). They also had more often hypertension (59% vs. 53%, p<0.001), and less often vascular disease (12% vs. 21%, p<0.001, and reported more often symptoms both at inclusion and in the month prior to follow-up; 56% vs. 46%, p<0.001, and 31% vs. 23%, p<0.001, respectively. Women underwent cardioversion and ablation procedures less often than men (14% vs. 21% p<0.001 and 3% vs. 5%, p<0.001, respectively). Also for the combined rhythm control intervention cardioversion and ablation, women underwent cardioversion or ablation less often than men (unadjusted odds ratio was 0.63 95% CI (0.55-0.73)), regardless of age, and the type of AF (i.e. paroxysmal or persistent AF) at inclusion (adjusted odds ratio 0.77 95% CI (0.62-0.92)). No differences were observed for ischemic and bleeding events, all-cause mortality, or AF progression patterns. This study showed that men and women with new AF differ in age, comorbidities, AF pattern, symptoms, and disease management in the first year. These findings are building blocks for more individualized sex-specific AF care, but also further research on sex differences in AF patients. (**Chapter 6**)

CONTINUATION OF THE DISEASE TRAJECTORY OF MRS. VERBURG, OUR CASE PRESENTED IN THE INTRODUCTION OF THE THESIS

Ten years later, Mrs. Verburg is now 80 years old, and she visits the physician assistant (PA) of the general practice for one of her regular cardiovascular risk management check-ups. Over the last few years, her health substantially deteriorated. Her AF became permanent, and she was additionally diagnosed with hypertension and heart failure with preserved ejection fraction. She now also uses enalapril 10 mg twice daily, and the metoprolol she already used was raised to 50 mg twice daily. She still uses apixaban 5 mg twice daily for stroke prevention. After her finishing chemotherapy, the nose bleeding fortunately stopped. However, her exercise capability has greatly reduced over the last few years, and she no longer is able to bike. She uses the car to leave her house. In addition, she has developed neuropathy of her feet as a result of the chemotherapy which makes driving her car more difficult and she fears becoming more dependent and homebound. Four weeks ago, Mrs. Verburg was admitted to the hospital for pneumonia. After treatment with oxygen and intravenous amoxicillin for 5 days, she was released home. Mrs. Verburg tells the PA that she is still very tired and wants to know what can be done to improve her energy level. On physical examination, the PA detects an irregular pulse

of 60 beats per minute (heart rate 84 beats per minute) and blood pressure of 158/98 mmHg (mean of two measurements). Routine blood and urine examination show a reduced eGFR of 45 ml/min/1.72 m2 and mild proteinuria. The PA schedules a consultation for Mrs. Verburg with the GP to discuss the decline in health and renal function, and whether further steps in hypertension management should be taken. Is a third antihypertensive, a switch to another antihypertensive, or other medication adjustment needed (apixaban)? Or is even a new consultation with the cardiologist indicated?

BALANCING RISKS IN FRAIL AF PATIENTS

The case of Mrs. Verburg illustrates what often happens over time in patients with AF. The AF becomes permanent, more comorbidities develop, and along with aging and an increase in frailty, the likelihood of hospitalizations increases. These hospitalizations are not only AF-related but even more directly related to non-cardiac causes. Indeed, it has been shown that in older patients with AF and multiple comorbidities, the risk of (mainly non-cardiac) hospitalization and all-cause mortality is high.[7] Balancing the risk of thromboembolic events and the risk of bleeding becomes even more difficult in these patients because both risks increase with aging in patients with AF, although, in general, the thromboembolic risk remains higher than the risk of CRNM/major bleeding.[8,9] Importantly, however, the reduction in thromboembolic risk with oral anticoagulants treatment which is on a relative scale around 66% is invisible; these prevented strokes are not experienced by patients. In contrast, with aging, more bleeding occurs, certainly, also skin and nose bleeding as Mrs. Verburg already experienced. Predictors for bleeding tend to accumulate with aging, leading to an increased bleeding vulnerability. For example, in anticoagulated AF patients with reduced kidney function, the risk of clinically relevant bleeding was found to be around 10 times higher than the risk of thromboembolic events.[10] (Fear of) bleeding has a negative impact on adherence to anticoagulants, which results in an increased risk of thromboembolic events. Another reason for increased bleeding risk in elderly AF patients is a poor nutritional status with weight loss, which along with deterioration of kidney function increases the risk of overdosing of direct oral anticoagulants (DOAC). The balance between bleeding and thromboembolic events is thus fragile and changes dynamically over time, asking for continuous monitoring and balancing of risks.

IMPROVEMENT OF BALANCING RISKS AND BENEFITS IN AF PATIENTS

Therefore, to address these interacting problems adequately in frail patients with AF such as Mrs. Verburg now, it is important to not only focus on AF itself but apply a holistic approach paying also attention to the medication, cardiovascular, and non-cardiovascular comorbidities. E.g., in case of Mrs. Verburg, the dose of apixaban should be adjusted (because of her age, and lowered eGFR) to prevent bleeding complications, lowering the dose of metoprolol could be considered to improve her symptoms of tiredness and adding another antihypertensive drug to lower her blood pressure. By referring Mrs. Verburg for cardiac evaluation, echocardiography could reveal e.g., valvular disease or negative

change in left ventricular ejection fraction, and Holter monitoring might show bradycardia, which could also explain her symptoms of tiredness, and which might necessitate further adjustment of the medication. As was shown in this thesis, older AF patients with comorbidities have a high all-cause mortality risk, and these patients in particular benefit from an integrated cardiovascular care approach.[6] Since cardiovascular and non-cardiovascular comorbidities often interact and aggravate the systemic effects of AF, these non-cardiovascular comorbidities also need attention in clinical care but also in research, e.g., by *a priori* including these outcomes in AF studies. This is supported by the fact that in the ALL-IN trial the largest effect of integrated care was seen on non-cardiovascular mortality.[6] Among the causes of non-cardiovascular mortality were diseases such as malignancy and serious infections/sepsis, often entangled with the deterioration of the cardiac function caused by AF in this mainly elderly population. It could be hypothesized that integrated care leads to early detection of such imminent deterioration.

Besides offering an integrated care approach to AF patients, we also need to improve individual bleeding risk prediction in order to better balance patients' risk of bleeding and thromboembolism. Validated bleeding risk models for the prediction of the bleeding risk in patients with cancer are lacking. This thesis showed that bleeding risk prediction, based on existing bleeding risk models developed in AF and VTE patients, including an updated bleeding risk model, is particularly difficult in patients with cancer using anticoagulants. Several steps need to be taken to improve bleeding risk prediction. First, we need to identify new predictors of bleeding and include these in bleeding risk models, e.g., cancer-specific predictors. Moreover, the modeling itself, and the reporting on bleeding risk models need improvement. All (non-cancer specific) bleeding risk models included in our study had a high risk of bias according to the PROBAST guidelines and this was mainly due to lack of reporting of relevant information on e.g., predictor selection, and due to methodological issues (i.e., not handling missing data appropriately or not accounting for competing risk). Improvement of (reporting of) prediction models is necessary in order to lead to clinically relevant results which then form the building blocks for adequately informing guideline makers and help improve patient care. Moreover, we need to improve our knowledge of so-called modifiable bleeding risk factors. Often, *predictors* for bleeding and *modifiable risk factors* for bleeding are used loosely and interchangeably. This, however, is a mistake if looked upon from a methodological point of view. In fact, although predictors for bleeding and modifiable bleeding risk factors can overlap, there is an important difference. When studying predictors of bleeding we are not interested in a causal relationship, yet when studying modifiable risk factors, we are, as the aim of studying these factors is to change (or modify) them so that bleeding risk can be reduced. For example, age and a history of bleeding are predictors of bleeding, yet these are not modifiable risk factors (they cannot be changed or modified). However, for example, there is a causal relationship between liver disease (e.g., by decreased synthesis of clotting factors) and bleeding. Since liver disease can be potentially influenced, this is a modifiable risk factor for bleeding. Therefore, to study modifiable risk factors for bleeding in AF, eti-

ologic studies are necessary, rather than prediction modeling studies. This subsequently brings adjusting for potential confounders to the table, a delicate and often difficult discussion on when a certain variable should be considered as a confounder or a mediator of the observed effect, let alone that adjustment of confounding by indication needs to be considered (e.g., by inverse probability of treatment weighting). While a mediator is part of the causal pathway between the determinant and outcome, a confounder is not part of the causal pathway but influences both the determinant and outcome and thereby distorts this relationship. Finally, ideally, to study whether *treating* these modifiable risk factors in AF patients using anticoagulants indeed reduces the risk of bleeding, randomized controlled trials (RCTs) are needed. RCTs specifically to address the problem of treating modifiable risk factors for bleeding in AF patients are missing altogether. This is detrimental because in our aging anticoagulated population we observe many, sometimes even fatal, bleeding events. We thus should put more effort into scientifically sound RCT studies on bleeding risk stratification. Instead of performing conventional RCTs, registry-based trials could be considered for studying the treatment of modifiable risk factors, with the advantages of easy participant recruitment, and study participants coming from a real-life population.

Ultimately, we want to reduce the risk of bleeding in patients using anticoagulants. There are several ways already at hand to achieve this. First, correct prescription (i.e., prevention of overdosing, underdosing, and unplanned stops) of anticoagulants. The DUTCH-AF registry will evaluate guideline non-adherence and the association with adverse events such as bleeding.[11] This can provide insights that can be brought back to physicians and thus be useful to help improve the quality of care of AF patients using anticoagulants and reduce the risk of bleeding. Second, fragmentation of anticoagulation care should be prevented. Due to a large transition of vitamin-k-antagonists (VKA) use to mainly DOAC use, the role of thrombosis services in managing patients on anticoagulants is reduced, and instead different healthcare givers are involved in anticoagulation care. Good collaboration between these healthcare providers is necessary and the Dutch '*landelijke transmurale afspraak (LTA) Antistollingszorg*' is helpful for achieving this. Agreements on anticoagulation management between e.g., general practitioners, medical specialists, and thrombosis services are clearly noted in the LTA.[12] Although the transition of VKA to mainly DOAC in AF patients has already occurred, it is unclear whether it is safe to switch from VKA to DOAC in frail AF patients, and this is currently investigated in the FRAIL-AF study.[7] Third, we could improve anticoagulation therapy itself to reduce the risk of bleeding, yet, without increasing the risk of thromboembolism. Although compared to VKA, DOAC use is associated with a reduced risk of invalidating intracerebral bleeding, the risk of major bleeding is still considerable. Therefore, there is a need for new anticoagulants that have a lower bleeding risk. Currently, studies are ongoing on factor XIa inhibitors for the prevention of thromboembolic events in AF. By inhibiting factor XIa, the amplification phase of the coagulation cascade is inhibited (see Figure 1 of the introduction of this thesis) and therefore countering thrombus formation, yet by affecting hemostasis less and thus likely reducing the risk of bleeding. The results of a phase 2 study in patients

with AF comparing the factor XIa inhibitor asundexian with apixaban were promising.[13] In this study, 755 patients (mean age of 73.7 ± 8.3 years) were randomly assigned to either a high or low dose of asundexian, or to a standard dose of apixaban. During a follow-up of 12 weeks, the occurrence of major and CRNM bleeding was registered. Less bleeding occurred in patients using asundexian compared to patients using apixaban. Importantly, however, this study was not powered to compare the occurrence of thrombotic events in both groups. Results of adequately powered phase 3 trials are needed in order to study the most important clinical outcomes of patients with AF using factor XIa inhibitors thromboembolic events and major/CRNM bleedings. These phase 3 studies are currently underway.

BALANCING RISKS AND BENEFITS IN THE LAST PHASE OF LIFE

In summary, there is an ongoing discussion on anticoagulation treatment and how to improve it, optimally balancing the risk of bleeding and the reduction in the risk of thromboembolic events in everyday patients with AF. From a scientific point of view, we explored and analyzed a few of these 'balancing acts' in clinical situations and discussed ways how to improve upon them. However, there are still many gaps in knowledge. A final exemplification of this gap is how to proceed in patients using anticoagulants while in the last phase of their life. Anticoagulants are often continued, also in the very last phase of life, despite a substantial risk of bleeding while possibly the benefit of anticoagulation is not substantial anymore.[14–16] There is very little known on how to predict the risk of bleeding and risk of thromboembolism in patients in the last phase of life and to decide whether and when to stop anticoagulants. In our aging society with increasing life expectancy, an increasing number of patients are expected to use anticoagulants and this calls for more knowledge on how to improve decision-making on (dis)continuation of anticoagulants in the last phase of life. This will be investigated by the EU-sponsored Serenity consortium.

Indeed, research on thrombosis and bleeding, on clot formation and clot resolution, will continue, and perhaps finding 'the holy grail' on the prevention of thrombosis while not affecting hemostasis too much is not possible. Nevertheless, the dilemma of balancing risks and benefits in patients with thromboembolic disease will continue to exist.

TABLE 1 Overview of integrated AF care studies

Study name, country	Year of publication	Setting	Definition integrated care	Comparator	Main results and conclusion
ALL-IN (6) Netherlands	2020	Primary care Cluster RCT	Anticoagulation monitoring in primary care, quarterly checkups for AF and its related comorbidities, and easy-access consultation with AF specialists	Usual care: yearly consultation cardiologist or "ad hoc" consultation GP initiated by patient	Significant reduction in all-cause mortality (adjusted hazard ratio 0.55; 95% CI [0.37–0.82]).
Cox et al. (17) Canada	2020	Primary care Cluster RCT	Access for primary care physicians and patients to a computerized clinical decision support system for AF management	Usual care (not specified)	No significant reduction in composite of unplanned cardiovascular hospitalizations and AF-related emergency department visits (hazard ratio 0.98 95% CI [0.71-1.37]
RACE-4 (18) Netherlands	2019	Outpatient clinic RCT	Nurse-led care (using a decision-support tool), supervised by a cardiologist	Usual care: routine outpatient management by cardiologist	No reduction in composite of cardiovascular death and cardiovascular hospital admissions (hazard ratio 0.85, 95% CI [0.69 - 1.04]). Only significant reduction in subgroup of experienced centers.
Vinereanu et al. (19) Five countries*	2017	Outpatient clinic Cluster RCT	Education of providers and patients on anticoagulants, with regular monitoring and feedback	Control group: providers in anticoagulation care should review guidelines, webinars/podcasts and monograph	Significant increase in the proportion of patients treated with oral anticoagulants (odds ratio change in use of anticoagulants between groups 3.28 95% CI [1.67–6.44]).
Carter et al. (20) Canada	2016	Outpatient clinic "Before-and-after" study	Nurse-run, physician-supervised AF clinic	Before: usual AF management	Significant reduction in composite of death, cardiovascular hospitalization, and AF-related emergency department visits (odds ratio 0.71; 95% CI [0.59 – 1]).

TABLE 1 Overview of integrated AF care studies (continued)

SAFETY (21) Australia	2015	Hospital-based RCT	Home visit and holter monitoring after hospital discharge by a cardiac nurse with prolonged follow-up and multidisciplinary support as needed	Standard management: routine primary care and hospital outpatient follow-up	Significant more days alive and out of hospital (effect size 0.22, 95% CI [0.21–0.23]). No significant prolonged event-free survival (hazard ratio 0.97, 95% CI [0.76–1.23]).
Hendriks et al. (22) (23) Netherlands	2012, 2019	Outpatient clinic RCT (mono-center)	Nurse-led care (using decision-support software) supervised by a cardiologist	Usual care: by a cardiologist in outpatient clinic	Significant reduction in composite of cardiovascular hospitalizations and cardiovascular mortality (hazard ratio 0.65; 95% CI [0.45–0.93]). Post-hoc analysis 2019: Significant reduction in all-cause mortality (hazard ratio 0.44, 95% CI [0.23-0.85])

* Argentina, Brazil, China, India, Romania

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AUTHORSHIP STATEMENT

The idea and set-up of the general discussion were mine; I conducted the literature search and wrote the general discussion. During the whole process, I asked for and implemented input and feedback from my supervisory team.

SUMMARY

INTRODUCTION

In thromboembolic disease, a blood clot is formed, which can travel through the bloodstream, lodge in a blood vessel, and lead to an interruption of blood flow. When thromboembolism occurs in the venous system, this is called venous thromboembolism (VTE). The most common manifestations of VTE are deep venous thrombosis (DVT) and pulmonary embolism (PE). Another manifestation of thrombosis is arterial thromboembolism, in which a blood clot obstructs an artery and causes tissue ischemia. An important risk factor for arterial thromboembolism, notably in the brain, is atrial fibrillation (AF), a common and important heart rhythm disorder. Anticoagulation is the cornerstone in thromboembolic prevention (mainly of ischemic stroke) in patients with AF, but also in the management of those with VTE and for primary prevention of VTE. Although anticoagulants are effective in the prevention and treatment of thromboembolic disease, the downside is the increased risk of bleeding. Since both thromboembolic and bleeding events can have severe consequences, the risks of thromboembolism should be carefully weighed against the risks of bleeding events due to anticoagulants. To carefully decide on the best treatment option, physicians can use a *risk score* or *risk model* to estimate the risk of thromboembolic events and the risk of bleeding risk associated with anticoagulation. These scores and models can help to identify patients at increased risk for bleeding. Balancing of risks also plays an important role in the diagnosis of thromboembolic disease, that is, in finding a balance between the risks of over- and underdiagnosis. The objective of this thesis is to study the challenges related to balancing risks in patients with thromboembolic disease.

DIAGNOSTIC DELAY IN PATIENTS WITH PULMONARY EMBOLISM

Diagnostic delay can be considered as underdiagnosis together with missed or misclassified disease. Diagnostic delay in patients with PE is common, yet the prevalence and extent of the delay have never been systematically reviewed. In **Chapter 2** we report the results of a systematic review and meta-analysis on diagnostic delay in PE. The pooled estimate of the mean delay was 6.3 days. The percentage of patients having more than seven days of delay varied between 18% and 38% in studies. Although the results of the

studies were mixed and at points conflicting, coughing, chronic lung disease, and heart failure seemed to be associated with a higher risk of delay. Recent surgery, hypotension, and (in most of the studies) chest pain were associated with a lower risk of delay. Our findings emphasize the importance of increasing awareness of PE by organizing events such as the World Thrombosis Day.[1]

BLEEDING RISK IN CANCER PATIENTS USING ANTICOAGULANTS

Cancer patients are at increased risk of bleeding. Periods of increased hypercoagulability alternate with increased bleeding risk both caused by cancer itself or its chemotherapeutic treatments. Cancer patients who use anticoagulants indicated for thromboembolic disease are even more at risk of bleeding. Thus, in cancer patients on anticoagulants, it is very difficult to adequately balance the risks and benefits of anticoagulation during their disease trajectory. In **Chapter 3** the results of a study on the bleeding risk in patients with cancer using anticoagulants are reported. In this study, we aimed to (i) externally validate existing bleeding risk models and (ii) internally validate an updated model in patients with cancer who used anticoagulants for concurrent VTE and/or AF. Five bleeding risk models were selected from the literature for validation in a retrospective, observational cohort consisting of routine primary healthcare data. The validation cohort in which we evaluated these five models consisted of 1304 cancer patients, mean age 74.0±10.9 years, 52.2% men. In total 215 (16.5%) patients developed a first major or CRNM bleeding during a mean follow-up of 1.5 years incidence rate; 11.0 per 100 person-years (95% CI 9.6-12.5). The c-statistics of the five selected bleeding risk models were low, around 0.56. A c-statistic of 0.50 is comparable with 'flipping a coin' so these models do not accurately distinguish between patients who will develop bleeding or not. Internal validation of an updated model accounting for death as competing risk showed a slightly improved c-statistic of 0.61 (95% CI 0.54-0.70). Upon updating, only age and a history of bleeding appeared to contribute to the prediction of bleeding. This study thus shows that predicting bleeding risk in cancer patients is very difficult with existing bleeding risk models. Future studies may use our updated model as a starting point for further upgrading of bleeding risk models in cancer patients. If possible, cancer-specific predictors (type of cancer, chemotherapy) may be considered to be added to these models.

PREDICTION OF THE INDIVIDUAL TREATMENT BENEFIT OF INTEGRATED AF CARE

Integrated care is recommended (class IIa, level B recommendation) by the 2020 guideline on atrial fibrillation of the European Society of Cardiology. It should entail (i) stroke prevention, (ii) symptom control, and (iii) management of comorbidities in a multidisciplinary setting.[2] The ALL-IN trial showed that integrated care is effective in reducing all-cause mortality by 45% in patients with AF in primary care.[3] Integrated AF care in the ALL-IN study comprised of (i) anticoagulation monitoring organized in primary care, (ii) quarterly checkups for AF and its related comorbidities paying special attention to the possible development of heart failure, and (iii) easy-access consultation of AF specialists

and thrombosis service. Although this study evidently showed that overall integrated primary AF care is beneficial, some individuals may benefit more than others, while others based on certain characteristics may profit less. In **Chapter 4** we report the results of an analysis of heterogeneity of the treatment effect in the ALL-IN trial. We aimed to predict the individual treatment benefit of such integrated AF care in an additional analysis of the cluster-randomized ALL-IN trial to better prioritize healthcare resources and efforts for AF patients who are most likely to benefit. Cox proportional hazard analysis with the variables from the CHA_2DS_2-VASc score was used to predict all-cause mortality in the ALL-IN trial. Among 1,240 AF patients included in the ALL-IN trial (median age 77 (IQR 11) years, 49.4% women) the model for predicting short-term all-cause mortality showed a c-statistic of 0.72 (95% CI 0.66-0.78). Patients receiving usual care had an absolute risk of all-cause mortality of 30.9% in the highest-risk quarter, while this was 4.6% in the lowest-risk quarter. On the relative scale, there was no evidence of treatment heterogeneity. However, there was substantial treatment heterogeneity on the absolute scale: integrated care reduced the risk of mortality by 3.3% (95% CI -0.4% - 7.0) in the lowest risk-quarter while this was 12.0% (95% CI 2.3% - 21.6) in the highest risk quarter. This study thus shows that while the relative degree of benefit from integrated care is comparable for different individuals with AF, the absolute benefit is by far the greatest in patients with the highest predicted risk, being older and more frail AF patients. This should serve as an exemplification that in particular in older AF patients with multimorbidity offering an integrated AF approach with multiple control visits yearly including AF care but also paying attention to comorbid conditions is highly beneficial.

EVALUATION OF AF MANAGEMENT IN EVERYDAY CLINICAL PRACTICE

The increasing prevalence of AF in our aging society, and its associated adverse events and healthcare burden ask for optimization and where needed tailoring of AF management. Observational data can be used to evaluate how patients are managed in everyday clinical practice. The DUTCH-AF registry primarily aims to determine the clinical impact of non-adherence and non-persistence to anticoagulation therapy and its predictors. In addition, it aims to validate and refine bleeding risk models. In the near future, registry-based randomized controlled trials are planned, using the registry as a starting point for patient recruitment and follow-up. The DUTCH-AF registry is a unique nationwide, prospective registry of patients with newly diagnosed non-valvular AF. Patients are enrolled from Dutch general practices, thrombosis services, and hospitals. End of 2021 the consortium of researchers managed to include the targeted 6000 patients. A follow-up duration of 2 years is planned. The design of this study is described in **Chapter 5**.

SEX DIFFERENCES IN AF PATIENTS

There is evidence of sex differences in AF patients, yet little is known about sex differences in patients with early AF. Since most adverse events occur in the first year after diagnosis, this year is particularly important for studying sex differences because it may open up an

avenue to individualized sex-tailored care right from the start. We used data from 5,469 participants of the DUTCH-AF registry (chapter 5) to describe sex differences at diagnosis and differences in AF management in the first year of follow-up. At inclusion, women were older than men (median 73 vs. 69 years, p<0.001), had more often paroxysmal AF (66% vs. 55%, p<0.001), and less often persistent AF (27% vs. 37%, p<0.001). They also had more often hypertension (59% vs. 53%, p<0.001), and less often vascular disease (12% vs. 21%, p<0.001), and reported more often symptoms both in the month before inclusion and in the month before follow-up; 56% vs. 46%, p<0.001, and 31% vs. 23%, p<0.001, respectively. Women underwent cardioversion and ablation procedures less often than men (14% vs. 21%, p<0.001, and 3% vs. 5%, p<0.001, respectively). Also, for the combined rhythm control intervention cardioversion and ablation, women underwent cardioversion or ablation less often than men (unadjusted odds ratio was 0.63 95% CI (0.55-0.73), regardless of age, and the type of AF (i.e., paroxysmal or persistent AF) at inclusion (adjusted odds ratio 0.77 95% CI (0.62-0.92)). No differences were observed for ischemic and bleeding events, all-cause mortality, or AF progression patterns, but the number of these events was rather small. This study showed that males and females with new AF differ in age, comorbidities, AF pattern, symptoms, and disease management in the first year. These findings are building blocks for more individualized sex-specific AF care, but also for further research on sex differences in AF patients. (**Chapter 6**)

In the General Discussion (**Chapter 7**) the main findings of this thesis are presented, the dilemma of balancing risks in frail patients with AF is further illustrated, and possible solutions for dealing with this dilemma are discussed. What happens in most patients with AF, is that over time the AF becomes permanent, more comorbidities develop, and along with aging and an increase in frailty, the likelihood of hospitalizations increases. Balancing the risk of thromboembolic events and the risk of bleeding becomes even more difficult in these patients because both risks increase with aging in patients with AF, although, in general, the thromboembolic risk remains higher than the risk of CRNM/major bleeding.[4,5] The balance between bleeding and thromboembolic events is fragile and changes dynamically over time, asking for continuous monitoring and balancing of risks. To address these interacting problems adequately in frail patients with AF, it is important to not only focus on AF itself but apply a holistic approach also paying attention to the medication, cardiovascular, and non-cardiovascular comorbidities. Besides offering an integrated care approach to AF patients, we also need to improve individual bleeding risk prediction to better balance patients' risk of bleeding and thromboembolism. Ultimately, we want to reduce the risk of bleeding in patients using anticoagulants. There are several ways already at hand to achieve this. First, by improving correct prescription (i.e., prevention of overdosing, underdosing, and unplanned stops) of anticoagulants. Second, by preventing fragmentation of anticoagulation, and by good collaboration between these healthcare providers. Third, we could improve anticoagulation therapy itself to reduce the risk of bleeding, yet, without increasing the risk of thromboembolism, by developing new anticoagulants that have a lower bleeding risk. Currently, studies are ongoing on factor XIa inhibitors for the prevention of thromboembolic events in AF. Lastly, there is

very little known on how to predict the risk of bleeding and risk of thromboembolism in patients with cancer in the last phase of life and to decide whether and when to stop anticoagulants. In our aging society with increasing life expectancy, an increasing number of patients are expected to use anticoagulants, and this calls for more knowledge on how to improve decision-making on (dis)continuation of anticoagulants in the last phase of life. This will be investigated by the EU-sponsored Serenity consortium.

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SAMENVATTING

INLEIDING

Bij trombo-embolische aandoeningen is er sprake van een stolsel, dat zich door de bloedbaan kan verplaatsen en in een bloedvat vast kan komen te zitten, wat kan leiden tot een onderbreking van de bloeddoorstroming. Wanneer een trombo-embolie optreedt in het veneuze systeem wordt dit veneuze trombo-embolie genoemd (VTE). De meest voorkomende uitingsvormen van VTE zijn diep-veneuze trombose (DVT) en longembolie (LE). Een andere vorm van trombo-embolie is arteriële trombo-embolie, waarbij een stolsel de bloeddoorstroming in een slagader blokkeert waardoor ischemie (zuurstoftekort) kan ontstaan. Een belangrijke risicofactor voor arteriële trombo-embolie, met name in de hersenen, is atriumfibrilleren (AF), een veel voorkomende en belangrijke hartritmestoornis. Antistollingsmedicatie is de hoeksteen in de preventie van trombo-embolieën (met name van een herseninfarct) bij patiënten met AF, maar ook voor de primaire preventie en behandeling van VTE.

Ondanks dat antistollingsmedicatie effectief is in de preventie en behandeling van trombo-embolieën, is er de keerzijde van het toegenomen risico op bloedingen. Aangezien zowel trombo-embolische complicaties als bloedingen ernstige gevolgen kunnen hebben, moeten de risico's van beide worden afgewogen. Om dit zorgvuldig te doen kunnen *risicoscores* of *risicomodellen* worden gebruikt. Deze scores en modellen kunnen helpen bij het inschatten van het risico op trombo-embolieën en het identificeren van patiënten met een verhoogd risico op bloedingen. Het balanceren van risico's speelt ook een belangrijke rol in het diagnosticeren van trombo-embolische aandoeningen, namelijk in het vinden van een balans tussen het risico op onder- en overdiagnose. Het doel van dit proefschrift is om uitdagingen gerelateerd aan het balanceren van risico's bij patiënten met trombo-embolische aandoeningen te bestuderen.

DIAGNOSTISCHE VERTRAGING VAN LONGEMBOLIE

Diagnostische vertraging kan samen met het missen van een diagnose of het verkeerd classificeren van een ziekte beschouwd worden als onderdiagnostiek. Het is onbekend hoe vaak diagnostische vertraging precies voorkomt, om hoeveel dagen vertraging het gaat en welke patiënten het hoogste risico lopen op diagnostische vertraging. In **hoofd-**

stuk 2 rapporteren wij de resultaten van een systematische review en meta-analyse van diagnostische vertraging bij longembolie. De samengevoegde schatting van de vertraging was 6,3 dagen. Het percentage patiënten met meer dan zeven dagen vertraging varieerde tussen de 18% en 38%. Hoewel de resultaten van de studies wisselend en soms tegenstrijdig waren, leken hoesten, chronische longziekte en hartfalen verband te houden met een hoger risico op diagnostische vertraging. Recente chirurgie, lage bloeddruk en (in de meeste studies) pijn op de borst werden in verband gebracht met een lager risico op vertraging. Deze bevindingen onderstrepen het belang van het creëren van meer bewustwording over de diagnose van longembolie, bijvoorbeeld door het organiseren van evenementen zoals de "Wereld Trombose Dag". [1]

BLOEDINGSRISICO BIJ PATIËNTEN MET KANKER DIE ANTISTOLLING GEBRUIKEN

Patiënten met kanker hebben een verhoogd risico op bloedingen. Periodes van verhoogde stollingsneiging worden afgewisseld met een verhoogd risico op bloedingen, veroorzaakt door zowel de kanker zelf als door bijvoorbeeld chemotherapeutische behandelingen. Bij kankerpatiënten die antistolling gebruiken, is het dus belangrijk om een goede afweging te maken van de risico's en de voordelen van antistolling tijdens hun ziektetraject. In **hoofdstuk 3** beschrijven wij de resultaten van een studie naar het bloedingsrisico bij patiënten met kanker die antistolling gebruiken. De doelen van deze studie waren om (i) bestaande modellen voor het voorspellen van bloedingen extern te valideren en (ii) een bijgewerkt model intern te valideren bij patiënten met kanker die antistolling gebruiken voor VTE en/of AF. Vijf modellen voor het voorspellen van bloedingen werden op basis van de literatuur geselecteerd voor validatie in een retrospectief, observationeel cohort op basis van routinematig verzamelde data uit de eerstelijnsgezondheidszorg. Het validatiecohort bestond uit 1304 kankerpatiënten (gemiddelde leeftijd 74,0±10,9 jaar en 52,2% man). In totaal trad bij 215 (16,5%) patiënten een eerste grote of klinisch relevante bloeding op tijdens een gemiddelde follow-up van 1,5 jaar; mate van optreden 11,0 gevallen per 100 persoonsjaren (95% CI 9,6-12,5). De vijf modellen bleken niet goed te voorspellen of patiënten een bloeding zouden ontwikkelen. De zogenaamde c-statistieken waren laag, rond 0,56. Ter vergelijking, een c-statistiek van 0,50 zou neerkomen op het 'opgooien van een muntje'. Interne validatie van een bijgewerkt model, rekening houdend met overlijden als concurrerend risico, toonde een iets hogere c-statistiek van 0,61 (95% CI 0,54-0,70). Alleen leeftijd en voorgeschiedenis van bloedingen bleken bij te dragen aan de voorspelling van bloedingen. Deze studie toont dus aan dat het voorspellen van het bloedingsrisico bij kankerpatiënten zeer moeilijk is op basis van de bestaande modellen. Toekomstige studies kunnen ons bijgewerkte model gebruiken voor het verder ontwikkelen van modellen voor het voorspellen van bloedingen in deze populatie. Indien mogelijk kan worden overwogen kankerspecifieke voorspellers (bijvoorbeeld type kanker, chemotherapie) aan deze modellen toe te voegen.

VOORSPELLEN VAN HET INDIVIDUELE BEHANDELVOORDEEL VAN INTEGRALE AF-ZORG

Integrale zorg wordt aangeraden (klasse IIa, niveau B aanbeveling) in de Europese richtlijn voor atriumfibrilleren uit 2020. Het zou moeten bestaan uit: (i) preventie van een herseninfarct, (ii) het onder controle krijgen van symptomen en (iii) het behandelen van comorbiditeit in een multidisciplinaire samenhang.[2] De ALL-IN studie toonde aan dat integrale AF-zorg in de eerste lijn effectief is in het verminderen van de totale sterfte met 45%.[3] Integrale AF-zorg in de ALL-IN studie bestond uit (i) controle van antistolling in de huisartsenpraktijk, (ii) driemaandelijkse controles voor AF en gerelateerde comorbiditeit, waarbij speciale aandacht werd geschonken aan de mogelijke ontwikkeling van hartfalen, en (iii) laagdrempelig overleg met AF-specialisten en trombosedienst.

Hoewel deze studie een duidelijk gunstig effect laat zien van integrale AF-zorg voor een gemiddelde patiënt, kan het zijn dat de ene patiënt meer baat bij integrale zorg heeft dan de andere. In **hoofdstuk 4** rapporteren wij de resultaten van een analyse naar heterogeniteit in het behandelingseffect binnen de ALL-IN studie. In deze aanvullende analyse van de cluster-gerandomiseerde ALL-IN studie wilden we het individuele behandelingsvoordeel van dergelijke integrale AF-zorg voorspellen met als doel om middelen en inspanningen te kunnen prioriteren voor AF-patiënten die er de meeste baat bij zullen hebben. *Cox proportional hazard*-analyse werd gebruikt om de totale sterfte te voorspellen in de ALL-IN studie op basis van de variabelen van de zogenaamde CHA_2DS_2-VASc score. Onder de 1240 AF-patiënten die deelnamen aan het ALL-IN-onderzoek (mediane leeftijd 77 (IQR 11) jaar, 49,4% vrouw) bleek het model redelijk goed in staat de totale sterfte te voorspellen (c-statistiek 0,72 (95% CI 0,66-0,78)). Patiënten die de gebruikelijke zorg kregen, hadden een absoluut risico op totale sterfte van 30,9% in het kwart van de patiënten met het hoogste risico, terwijl dit 4,6% was in het kwart van de patiënten met het laagste risico. Op de relatieve schaal waren er geen aanwijzingen voor heterogeniteit in het behandeleffect. Op de absolute schaal was er echter een aanzienlijke heterogeniteit: integrale zorg verminderde het risico op sterfte met 3,3% (95% CI -0,4% - 7,0%) in het kwart van de patiënten met het laagste risico, terwijl dit 12,0% (95% CI 2,3% - 21,6%) was in het kwart met het hoogste risico. Deze studie toont dus aan dat, terwijl het relatieve voordeel van integrale zorg vergelijkbaar is voor verschillende AF-patiënten, het absolute voordeel verreweg het grootst is bij patiënten met het hoogste voorspelde risico, dat wil zeggen de oudere AF-patiënten met meerdere comorbiditeiten. Dit betekent dat in het bijzonder bij oudere AF-patiënten met multimorbiditeit het aanbieden van integrale AF-zorg met meerdere controlebezoeken per jaar, bestaande uit AF-zorg maar ook met aandacht voor comorbide aandoeningen, zeer gunstig is.

EVALUATIE VAN AF-ZORG IN DE DAGELIJKSE KLINISCHE PRAKTIJK

De toenemende prevalentie van AF in onze vergrijzende samenleving en daarmee gepaard gaande complicaties en toegenomen zorglast vragen om optimalisering en waar

nodig aanpassing van de AF-zorg. Observationele gegevens kunnen worden gebruikt om te evalueren hoe patiënten in de dagelijkse klinische praktijk worden behandeld. De DUTCH-AF registratie beoogt in de eerste plaats het klinische effect te bepalen van de therapie(on)trouw van antistolling en de voorspellers daarvan. Daarnaast is het doel om modellen voor het voorspellen van het bloedingsrisico te valideren en te verfijnen. In de nabije toekomst worden zogenaamde "registry-based trials" gepland, waarbij de registratie als uitgangspunt wordt gebruikt voor de werving en follow-up van patiënten voor nieuwe gerandomiseerde studies. De DUTCH-AF registratie is een uniek landelijk prospectief register van patiënten met recent gediagnosticeerd niet-valvulair AF. Patiënten werden geïncludeerd vanuit Nederlandse huisartsenpraktijken, trombosediensten en ziekenhuizen. Eind 2021 slaagde het consortium van onderzoekers erin de beoogde 6000 patiënten te includeren. Een follow-up van 2 jaar is gepland. De opzet van deze studie wordt beschreven in **hoofdstuk 5**.

SEKSEVERSCHILLEN BIJ PATIËNTEN MET ATRIUMFIBRILLEREN

Er zijn aanwijzingen voor man-vrouwverschillen bij AF, maar er is nog weinig bekend over man-vrouwverschillen bij patiënten met recent gediagnosticeerd AF. Aangezien de meeste complicaties (zoals het optreden van een herseninfarct of bloedingen) zich voordoen in het eerste jaar na de diagnose, is het van groot belang om man-vrouwverschillen direct na de diagnose beter in beeld te brengen. Hiermee kan een weg worden geopend naar zorg-op-maat vanaf de diagnose. Wij hebben gegevens gebruikt van 5469 deelnemers aan het DUTCH-AF register (zie hoofdstuk 5) om man-vrouwverschillen bij diagnose en verschillen in behandeling in het eerste jaar van follow-up te beschrijven. Bij inclusie waren vrouwen ouder dan mannen (mediaan 73 vs. 69 jaar, p<0,001), hadden vaker paroxysmaal AF (66% vs. 55%, p<0,001), en minder vaak persisterend AF (27% vs. 37%, p<0,001). Zij hadden ook vaker hoge bloeddruk (59% vs. 53%, p<0,001), en minder vaak vasculaire aandoeningen (12% vs. 21%), p<0,001, en rapporteerden vaker symptomen zowel in de maand vóór inclusie als in de maand vóór follow-up (56% vs. 46%, p<0,001, respectievelijk 31% vs. 23%, p<0,001). Vrouwen ondergingen minder vaak cardioversie- en ablatieprocedures dan mannen (14% vs. 21% p<0,001 en 3% vs. 5%, p<0,001, respectievelijk). Ook voor de gecombineerde ritmecontrole-interventie cardioversie en ablatie ondergingen vrouwen minder vaak cardioversie of ablatie dan mannen (ongecorrigeerde *odds ratio* was 0,63 (95% CI 0,55-0,73), ongeacht de leeftijd en het type AF (d.w.z. paroxismaal of persisterend AF) bij inclusie (gecorrigeerde *odds ratio* 0,77 (95% CI 0,62-0,92)). Er werden geen verschillen waargenomen voor ischemische complicaties en bloedingen, totale sterfte, en AF progressiepatronen. Deze studie toonde aan dat er man-vrouwverschillen bestaan bij AF in leeftijd, comorbiditeit, AF patroon, symptomen en behandeling in het eerste jaar. Deze bevindingen vormen de bouwstenen voor meer geïndividualiseerde seksespecifieke AF-zorg, maar ook voor verder onderzoek naar man-vrouwverschillen bij AF-patiënten. (**hoofdstuk 6**)

In de Algemene Discussie (**hoofdstuk 7**) worden de belangrijkste bevindingen van dit proefschrift gepresenteerd, wordt het dilemma van het afwegen van risico's bij kwetsbare patiënten met AF verder geïllustreerd, en worden mogelijke oplossingen voor het omgaan met dit dilemma besproken. Bij de meeste AF-patiënten wordt AF permanent, ontstaat er meer comorbiditeit , en samen met het ouder worden en een toename van de kwetsbaarheid neemt de kans op ziekenhuisopnames toe. Bij deze patiënten is het afwegen van het risico op trombo-embolische complicaties en het risico op bloedingen nog moeilijker, omdat beide risico's toenemen met het ouder worden bij patiënten met AF. Desondanks geldt dat, in het algemeen, het trombo-embolische risico hoger blijft dan het risico op ernstige bloedingen.[4,5] Het evenwicht tussen bloedingen en trombo-embolische complicaties is fragiel en dynamisch. Dit vergt voortdurende controle en afweging van risico's. Om deze op elkaar inwerkende problemen adequaat aan te pakken bij kwetsbare patiënten met AF is het belangrijk om zich niet alleen te richten op het AF zelf, maar een holistische benadering toe te passen waarbij ook aandacht wordt besteed aan de medicatie en comorbiditeit. Naast een integrale zorgaanpak voor AF-patiënten, moeten we ook het bloedingsrisico beter leren voorspellen, om het risico van patiënten op bloedingen en trombo-embolie beter te kunnen inschatten. Uiteindelijk willen we het risico op bloedingen verminderen bij patiënten die antistolling gebruiken. Er zijn verschillende manieren om dit te bereiken. Ten eerste door het correct voorschrijven (d.w.z. het voorkomen van overdosering, onderdosering en ongeplande onderbrekingen) van antistolling. Ten tweede door versnippering van de antistollingszorg te voorkomen en door een goede samenwerking tussen zorgverleners die betrokken zijn bij de antistollingszorg. Ten derde zouden we de antistollingsbehandeling kunnen verbeteren om het risico op bloedingen te verminderen zonder het risico op trombo-embolie te verhogen, door het ontwikkelen van nieuwe antistollingsmiddelen met een lager bloedingsrisico. Momenteel lopen er studies naar factor XIa-remmers voor de preventie van trombo-embolische complicaties bij AF. Ten slotte is er zeer weinig bekend over hoe het risico op bloedingen en het risico op trombo-embolieën bij patiënten met kanker in de laatste levensfase kan worden voorspeld en hoe kan worden beslist of en wanneer met antistolling moet worden gestopt. In onze vergrijzende samenleving met een toenemende levensverwachting zullen naar verwachting steeds meer patiënten antistolling gebruiken, en dit vraagt om meer kennis over hoe de besluitvorming over (dis)continuering van antistolling in de laatste levensfase kan worden verbeterd. Dit zal worden onderzocht door het door de EU gesponsorde Serenity-consortium.

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