Stroke risk stratification in atrial fibrillation

The CHA_2DS_2-VASc score and beyond

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PAPERS

The following papers have inspired the topic of this thesis:

Paper 1

Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Lip GY, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. American Journal of Medicine. 2013;126:640.e9-640.e17.

Paper 2

Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen TB. Alcohol intake and prognosis of atrial fibrillation. Heart. 2013;99:1093-1099.

Paper 3

Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen TB. Female sex as a risk factor for thromboembolism and death in patients with incident atrial fibrillation: the prospective Danish Diet, Cancer and Health study. Thrombosis and Haemostasis. 2014;112:789-795.

Paper 4

Overvad TF, Skjøth F, Lip GY, Lane DA, Albertsen IE, Rasmussen LH, Larsen TB. Duration of diabetes mellitus and risk of thromboembolism and bleeding in atrial fibrillation: nationwide cohort study. Stroke. 2015;46:1268-1274.

ENGLISH SUMMARY

Atrial fibrillation is a ubiquitous supraventricular cardiac arrhythmia in clinical practice, affecting millions of individual across the globe. One major concern related to atrial fibrillation is the occurrence of ischaemic stroke or systemic embolism caused by embolising blood clots following blood stasis in the left atrium. Antithrombotic therapy, mainly oral anticoagulants, is highly effective for preventing such embolic events, but it involves a trade-off, since it also may cause severe and life-threatening bleeding. To navigate the clinical conundrum of which patients to offer antithrombotic treatment, stroke risk stratification tools have been developed in order to identify patients at sufficiently high risk for ischaemic events, for which there is an assumed net clinical benefit. The CHA_2DS_2-VASc score is the most widely recommended tool for this purpose. However, various guideline committees disagree on the risk score threshold above which antithrombotic treatment should be offered. More specifically, there is no consensus about if and which antithrombotic agent should be offered to patients with scores of 1 and 2. These discrepancies reflect several unresolved issues regarding stroke risk stratification in atrial fibrillation: 1) Most guidelines recommend antithrombotic treatment also to patients who were largely not included in the randomised trials of stroke prevention in atrial fibrillation, that is, patients with low CHA_2DS_2-VASc scores, 2) recommendations are instead based on observational studies, which provide conflicting evidence as to whether patients with lower CHA_2DS_2-VASc scores stand to gain from such treatment, 3) the CHA_2DS_2-VASc score shows signs of miscalibration: depending on the population studied, the absolute risk among patients with CHA_2DS_2-VASc scores 0-2 is highly variable. Some of these limitations of stroke risk stratification using CHA_2DS_2-VASc may pertain to the dichotomous and simplistic categorisation of the included risk components. In order to meet these limitations, several investigations into novel prognostic markers beyond the CHA_2DS_2-VASc score have been made. These include attempts to identify novel risk markers, including various electro- and echocardiographic features, additional comorbidities, lifestyle-related factors, and biomarkers. Also, investigations into refinement of stroke risk stratification by breaking down existing CHA_2DS_2-VASc components, including heart failure, age, diabetes mellitus, and previous stroke, have also yielded promising results for some components. Refined stroke risk stratification models may form the basis for more consistent risk calculations that allow for deriving more precise risk estimates for the individual patient with atrial fibrillation, and hereby optimise the widespread use of these potentially harmful antithrombotic drugs.

DANSK RESUMÉ

Atrieflimren er en hyppigt forekommende supraventrikulær hjertearytmi, der påvirker millioner af mennesker verden over. En af hovedbekymringerne relateret til atrieflimren er risikoen for iskæmisk apopleksi, som skyldes dannelsen af blodkoagler grundet stase af blodet i venstre atrium, med efterfølgende embolisering til hjernens karsystem. Antitrombotisk behandling, overvejende i form af antikoagulationsbehandling, er særdeles effektiv til forebyggelse af sådanne embolier, men kan forårsage alvorlig og livstruende blødning. Dette gør beslutningen om hvilke patienter, der bør tilbydes antitrombotisk behandling, til et klinisk dilemma. Som hjælp til denne beslutning er der udviklet risikoscoresystemer for iskæmisk apopleksi, som forventes at kunne identificere patientgrupper, som har en forventet fordel af antitrombotisk behandling. CHA_2DS_2-VASc scoren er det hyppigst anbefalede værktøj til dette formål. Blandt forskellige atrieflimren-guidelines er der dog uenighed om hvilken tærskelværdi, der bør udløse en indikation for antitrombotisk behandling. Mere specifikt er der uenighed om hvilket antitrombotisk behandling, hvis nogen overhovedet, skal tilbydes patienter med CHA_2DS_2-VASc scorer på 1 og 2. Disse uenigheder afspejler nogle uafklarede aspekter vedrørende brug af risikostratifikation blandt patienter med atrieflimren: 1) De fleste guidelines anbefaler antitrombotisk behandling til patienter med lave CHA_2DS_2-VASc scorer, patienter der ikke var inkluderet i de randomiserede forsøg, der testede antitrombotisk behandling til forebyggelse af iskæmisk apopleksi, 2) anbefalingerne bygger i stedet på observationelle studier, som indtil nu har vist modstridende resultater for hvorvidt sådanne patienter har gavn af antitrombotisk behandling, 3) CHA_2DS_2-VASc viser tegn på miskalibrering, da den observerede absolutte risiko for iskæmisk apopleksi blandt patienter med CHA_2DS_2-VASc scorer på 0-2 varierer meget på tværs af studiepopulationer. Nogle af disse svagheder ved risikostratifikation ved brug af CHA_2DS_2-VASc kan muligvis tilskrives dens for-simplede design, hvor de fleste score-komponenter er dikotomiserede. I forsøget på at imødekomme nogle af disse svagheder, har adskillige studier undersøgt mulighederne for at forbedre scoren. Det har været forsøgt at identificere nye risikofaktorer, som kan bidrage med yderligere prognostisk information ud over de eksisterende CHA_2DS_2-VASc faktorer. Undersøgte faktorer inkluderer elektro- og ekkokardiografiske parametre, yderligere komorbiditet, livsstilsfaktorer og biomarkører. Det er desuden undersøgt, om de eksisterende CHA_2DS_2-VASc faktorer kunne underopdeles, herunder hjertesvigt, alder, diabetes mellitus, og tidligere apopleksi/emboli, hvoraf nogle har vist lovende resultater. Raffinerede risikostratifikationsmodeller kan muligvis bidrage til mere konsistente risiko-beregninger, der kan forudsige risikoniveauet mere præcist for den enkelte patient med atrieflimren, og herved optimere den udbredte brug af potentielt skadelige antitrombotiske lægemidler.

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A number of people have contributed in one way or another to the formation of this thesis. First of all, thank you to my supervisors, Torben Bjerregaard Larsen, Flemming Skjøth and Lars Hvilsted Rasmussen, for making this project possible, for believing in me, for stimulating research and non-research conversations, and also for letting me pursue my own ideas along the way.

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Thure Filskov Overvad

April 2016

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

Atrial fibrillation is a supraventricular arrhythmia characterised by disorganised atrial depolarisations that limit effective atrial contraction and cause irregular and often rapid beating of the heart.[1] Both structural and electrophysiological changes contribute to the promotion of such abnormal impulses.

The pathogenesis behind atrial fibrillation is complex and only partially understood.[2] Atrial fibrillation aetiology involves environmental factors, genetic traits, and their epigenetic interactions.[3,4] Identified predisposing factors range from age, cardiovascular diseases, thyroid disorders, obesity, lifestyle, inflammation, and drugs, to more exotic factors such as scorpion venom.[5–15] Potential iatrogenic causes due to medical treatment have likewise been identified.[16,17] Hence, atrial fibrillation is a common manifestation in a phenotypically diverse group of patients with varying underlying genetic, lifestyle-related, and comorbid characteristics.

The prevalence of atrial fibrillation increases steeply with age, from 1/1000 in those aged <35 years to 1/10 in those aged 85 years or older.[18] In 2012, more than 100.000 people were affected by atrial fibrillation in Denmark.[19] Since the average life expectancy is increasing, the overall prevalence of atrial fibrillation is expected to rise accordingly. The prevalence of several factors predisposing to atrial fibrillation such as obesity, diabetes mellitus and improved survival after myocardial infarction is also increasing, altogether making atrial fibrillation resemble a pandemic.[20] The future perspectives of the epidemiology of atrial fibrillation are not less daunting: It has been predicted that the overall prevalence of atrial fibrillation in USA and Europe will triple within 2050.[21,22] Accordingly, atrial fibrillation is subject to substantial academic attention. A PubMed search for 'atrial fibrillation' limited to studies published within the last five years yielded >20,000 records.[23]

Atrial fibrillation causes a variety of symptoms, including palpitations, chest pain, dyspnoea, and dizziness or faintness, which also impair quality of life.[24,25] However, much of the academic interest in atrial fibrillation revolves around another common and feared complication, which is cardioembolic stroke or systemic embolism arising from blood stasis in the left atrium due to inefficient atrial contractions.[26–29]

1.1. ATRIAL FIBRILLATION AND STROKE

The relationship between atrial fibrillation and ischaemic stroke is long-established,[30] and although stroke rates related to atrial fibrillation have declined

over the last 50 years, stroke remains a trademark complication of atrial fibrillation.[31] Compared with strokes unrelated to atrial fibrillation, the case-fatality rate is higher in patients with atrial fibrillation, which reflects more severe strokes also with a higher recurrence rate.[27,32]

Just as the aetiology of atrial fibrillation is complex and diverse, so is the associated stroke risk following onset of the rhythm disorder. While cardioembolic stroke is the predominant subtype observed in such patients, other subtypes occur as well.[33] This reflects the fact that many predisposing factors for atrial fibrillation are also known causes of ischaemic stroke on a general population level.[34]

1.2. ATRIAL FIBRILLATION AND ANTITHROMBOTIC TREATMENT

The present thesis concerns stroke risk stratification in patients with non-valvular atrial fibrillation and the appertaining decision about whether or not to initiate antithrombotic treatment. Notwithstanding an on-going discussion on how to define valvular atrial fibrillation, it is often referred to as patients with atrial fibrillation and mechanical prosthetic heart valves or significant rheumatic mitral valve disease.[35] At present, such patients with valvular atrial fibrillation have an indisputable indication for thromboprophylaxis with warfarin due to a high risk of thromboembolism involving a mechanism of thrombosis that is often qualitatively different from that in non-valvular atrial fibrillation.[36] Therefore, all mentions of atrial fibrillation in this thesis refer to patients with non-valvular atrial fibrillation as per the definition above, unless specifically noted.

Antithrombotic treatment is a cornerstone in the prevention of stroke and systemic embolism in patients with atrial fibrillation. For decades, the only available class of drugs for oral anticoagulation in patients with atrial fibrillation was the vitamin K antagonists (VKAs).[37,38] Treatment with a VKA, more specifically warfarin, has proven highly effective for the prevention of stroke in patients with atrial fibrillation, preventing approximately 2/3 of all strokes compared with placebo.[39] In comparison, antiplatelet therapy with aspirin prevents approximately 1/5 strokes.[39] However, frequent monitoring and dose adjustment of warfarin treatment is necessary to maximise the time in therapeutic range (TTR), which is defined as an International Normalised Ratio (INR) level within a narrow target range of 2 to 3. Figure 1 illustrates the importance of tight control; when the INR falls below the desired target range, the risk of thromboembolic events is high, and when INR rises above the target range, bleeding events become more and more frequent.[40] However, achieving tight control is difficult, as indicated in a recent report from the United States, which demonstrated a mean TTR around 50% among 138,319 patients with atrial fibrillation treated in physician practices, reflecting an overall poor degree of anticoagulant control.[41] This is partly due to warfarin being an inconvenient drug with multiple food and drug interactions that make the quality

and effectiveness of the treatment highly variable.[37,42] The inconveniences associated with warfarin and the difficulties obtaining a reasonable TTR have initiated a search for alternative oral anticoagulant agents with capacities that overcome some of these issues.

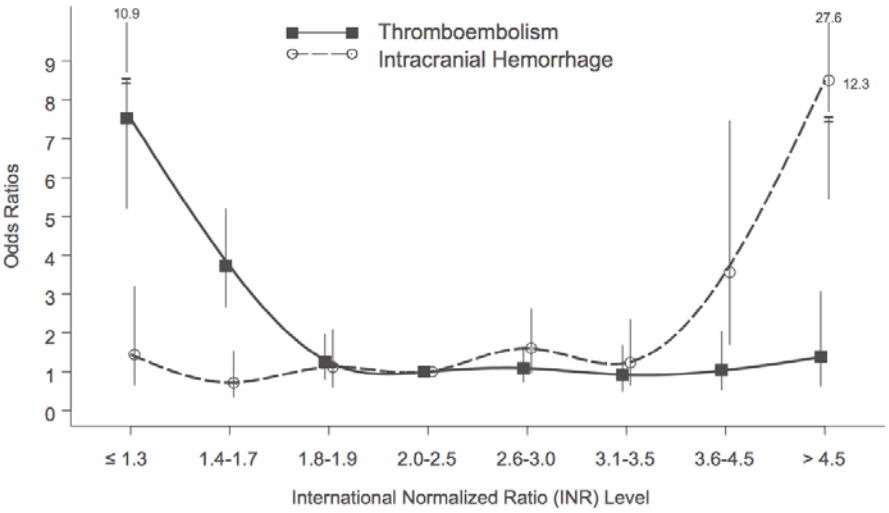

Figure 1 *Odds ratios for thromboembolism and intracranial haemorrhage during treatment with warfarin according to International Normalised Ratio (INR) level in patients with non-valvular atrial fibrillation. INR-level 2.0-2.5 is reference. Vertical lines are 95% confidence intervals. Reproduced with permission from Singer et al.*[40]

In recent years, four such alternatives, the non-vitamin K antagonist oral anticoagulants (NOACs), have gained approval for stroke prevention in atrial fibrillation, all directly targeting specific components in the coagulation cascade.[43] These include a direct thrombin inhibitor, dabigatran etexilate, and three factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban.[44–47] Neither require regular monitoring or dose adjustments and they all have substantially fewer food and drug interactions compared with warfarin.[48] In the randomised trials testing these NOACs against warfarin, the NOACs were found as least as effective and in some instances superior to warfarin for stroke prevention in atrial fibrillation, with similar or better safety profiles in terms of bleeding risk.[49] They are also estimated to be cost-effective alternatives to warfarin, although with varying cost-effectiveness according to the compared mean TTR.[50] Altogether, the NOACs have proven attractive alternatives to warfarin for stroke prevention, but despite the potential gain in net clinical benefit using these drugs, the trade-off between preventing ischemic events at the cost of bleeding risk remains an issue, and they are therefore still insufficiently safe to be administered to all patients with atrial fibrillation. To aid in the decision of which patients should be offered

anticoagulation, stroke risk scores have been developed aiming to identify patients at sufficiently high risk of a thromboembolic event, among which the balance between prevention of thrombosis and induction of bleeding is in favour of the former.

1.3. STROKE RISK SCORES

For many years, guidelines have recommended the $CHADS_2$ score as the primary tool for stroke risk stratification in patients with atrial fibrillation (Table 1). The $CHADS_2$ score was introduced in 2001 and was derived from factors associated with stroke risk in the control arms of the early atrial fibrillation trials testing dose-adjusted warfarin against aspirin or placebo.[51] In 2010, a refined version of the $CHADS_2$ score was proposed, the CHA_2DS_2-VASc score, which added some additional risk factors and included age in three categories (Table 1).[52] The CHA_2DS_2-VASc score has since dethroned the $CHADS_2$ score as the preferred tool for stroke risk stratification in patients with atrial fibrillation.[52] This shift in strategy was partly due to several reports on stroke risk in patients with a $CHADS_2$ score 0, who were previously considered low-risk patients without a clear indication for anticoagulant treatment. When such patients were further stratified by CHA_2DS_2-VASc score, stroke rates per 100 person-years ranged from 0.8 (CHA_2DS_2-VASc=0) to 3.2 (CHA_2DS_2-VASc=3), indicating that $CHADS_2$=0 cannot nessecarily be considered 'low-risk'.[53–55] Moreover, these figures also illustrate the key competency of the CHA_2DS_2-VASc score, namely the identification of 'truly low-risk' patients with no need for thromboprophylaxis.

Table 1. The $CHADS_2$ and CHA_2DS_2-VASc stroke risk scores.

$CHADS_2$	Score	**CHA_2DS_2-VASc**	Score
Congestive heart failure	1	Congestive heart failure or left ventricular dysfunction	1
Hypertension	1	Hypertension	1
Age ≥75 years	1	Age ≥75 years	2
Diabetes mellitus	1	Diabetes mellitus	1
Prior Stroke or transient ischaemic attack	2	Prior Stroke, transient ischaemic attack, or systemic embolism	2
		Vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque)	1
		Age 65-74 years	1
		Sex category [female]	1
Maximum score	**6**	**Maximum score**	**9**

The $CHADS_2$ score was the primary tool for stroke risk stratification in European Guidelines until 2010 and in American guidelines until 2014.[56–58] Hereafter, the CHA_2DS_2-VASc score has been the preferred tool. The CHA_2DS_2-VASc score is currently endorsed by various national and international scientific committees, including, but not limited to, the American Heart Association/American College of Cardiology/Heart Rhythm Society,[58] the American College of Chest Physicians,[59] the Canadian Cardiovascular Society,[60] the European Society of Cardiology,[61] the National Institute for Health and Care Excellence,[62] and the Asia Pacific Heart Rhythm Society.[63] Despite this near global endorsement of the CHA_2DS_2-VASc score, there is no consensus on how to actually use the score. For example, European, American and Canadian guidelines differ in their recommendations for patients with CHA_2DS_2-VASc scores of 1 and 2. Treatment options for patients with similar score levels range from no antithrombotic therapy to aspirin to oral anticoagulation (Table 2). Why these discrepancies?

Table 2. Conflicting guideline recommendations for antithrombotic management of women and men with atrial fibrillation anno 2016

<table>
<tr><th></th><th colspan="3">Women</th><th colspan="3">Men</th></tr>
<tr><th>CHA_2DS_2-VASc risk score level</th><th>AHA</th><th>ESC</th><th>CCS</th><th>AHA</th><th>ESC</th><th>CCS</th></tr>
<tr><td>0</td><td colspan="3">N/A*</td><td colspan="3">No therapy</td></tr>
<tr><td>1</td><td>OAC, aspirin, or no therapy</td><td colspan="2">No therapy</td><td>OAC, aspirin, or no therapy</td><td>OAC</td><td>If vascular disease: aspirin, otherwise OAC</td></tr>
<tr><td>2</td><td colspan="2">OAC</td><td>If vascular disease: aspirin, otherwise OAC</td><td colspan="3">OAC</td></tr>
<tr><td>>2</td><td colspan="6">OAC</td></tr>
</table>

OAC oral anticoagulation; **AHA** American Heart Association; **ESC** European Society of Cardiology; **CCS** Canadian Cardiovascular Society.
*All women are attributed 1 point due to female sex in the CHA_2DS_2-VASc score.

A historical look at the evolvement of antithrombotic agents for prevention of stroke and systemic embolism in patients with atrial fibrillation provides an explanation for these inconsistencies. The earliest trials testing dose-adjusted warfarin against aspirin or placebo in patients with non-valvular atrial fibrillation included mainly older patients with established comorbidities.[64,65] Thus, patients

who at the time would have been categorised into lower CHA_2DS_2-VASc score groups of 0, 1 or 2 were largely not included. Observations from the control arms of the early trials found that stroke risk in atrial fibrillation was not uniform, but varied according to certain patient characteristics, including age, previous stroke, hypertension, and diabetes mellitus.[66] Another important observation, however, was that patients aged <65 years without any of these comorbidities had low absolute stroke rates of ≈1 per 100 person-years, even when left untreated, suggesting that oral anticoagulation may be without benefit in these patients. These observations essentially gave rise to the 2006 joint American/European guideline advocacy for anticoagulation to patients with atrial fibrillation and a $CHADS_2$ score ≥ 1.[56]

The later trials testing the NOACs against warfarin did inevitably also only include patients with an existing indication for warfarin as defined by guidelines at the time.[56] When the NOAC trials had finalised, the sum of evidence suggested that the NOACs had an overall favourable risk-benefit profile compared with warfarin, with lower risk of stroke, intracranial haemorrhage, and mortality, and with similar risk of major bleeding, albeit a higher risk of gastrointestinal bleeding.[67] The NOACs hereby met the expectations with respect to hard endpoints, but also with intriguing hints of superiority. Would these findings justify escalating the number of atrial fibrillation patients eligible for oral anticoagulation? Indeed, the safety profile of the NOACs have essentially led to the more inclusive guideline recommendations presented in Table 2 compared with those of the $CHADS_2$ era. The absolute number of patients affected by this shift in guideline recommendations illustrates the impact of these changes. When the American guidelines introduced the threshold for oral anticoagulation as a CHA_2DS_2-VASc score of ≥1 in 2014,[58] to replace the 2006 recommendation of a $CHADS_2$ score of ≥1,[56] the number of patients eligible for anticoagulation in the United States alone rose by approximately one million overnight.[68]

In summary, the lack of a universal consensus on treatment thresholds is due to the fact that current American and European guideline recommendations both extend beyond what has been specifically tested in randomised trials, as such trials included only few patients with lower CHA_2DS_2-VASc scores, and were only designed to demonstrate the overall effectiveness of anticoagulation, and not the effect across specific subgroups based on the CHA_2DS_2-VASc score. This means that the recommendations for patients with lower CHA_2DS_2-VASc scores are currently based on data from non-randomised cohort studies, and there is at present no universal agreement on the extent to which such studies justify anticoagulating such patients.[69] Nonetheless, recent register-based real-world data have indicated an overall positive net clinical benefit for anticoagulants also in patients with a CHA_2DS_2-VASc score of 1,[70–72] but such observational studies of drug effects are inherently prone to confounding by indication, and may underestimate patients' risk score levels by relying on information from administrative registries to

calculate the score level, information which for some score components may be incomplete.

The 'tipping' point

For which patient groups do the benefits outweigh the risks when on anticoagulant treatment? A modelling analysis based on data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial testing dabigatran against warfarin suggested that the estimated ischaemic stroke rate threshold per 100 person-years above which there is a benefit from anticoagulation, the so-called 'tipping point', was 0.9 for dabigatran and 1.7 for warfarin.[73] Assuming these 'tipping points' are trustworthy, the question is if the CHA_2DS_2-VASc score reliably and consistently identifies patients with risks below and above these thresholds. Evidence suggests that it does not. In patients with CHA_2DS_2-VASc=0, rates of a thromboembolic event per 100 person-years from various non-anticoagulated populations range from 0.04 to 2.4, while in patients with CHA_2DS_2-VASc=1 the reported rates range from 0.10 to 6.6,[74,75] rates that also depend on which factor contributes to the score of 1.[69] In other words, depending on the populations studied, the risk in patients with both CHA_2DS_2-VASc scores of 0 and 1 may lie either below or above the suggested 'tipping point'. By use of a more technical term, this inconsistency in observed risk is referred to as miscalibration.[76]

'Shared' risk factors

Many risk factors for ischaemic stroke in patients with atrial fibrillation are also risk factors for bleeding once anticoagulant treatment is initiated, so called 'shared' risk factors.[77] Obviously, this is a clinical dilemma, and most guidelines recommend formal bleeding risk assessment using the HAS-BLED (uncontrolled hypertension, abnormal renal/liver function, previous stroke, bleeding history/predisposition, labile INR, age >65 years, and drugs/alcohol concomitantly) score.[58,61,78] However, bleeding risk is generally not considered a contraindication to anticoagulant treatment, and, therefore, the issue of 'shared' risk factors and bleeding risk prediction in general is not discussed in the present review.[49,79,80]

1.4. ROOM FOR IMPROVEMENT

The lack of a universal consensus for use of antithrombotic agents in atrial fibrillation emphasises the need for additional studies aiming to improve stroke risk stratification. Notwithstanding these guideline differences, they do have something in common: guideline recommendations are not followed in clinical practice, reflected by numerous reports on a gap between guideline recommendations and real-world actual usage.[81] Adding to this, the widely adopted CHA_2DS_2-VASc score used for stroke risk stratification performs very differently depending on the population studied.[69,74,82] There is room for improvement.

CHAPTER 2. AIMS AND SCOPE

This thesis concerns stroke risk stratification and the appertaining decision on whether or not to initiate antithrombotic treatment in patients presenting with atrial fibrillation. The vantage point for discussing this matter will be the CHA_2DS_2-VASc score, which is the most widely recommended decision tool for this particular purpose. The current thesis has been structured as a review article that aim to discuss the following:

i) The CHA_2DS_2-VASc score, hereunder presentation of the individual components and recommendations for its use, including some potential drawbacks of using CHA_2DS_2-VASc for stroke risk stratification purposes.

ii) A review of studies aiming to refine stroke risk stratification by adding novel risk markers to or refining the existing components of the CHA_2DS_2-VASc score.

iii) Methodological considerations related to stroke risk prediction research using the papers forming the basis for this thesis for illustrative purposes.

iv) A summarising discussion on the current approach to stroke risk stratification and potential suggestions on how to move forward.

The reader will soon learn that the structure of this thesis deviates somewhat from a traditionally structured thesis. The aim has been to tell the story about the overall topic that my own papers revolve around, that is, stroke risk stratification in atrial fibrillation. Consequently, the structure of this thesis is not dictated by the content of my own papers, and my own studies will not be presented chronologically, but in the order in which they are relevant to the content of the present review. Therefore, the initial description of my individual studies is also somewhat shorter than how studies are traditionally presented in a thesis, but full text versions are available in the Appendix. When described, my own studies will be highlighted by *** PAPER X ***, so that there should remain no confusion about when I refer to my own studies.

CHAPTER 3. STROKE RISK STRATIFICATION USING THE CHA_2DS_2-VASc SCORE

The CHA_2DS_2-VASc score was introduced in 2010,[52] and considering its relatively short lifespan, it has been very extensively validated for the prediction of ischaemic stroke or systemic embolism in patients with atrial fibrillation,[55,72,83–105] as well as a variety of other adverse cardiovascular outcomes both in patients with and without atrial fibrillation.[106–116] However, for the specific purpose of using CHA_2DS_2-VASc to guide antithrombotic therapy in patients with atrial fibrillation, studies investigating the outcome of ischaemic stroke or systemic embolism in non-anticoagulated populations are of primary interest. For this particular purpose, a meta-analysis investigating the predictive ability of the CHA_2DS_2-VASc score reported a pooled C statistic of 0.68,[117] a level of discrimination that is generally considered modest or even inadequate.[118]

3.1. FROM PREDICTION MODEL TO DECISION RULE

Prediction of ischaemic stroke and systemic embolism among patients with atrial fibrillation has proven difficult.[119] Multiple risk scores for use in patients with atrial fibrillation exist, but their discriminative abilities, as measured by the C statistic, are often mediocre and largely similar among the wide array of available scores.[51,85,87,104,120–122] So how did the CHA_2DS_2-VASc score, a prediction model with inadequate discriminative power, evolve into a globally endorsed clinical decision rule? The answer to this question concerns another important capacity of a prediction model: calibration.[123] Text Box 1 provides brief definitions of terms often used to describe the performance of a risk prediction model.

In acknowledgement of the lack of a risk score with convincing discriminative abilities, focus has shifted from discriminative ability to calibration and negative predictive values. Whether the CHA_2DS_2-VASc score possesses such calibration capacities will be discussed later on, but there is a general agreement that the risk among patients with CHA_2DS_2-VASc=0 does not justify any preventive antithrombotic treatment and that patients with CHA_2DS_2-VASc>2 should be offered anticoagulation, see Table 2.[58,60,61] This risk factor-based approach based on the CHA_2DS_2-VASc score entails that, depending on which guideline you adhere to, each individual component may trigger an indication for anticoagulant treatment.

Text box 1. Definitions of terms related to the performance of a prediction model

Discrimination Expresses the ability of a model to discriminate between future cases and non-cases. Often measured using the C statistic, which for dichotomous outcome can be interpreted as the probability that a future case will obtain a higher score than a future non-case. The C statistic ranges from 0 to 1. A value below 0.5 indicates negative discriminative ability, a value of 0.5 indicates no discriminative ability (like tossing a coin), and values above 0.5 indicate positive discriminative ability, with a value of 1 reflecting perfect discrimination. It is calculated as the area under the receiver-operating curve, reflecting a summary of the sensitivity and specificity across all possible scores of a risk model.

Sensitivity The proportion of future cases scoring above a given threshold in a prediction model.

Specificity The proportion of future non-cases scoring below a given threshold in a prediction model.

Positive predictive value The probability that a subject scoring above a given threshold will eventually become a case.

Negative predictive value The probability that a subject scoring below a given threshold will not become a case.

Calibration How well the predicted absolute risks across risk score levels derived from the source population that gave rise to the model compare to the observed absolute risks in a different population.

Since the presence of even a single component from CHA_2DS_2-VASc can be considered an indication for lifelong oral anticoagulant treatment, an overall evaluation of the predictive abiliy of the score is insufficent. In depth review of the validity of the individual components is paramount, as the risk associated with the presence of the individual component is likely to vary substantially.[69] Below follows a brief presentation of the CHA_2DS_2-VASc components discussed in light of the original CHA_2DS_2-VASc study.[52] External validation of a prediction model is important, especially since the CHA_2DS_2-VASc derivation study was based on only 25 thromboembolic events.[124,125] Therefore, data from selected external validation studies will be presented when discussing the individual components.

Congestive heart failure

The 'C' component in the CHA_2DS_2-VASc score covers heart failure or left ventricular ejection fraction ≤40%, and one point is given when either is present.[52,126] Interestingly, the 'C' component was not positively associated with thromboembolism in the original CHA_2DS_2-VASc study.[52] In a Danish validation study based on hospitalised patients, the risk of thromboembolism was higher for patients with CHA_2DS_2-VASc=1 due to heart failure compared with CHA_2DS_2-VASc=0 both after 1, 5, and 10 years of follow-up.[85] Reported event rates per 100 person-

years was below the 1.7 'tipping point' for VKA but above the 0.9 threshold for NOACs (see Table 3).[73] Other reports have questioned whether heart failure is useful as a predictor of ischemic stroke in patients with atrial fibrillation.[86,104]

Table 3. Thromboembolic event rates per 100 person-years after 1-year follow-up in patients with no or only one CHA_2DS_2-VASc component*

	Event rate (95% confidence interval)
CHA_2DS_2-VASc=0	0.78 (0.58-1.04)
Heart failure	1.50 (0.37-5.98)
Hypertension	2.14 (1.46-3.15)
Age ≥75 years	4.75 (4.14-5.44)
Diabetes mellitus	3.47 (1.65-7.27)
Previous thromboembolism	16.07 (11.64-22.18)
Vascular disease	0.75 (0.24-2.33)
Age 65-74 years	2.88 (2.29-3.62)
Female sex	1.24 (0.89-1.73)

* Event rates are from patients with CHA_2DS_2-VASc=1 (due to either heart failure, hypertension, diabetes mellitus, vascular disease, age 65-74, or female sex) or CHA_2DS_2-VASc=2 (due to age ≥75 or previous thromboembolism). Data from Olesen *et al.*[85]

Hypertension

In the CHA_2DS_2-VASc score, hypertension is defined as a resting blood pressure >140 mm Hg systolic and/or >90 mm Hg diastolic on at least 2 occasions or current use of antihypertensive pharmacologic treatment.[52] Hypertension triggers one point in the CHA_2DS_2-VASc score. This definition of hypertension was not associated with thromboembolic events in the original CHA_2DS_2-VASc study [odds ratio 1.01 (95% CI 0.38-2.66)].[52] In the Danish validation study, patients with CHA_2DS_2-VASc=1 due to hypertension, defined as users of at least two different antihypertensive drugs, were at higher risk of thromboembolism compared with the absence of hypertension.[85] The 1-year event rate per 100 person-years was 2.14 and thus above the recommended threshold for initiation of anticoagulant treatment whether with VKA of NOAC (see Table 3).[73] Nonetheless, using hypertension as a stand-alone criterion for initiating anticoagulant treatment has been questioned.[127]

Age

Age is the only factor that is included in three categories in the CHA_2DS_2-VASc score, with 0 points attributed to age <65, one point for age 65-74, and two points for age ≥75.[52] Event rates per 100 person-years were well above the threshold for initiating anticoagulation for both age 65-74 years and age ≥75 years, see Table 3.[85] It has been shown also in a randomised trial that patients aged ≥75 years on a group level benefit substantially from oral anticoagulant treatment.[128] Accordingly, various guidelines recommend unequivocally that such elderly patients are offered anticoagulant treatment.[58,60,61]

Diabetes mellitus

In the CHA_2DS_2-VASc score, diabetes mellitus is attributed one point and is defined as having a fasting glucose ≥7.0 mmol/L or treatment with an oral hypoglycaemic agent and/or insulin.[52] Diabetes was positively associated with thromboembolic risk in the original study, which has been confirmed in external validation studies.[52,85,104,129] Event rates among patients with CHA_2DS_2-VASc=1 due to diabetes have been reported to lie well above the threshold for assumed benefit from anticoagulant treatment.[73,85,130]

Previous stroke, systemic embolism, or transient ischaemic attack

Patients with a previous ischaemic event are generally considered high-risk patients, and such patients score a minimum of two points on the CHA_2DS_2-VASc score.[52] The high-risk nature of this subgroup of patients has been consistently confirmed, and patients with CHA_2DS_2-VASc=2 due to a previous ischaemic event exhibit by far the highest subsequent event rate of an additional thromboembolic event (see Table 3).[85] Consequently, major guideline committees agree that such patients should be offered anticoagulant treatment,[58,61] although it has been suggested that the preferred choice of antithrombotic agent perhaps should depend on the aetiological nature of the previous ischaemic event (e.g., cardioembolic or lacunar).[131–133]

Vascular disease

In the CHA_2DS_2-VASc score, a history of vascular disease is given one point and is defined as a history of myocardial infarction, peripheral artery disease, or aortic plaque.[52] The vascular disease component is one of three additional components included in the CHA_2DS_2-VASc score that were not encompassed by the $CHADS_2$ score.[134] Several studies have confirmed that vascular disease adds predictive value beyond the $CHADS_2$ score.[135,136] Nonetheless, patients with CHA_2DS_2-VASc=1 due to vascular disease had the lowest event rates in the large Danish validation study, a rate below the recommended threshold for anticoagulation, whether with NOACs or VKAs (Table 3) and similar to the rate observed in patients with CHA_2DS_2-VASc=0.[73,85] Nonetheless, both American and European guidelines provide the possibility of anticoagulating based on vascular disease alone, while Canadian guidelines recommend aspirin to men with CHA_2DS_2-VASc=1 and women with CHA_2DS_2-VASc=2 due to vascular disease (Table 2).[58,60,61]

Female sex

The first observations indicating that females have a higher risk of stroke than males when diagnosed with atrial fibrillation was from the early randomised trials testing warfarin against aspirin/placebo.[66] Accordingly, several pre-CHA_2DS_2-VASc guidelines recommended that female sex could be considered as a factor favouring initiation of antithrombotic treatment.[56,137] Female sex is also included in a Framingham atrial fibrillation stroke risk score from 2003.[138] In the CHA_2DS_2-VASc score, female sex is yet another component not originally included in the $CHADS_2$

score, and women are attributed one point due to female sex.[52] Given the rather inclusive nature of recommending oral anticoagulation based on female sex alone, the association between female sex and stroke risk in the context of atrial fibrillation has been extensively investigated.[139] Supporting the inclusion of female sex as a risk component, three large, register-based studies found an overall higher risk of stroke among women compared with men after taking into account components of the CHA_2DS_2-VASc score.[140–142] However, a Danish study indicated that this relationship was age-dependant, reporting a lower risk among women versus men in those aged <65 years, thus questioning whether female sex alone should trigger an indication for anticoagulant treatment.[142] Based on these observations, the European guidelines raised their threshold for oral anticoagulant treatment for women from CHA_2DS_2-VASc ≥1 in 2010 to CHA_2DS_2-VASc ≥2 in the 2012 edition.[57,61] Essentially ignoring these observations, current American guidelines still provide the possibility of anticoagulating based on female sex alone.[58]

*** PAPER 3 ***

It has been speculated whether the higher risk of stroke observed among females was due to an intrinsic risk of stroke in women, i.e., whether the physiological female sex was the underlying cause of this observed higher risk.[143] However, only few studies had actually adressed this issue with focus on causality. This is important, since what is observed within a framework of a risk prediction model must be interpreted seperately from causation. For example, confounding lifestyle factors such as smoking, alcohol, and anthropometric measures – factors which are not included in the CHA_2DS_2-VASc score – would need consideration when attempting causal inference. A few studies had previously aimed to elucidate whether female sex could be causally related to stroke risk in atrial fibrillation, but all such studies were register-based studies with lack of potentially confounding lifestyle information.[140–142] Using data from the Danish Diet, Cancer and Health cohort (see Text box 2 on page 35 for brief description of this cohort), we investigated this matter prospectively with concomitant control for important lifestyle stroke risk factors that may have confounded previous observations, including smoking, alcohol, and anthropometric measures.[144] Hence, this study focussed not on risk stratification but causation, although the idea sprung from observations from stroke risk stratification in atrial fibrillation. Using a Cox proportional hazards model, we observed a lower risk of stroke in women compared with men both before (HR 0.82, 95% CI 0.61–1.11) and after control for confounding (HR 0.77, 95% CI 0.55–1.13). The observations of a lower risk among females is not in concordance with most previous reports,[139] but this is likely explained by the relatively low mean age in the Diet, Cancer and Health cohort, and therefore in line with previous Danish observations.[142] Importantly, we found no profound confounding from lifestyle between sexes, adding further support to the

theory that there may exist an intrinsic sex-related difference in stroke risk in patients with atrial fibrillation that is modified by age.[143]

In summary, most of the components in the CHA_2DS_2-VASc score are positively associated with risk of thromboembolism in atrial fibrillation, although there are inconsistent reports about heart failure.[145] Based on data from the Danish validation study, which has been cited in most major guidelines, the event rate per 100 person-years in patients with CHA_2DS_2-VASc=1 varies markedly depending on which component contributes to the score, from 0.75 in vascular disease to 3.47 in diabetes mellitus.[85]

3.2. THE POTENTIAL IMPORTANCE OF ISCHAEMIC STROKE AETIOLOGY

Risk stratification using the CHA_2DS_2-VASc score is used for identifying patients who, on a group level, stand to gain from thromboprophylaxis, mainly with oral anticoagulants. Risk stratification is performed disregarding the fact that ischaemic stroke is an umbrella term encompassing several distinct pathophysiological processes with common clinical manifestations.[146] Oral anticoagulants primarily prevent ischaemic strokes of cardioembolic origin.[39,147–149] Although the majority of ischaemic strokes in patients with atrial fibrillation are of presumed cardioembolic origin (up to 80%), some strokes also occur due to non-embolic causes.[33,150] Current guideline recommendations for patients with lower CHA_2DS_2-VASc are based mainly on non-randomized studies that have ignored the distribution of ischemic stroke subtype associated with the individual CHA_2DS_2-VASc components.[53,85] This may prove to be an often-neglected crux of the matter, as the events of interest with respect to benefit of anticoagulation are strokes of cardioembolic origin.[149]

The fact that oral anticoagulants mainly target cardioembolic stroke raises the question whether CHA_2DS_2-VASc actually risk stratifies patients according to such events. In fact, the CHA_2DS_2-VASc score has not been prospectively investigated for its ability to predict and risk stratify patients specifically according to cardioembolic stroke. For example, that a 70-year-old patient with a CHA_2DS_2-VASc score of 4 due to vascular disease, diabetes mellitus, and hypertension has a higher risk of ischaemic stroke than a 70 year old patients with a CHA_2DS_2-VASc score of 1 (and therefore per definition without such comorbidities) is unsurprising, as the first patient presents with a cluster of known risk factors for ischaemic stroke also in the absence of atrial fibrillation. An intriguing question remains: does this first patient also have a higher risk of cardioembolic stroke? Although likely, another scenario is also likely, namely that the two patients have a similar risk of cardioembolic stroke due to their atrial fibrillation and that the first patient has an excess risk of atherosclerotic stroke due to his cluster of cardiovascular comorbidities.

The individual treatment-deciding components of the CHA_2DS_2-VASc score do not carry equal overall ischemic stroke risk,[69] but similarly do they in all probability not reflect similar ischaemic stroke subtype distributions.[151–154] Ischaemic stroke subtype distributions are largely unexplored across the individual CHA_2DS_2-VASc components, as the majority of CHA_2DS_2-VASc validation studies have obtained outcome information using administrative registries with an inevitable lack of such subtype information.[53,85,155,156] Such empirical data would provide more exhaustive stroke risk stratification in patients with atrial fibrillation, and may allow for further individualized antithrombotic strategies, especially among patients where there is no guideline consensus on if and which antithrombotic therapy should be offered. Depending on the proportion of non-cardioembolic ischemic stroke associated with each CHA_2DS_2-VASc component, such data may demonstrate that the absolute stroke risk reduction obtained with oral anticoagulation may vary across each individual CHA_2DS_2-VASc components. In other words, the stroke risk threshold needed for benefit of oral anticoagulation should perhaps be derived from the absolute risk of cardioembolic strokes specifically, and not using all ischaemic stroke subtypes combined.[73,157]

3.3. THE IMPLICATIONS OF SIMPLICITY

With the exception of age, the components of the CHA_2DS_2-VASc score are dichotomised, and therefore ignore for example disease severity. Is has been argued that this provides simplicity that enhances the implementation into clinical practice.[55,158] However, once a patient is considered eligible for anticoagulation when diagnosed with atrial fibrillation, the indication is for life. Considering the practical inconveniences, the expenses, and the potential bleeding risk associated with anticoagulant treatment, the current one-size-fits-virtually-all approach to stroke risk stratification using the CHA_2DS_2-VASc score, where almost all patients have an indication for anticoagulation, may have limited justification. Simplicity in stroke risk stratification is unarguable convenient for practicing physicians and for improving adherence to guideline recommendations, but from simplicity may also arise simplistic treatment decision that may be suboptimal for the individual patient. Identification of additional prognostic factors for stroke in atrial fibrillation may be needed to refine or consolidate the current recommendations on which patients to anticoagulate.

CHAPTER 4. REFINING THE CHA_2DS_2-VASc SCORE

The efforts to extend or refine the CHA_2DS_2-VASc score have been many. Two overall strategies have been applied. One has been to identify additional risk factors beyond those already included in the CHA_2DS_2-VASc score, and the other has been attempts to refine the score within its own boundaries by subdividing the original components. Table 4 summarises studies investigating potential additional stroke risk factors in atrial fibrillation beyond the CHA_2DS_2-VASc score. Table 5 presents studies attemping refinement to stroke risk stratification by breaking down the existing components. Tables 4 and 5 summarise only prospective studies reporting specifically on the outcome of stroke or systemic embolism, whereas cross-sectional studies and studies using surrogate stroke outcome measures (e.g., echocardiographically verified indications of thrombus in the left atrial appendage) are discussed in-text only. Unless noted, all results discussed and presented in Tables 4 and 5 and below are from analyses limited to specifically taking CHA_2DS_2-VASc components into account, either by adjustment or stratification.

4.1. ADDITIONAL PROGNOSTIC FACTORS

The following sections cover the literature aiming to identify additional prognostic factors for stroke in patients with atrial fibrillation beyond those included in the CHA_2DS_2-VASc score. The literature search was done among studies that cited the original CHA_2DS_2-VASc study.

Electrocardiographic and echocardiographic features

Atrial fibrillation can be subdivided into paroxysmal, persistent, or permanent, depending on the duration and intractability of the disorder, and progression from paroxysmal to persistent is known to worsen prognosis.[159] According to guidelines, the indications for oral anticoagulation are similar irrespective of the subtype of atrial fibrillation.[58] However, although not recommended by guidelines, evidence suggests that atrial fibrillation subtype perhaps does influence the decision of whether or not to anticoagulate in practice. Indeed, one contemporary study found that in atrial fibrillation patients admitted with an ischaemic stroke, underuse of oral anticoagulants was most frequent among those with paroxysmal atrial fibrillation.[160]

Several studies have investigated the risk of stroke according to atrial fibrillation burden or subtype, a few also specifically taking CHA_2DS_2-VASc components into account (see Table 4). Observations from the Loire Valley Atrial Fibrillation Project

suggested that the risk of stroke or thromboembolism was lowest in paroxysmal, intermediate in persistent, and highest in permanent atrial fibrillation.[161] This has since been supported by a post-hoc analysis of the aspirin arms of the ACTIVE-A and AVERROES trials, which found a similar dose-response relationship between atrial fibrillation subtype and risk of ischaemic or unspecified stroke or systemic embolism after adjustment for CHA_2DS_2-VASc score.[162] Conversely, Inuoe *et al.* found a slightly lower risk of stroke in persistent atrial fibrillation compared with paroxysmal, with similar stroke risk in paroxysmal and permanent after adjusment for warfarin treatment and CHA_2DS_2-VASc components.[163] Another study demonstrated a very modest increase in the discriminative ability of the CHA_2DS_2-VASc score as measured by the C statistic after adding information about the daily duration of atrial fibrillation.[164] Other published studies without specific adjustment for CHA_2DS_2-VASc components support the observations of a differential risk according to atrial fibrillation burden.[165–168]

Electrocardiography is diagnostic for atrial fibrillation and is therefore routinely performed in all such patients, but electrocardiographic features are at present not used for stroke risk stratification purposes. Using data from the RE-LY trial, Verdecchia *et al.* investigated the potential added prognostic value for stroke in anticoagulated patients from using left ventricular hypertrophy by electrocardiography.[169] Patients with such features were at higher risk of stroke than patients without in the subgroup with CHA_2DS_2-VASc scores ≥3, but not among patients with scores of 0-2, see Table 4.

The potential usefullness of echocardiographic features to guide antithrombotic treatment in addition to the CHA_2DS_2-VASc score has also been investigated. In a cohort of Taiwanese patients with atrial fibrillation who had catheter ablation performed, adding the atrium electromechanical interval (the time interval between the initiation of the P wave on electrocardiogram and the peak of the mitral inflow wave of the pulse wave Doppler imaging) to the CHA_2DS_2-VASc score, markedly improved the C statistics for ischemic stroke risk prediction from 0.75 to 0.85.[170]

A cross-sectional study using echocardiographic measures of stroke risk as a surrogate stroke outcome found an added predictive ability of the CHA_2DS_2-VASc score after adding measures of left atrial area and left ventricle global systolic function, with improvement in the negative predictive value for thromboembolic echocardiographic indications in patients with lower CHA_2DS_2-VASc scores and improved positive predictive value in patients with higher CHA_2DS_2-VASc scores.[171] Another cross-sectional study tested the ability of the CHA_2DS_2-VASc score with and without addition of various echocardiographic measures for predicion of left atrial spontaneous echo contrast or thrombus.[172] Among five tested measures (left atrial volume, impaired left atrial function, left ventricular systolic function, left ventricular hypertrophy, and left ventricle filling pressure), impaired left atrial

function, defined as left atrial emptying function ≤30%, yielded the largest improvement in predictive ability compared with the CHA_2DS_2-VASc score alone (C statistic before/after addition: 0.68/0.77).[172] Other echocardiographic features have also been linked to stroke risk in atrial fibrillation, but without specific investigations of a potential added value beyond the CHA_2DS_2-VASc score.[173]

Comorbidities

The CHA_2DS_2-VASc score includes several comorbidities that commonly exist among patients with atrial fibrillation, including congestive heart failure, hypertension, diabetes, previous stroke, and vascular disease. However, other diseases not included in the CHA_2DS_2-VASc score are known to be associated with risk of stroke in the general population. The potential for refining stroke risk stratification using additional comorbidities as prognostic risk markers has been investigated.

Chronic kidney disease has gained some attention, and a modified $CHADS_2$ score has previously been suggested, the R_2CHADS_2 score, which incorporates renal function (R_2), even given double weight, indicating an associated risk comparable to that of a previous stroke.[88] A few studies have also investigated whether renal function was associated with stroke risk in atrial fibrillation beyond the CHA_2DS_2-VASc score. Using a composite endpoint of hospitalization or death from stroke or systemic thromboembolism (peripheral-artery embolism, ischaemic stroke, or transient ischaemic attack), Olesen *et al.* found a higher risk among patients with non-end stage chronic kidney disease as well as patients with a kidney function requiring renal replacement therapy after adjustment for antithrombotic treatment, CHA_2DS_2-VASc components, and year of inclusion.[174] Another study found no improved predictive performance of the CHA_2DS_2-VASc score after including two levels of impaired renal function in a cohort of patients treated with a vitamin K antagonist.[175] An analysis from the Loire Valley Atrial Fibrillation Project found no improvement in predicting stroke risk when adding different categorisations of estimated glomerular filtration rate to the CHA_2DS_2-VASc score.[176]

A history of a gout attack necessitating long-term treatment with uric acid-lowering agents, a proxy for hyperuricaemia, is also associated with ischaemic stroke risk in atrial fibrillation after adjustment for CHA_2DS_2-VASc score.[177] Two studies using cross-sectional data support these observations, both finding higher levels of serum uric acid among patients with evidence of thromboembolic risk indicated by transesophageal echocardiography, irrespective of CHA_2DS_2-VASc scores.[178,179]

A history of falls has been reported to be associated with a higher risk of ischaemic stroke or thromboembolism after adjustment for CHA_2DS_2-VASc components, but only in anticoagulated patients, and not in the subset of patients not on anticoagulant treatment.[180]

Patients with psoriasis are at high risk of both atrial fibrillation and ischaemic stroke.[181] The potential of refining stroke risk stratification by taking into account a history of psoriasis has been investigated in a Danish nationwide study.[182] After adjustment for CHA_2DS_2-VASc components, patients with severe psoriasis were at higher risk of thromboembolism than patients without or with mild psoriasis. Importantly, thromboembolism rates in patients with CHA_2DS_2-VASc=0 and severe psoriasis were more than double the rate observed in patients with CHA_2DS_2-VASc=0 without severe psoriasis.[182]

Anthropometry and other lifestyle factors

Several lifestyle related factors are known causes of cardiovascular disease, including stroke.[183] However, prior to the conception of the CHA_2DS_2-VASc score, traditional stroke risk factors such as alcohol, smoking, and obesity had been inconsistently linked with stroke risk in atrial fibrillation, perhaps due to very crude assessment, e.g., alcohol habits dichotomised into users versus non-users, which for risk stratification purposes may prove insufficient.[184,185]

Data from a prospective Danish cohort, the Diet, Cancer and Health study (see Text Box 2 on page 30), has formed the basis for several investigations aiming to refine the CHA_2DS_2-VASc score using lifestyle data, including body mass index (BMI), alcohol intake, and smoking habits.[186–188]

*** PAPER 1 ***

Obesity is a known cause of atrial fibrillation and ischaemic stroke in the general population,[9,189] but the potential of incorporating anthropometric measures into stroke risk scores was previously unexplored.[120,129] In **Paper 1**, we aimed to investigate whether BMI would provide additional prognostic information beyond the CHA_2DS_2-VASc score components in the participants from the Diet, Cancer and Health cohort who developed atrial fibrillation after inclusion. BMI was categorised into normal weight (BMI 18.5-25), overweight (BMI >25-30) and obese (BMI >30) as encouraged by the World Health Organisation. We investigated this matter using a Cox proportional hazards model with control for CHA_2DS_2-VASc components. Using a composite endpoint of ischaemic stroke, systemic embolism, or death, we found a higher risk among overweight and obese patients with atrial fibrillation compared with normal weight, with hazard ratios of 1.31 (1.10-1.56) and 1.36 (1.11-1.65), respectively.[186] Underweight patients were excluded due to very few participants in this group. However, sex-stratified continuous analysis adjusted for CHA_2DS_2-VASc revealed that the associations were modified by sex, with J-shaped risk curve for men with a nadir around BMI 24-25 for men, and a U-shaped risk curve with the lowest risk observed in women with BMI 27-28. Furthermore, the higher risk was mainly driven by a higher risk of mortality, and not ischaemic stroke and systemic embolism (see Table 4).

Text box 2. Description of data sources used in Paper 1-4

The National Civil Registration System was established in 1968 and holds information on all Danish residents. In Denmark, all residents are assigned a unique national identification number, the CPR (Central Person Register)-number, which is stored in the Civil Registration System and allows for individual-level linkage of data from all national registries. The Civil Registration System contains information on, among other variables, date of birth, sex, immigrations and emigrations, and vital status.

The Danish National Patient Register holds information on all inpatient contacts to Danish hospital since 1977, including discharge diagnoses according to International Classification of Diseases (ICD)-8 (from 1977 through 1993) and ICD-10 (from 1994-present) codes. Since 1995, also information from emergency room contacts, hospital outpatient clinics, and psychiatric wards has been recorded. This register was used to identify comorbidities and stroke outcomes (death excluded, which is recorded in the Civil Registration System).

The Danish National Prescription Registry contains individual-level information on all prescription drugs claimed from Danish pharmacies since 1995, including Anatomical Therapeutic Chemical classification (ATC) code and dose units.

The Danish Diet, Cancer, and Health cohort was established from 1993-1997. It is a population-based cohort including 57,053 men and women aged 50-64 years and who were free from cancer at baseline and living in the urban areas of Aarhus and Copenhagen, the two largest cities in Denmark. All participants have provided very detailed lifestyle-data based on validated questionnaires, information which is rarely available from administrative registries. Using the unique identification number, lifestyle information from the participants can be linked to the above-mentioned registries allowing for virtually complete follow-up with respect to clinical outcomes and mortality.

Several other studies of anthropometry and stroke in atrial fibrillation without adjustment limited specifically to the CHA_2DS_2-VASc components have yielded conflicting results. A study using data from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial found no association between BMI and stroke incidence,[190] whereas a Chinese study using normal weight as reference suggested a higher risk of ischaemic stroke in overweight but not in obese patients, and a higher risk of systemic embolism in obese but not in overweight patients.[191] Another Chinese study found a non-significantly lower risk of stroke in both underweight, normal weight and obese patients compared with overweight patients.[192] A Japanese study investigating low body weight (defined using an arbitrary cut-off of ≤50 kg) as a stroke risk factor in atrial fibrillation found a hazard ratio of 2.13 (1.39-3.27) after adjustment for CHA_2DS_2-VASc components and renal function.[193] A cross-sectional study found the lowest prevalence of a left atrial appendage thrombus in normal weight subjects, but with no clear dose-response relationship according to higher weight.[194] In summary, the body of

evidence aiming to refine stroke risk stratification using anthropometric measures is at present very heterogeneous. Whether different anthropometric measures other than BMI, e.g., waist circumference, may prove more consistent as prognostic risk markers remains to be investigated.

*** PAPER 2 ***

Consumption of alcohol intake may trigger episodes of atrial fibrillation.[8,195] Alcohol is also a known culprit of ischaemic stroke in the general popualtion,[196] but alcohol intake is currently not included in any stroke risk score for use in patients with atrial fibrillation.[120,129] In **Paper 2**, also using data from the Diet, Cancer and Health cohort, we investigated the potential refinement to stroke risk stratification in atrial fibrillation by stratifying patients according to self-reported alcohol intake.[187] Alcohol intake was grouped into sex-specific exposure categories. In a Cox proportional hazards model, the risk of a composite endpoint of ischaemic stroke, systemic embolism, or death was highest in patients in the highest intake category, with a hazard ratio of 1.31 (1.09-1.58). However, sex stratified analyses revealed that the observed risk difference was mainly driven by a higher risk of mortality in men, whereas among women it was driven by a higher risk of ischaemic stroke or systemic embolism (see Table 4).

Smoking is an important cause of a broad range of adverse cardiovascular events, including ischaemic stroke,[197,198] but despite this smoking habits are not considered when deciding on whether or not to initiate anticoagulation in patients with newly diagnosed atrial fibrillation. Albertsen *et al.* investigated the potential added predictive value of further stratifying atrial fibrillation patients according to smoking habits.[188] Among both men and women, smoking habits were strongly related to a composite endpoint of ischaemic stroke, systemic embolism, or death in a dose-response manner, but the risk pattern for ischaemic stroke or systemic embolism alone was less consistent with a higher risk mainly observed among female smokers (see Table 4). The observation that smoking may identify atrial fibrillation patients at higher risk of stroke is further supported by Japanese data on patients with atrial fibrillation, among who a history of smoking was associated with a higher risk of death from stroke with a hazard ratio 4.7 (1.0-22.3) after adjustment for CHA_2DS_2-VASc score level.[199] However, smoking is also associated with bleeding risk once antithrombotic treatment is initatiated.[200,201]

The lifestyle factors suggested here have the advantage that they are readily available in clinical practice, but cultural differences in self-reported alcohol intake and smoking habits may complicate a universal uptake of using such parameters for stroke risk stratification purposes.[202]

Biomarkers

The potential link between biomarkers and thromboembolic risk in atrial fibrillation has been in the spotlight for several years,[203] but use of biomarkers for stroke risk stratification purposes has mainly played second fiddle to the perhaps more easily obtainable clinical characteristics currently encompassed by CHA_2DS_2-VASc.[204] For example, of 12 available stroke risk stratification schemes for use in patients with atrial fibrillation, none include biomarkers.[120]

Hijazi *et al.* investigated whether cardiac troponin I and N-terminal pro-B-type natriuretic peptide were associated with stroke or systemic embolism in anticoagulated patients included in the RE-LY trial.[205] Both biomarkers were able to risk stratify patients, also after adjustment for CHA_2DS_2-VASc score (see Table 4). These findings are supported by a cross-sectional study, in which cardiac troponin I provided additive predictive ability beyond the CHA_2DS_2-VASc score for prevalence of prothrombotic state in the left atrial appendage as indicated by echocardiography.[206] In another study, N-terminal pro-B-type natriuretic peptide was also strongly associated with stroke risk among 1172 patients with permanent atrial fibrillation on oral anticoagulation, and addition of the biomarker improved the predictive value of the CHA_2DS_2-VASc score.[207] Another randomised trial sub-study using data on anticoagulated patients from the ARISTOTLE trial found no added predictive ability by adding growth differentiation factor 15 to the CHA_2DS_2-VASc score when calculating the C statistic.[208] It must be noted, however, that the RE-LY and ARISTOTLE trials largely did not include patients with CHA_2DS_2-VASc scores of 0 and 1.

8-iso prostaglandin $F_{2\alpha}$, a marker of oxidative stress, was found to significantly improve the predictive value of CHA_2DS_2-VASc score for prediction of a composite cardiovascular outcome (fatal and nonfatal ischaemic stroke, fatal and nonfatal myocardial infarction, cardiac revascularisation/coronary artery bypass surgery and transient ischaemic attack) as reflected by improved C statistics.[209]

Several other biomarkers may prove useful for stroke risk stratification purposes in atrial fibrillation, but many remain to be investigated specifically for the outcome of stroke taking CHA_2DS_2-VASc components into account. Potential candidates include C-reactive protein, von Willebrand factor, D-dimer, interleukin-6, cystatin C, plasma asymmetric dimethylarginine, and urinary 11-dehydro-thromboxane B_2.[210–213]

Miscellaneous

Observations of markedly higher stroke rates in Asian populations than in Western populations with atrial fibrillation, also within similar levels of CHA_2DS_2-VASc score, have given rise to the idea that ethnicity, more particularly Asian or Chinese ethnicity, should be considered when considering thromboprophylaxis.[214,215] While this may prove beneficial, it is important to keep in mind that associations

observed in the context of risk prediction or risk stratification do not automatically imply causation. Differences in lifestyle, which is not taken into account in the CHA_2DS_2-VASc score, between Asian and Western populations may explain part of this observed higher risk. If the higher stroke risk observed in, e.g., Chinese populations is mainly due to unhealthy lifestyle or environmental factors and not a specific genetic susceptibility, then these observations cannot *per se* be extrapolated to Chinese patients who have immigrated to Western civilisations and adapted to local lifestyle patterns. This merits further investigation, but highlights the fact that treatment thresholds for antithrombotic treatment may need to be determined locally.

In summary, many additional factors prognostic for stroke in atrial fibrillation have been under investigation, ranging from electro-and echocardiographic features, lifestyle factors, additional comorbidities, and biomarkers. Many of these suggested factors are readily available in everyday clinical practice, and may potentially provide additional and clinically relevant stroke risk stratification in atrial fibrillation. Most studies used ischaemic stroke overall as the outcome and not cardioembolic stroke specifically. Indeed, some factors are more likely than others to risk stratify patients according to atherosclerotic stroke, e.g., smoking and BMI, whereas other factors have a stronger theoretical link with cardioembolism, e.g., biomarkers. Direct evidence that the investigated factors actually identify patients at high risk of cardioembolism would further favour their implementation into risk stratification in clinical practice. Also, most of the factors have been investigated only once and require replication in future studies.

Other patient characteristics exhibiting an association with stroke risk exist, which have not been investigated specifically for their prognostic contribution beyond the CHA_2DS_2-VASc score in patients with atrial fibrillation. These include previous venous thromboembolism,[216,217] previous retinal or vein occlusion,[218] rheumatoid arthritis,[219] sleep apnea,[220], genetic polymorphisms,[221] and left atrial appendage morphology.[222]

Table 4. Overview of studies investigating prognostic factors for stroke or systemic embolism beyond those included in the CHA_2DS_2-VASc score.

	Definition	Results (95% confidence interval)*
Electro- and echocardiographic features		
Atrial fibrillation subtype		
Banerjee *et al.*[161]	Persistent vs. paroxysmal Permanent vs. paroxysmal	Hazard ratio 1.13 (0.76–1.70) Hazard ratio 1.44 (0.96–2.16)
Vanascche *et al.* [162]	Persistent vs. paroxysmal Permanent vs. paroxysmal	Hazard ratio 1.44 (1.04-1.97) Hazard ratio 1.84 (1.44-2.36)
Inoue *et al.* [163]	Persistent vs. paroxysmal Permanent vs. paroxysmal	Hazard ratio 0.93 (0.86-0.99) Hazard ratio 1.01 (0.96-1.06)
Atrial fibrillation burden		
Boriani *et al.* [164]	A measure of daily duration of atrial fibrillation	C statistic before/after addition to the CHA_2DS_2-VASc score: 0.90 (0.84-0.96) / 0.91 (0.86-0.93)
Other		
Verdecchia *et al.* [169]	Left ventricular hypertrophy by electrocardiography	Unadjusted hazard ratio in patients with CHA_2DS_2-VASc 0-2: 1.01 (0.49-2.08) Unadjusted hazard ratio in patients with CHA_2DS_2-VASc >2: 1.55 (1.19-2.01)
Chao *et al.* [170]	Atrium electromechanical interval (ms) in three categories: <134 [0 points], 134–145 [1 point], and ≥145 [2 points]	C statistic before/after addition to the CHA_2DS_2-VASc score: 0.75 / 0.85, p=0.01
COMORBIDITIES		
Chronic kidney disease		
Olesen *et al.* [174]	Kidney disease status: No renal disease Non-end stage chronic kidney disease Kidney disease requiring renal-replacement therapy	Hazard ratios: 1 [ref] 1.49 (1.38-1.59) 1.83 (1.53-2.14)
Roldan *et al.* [175]	Estimated glomerular filtration rate [eGFR - mL/min/1.73 m^2): Moderate (eGFR 30-60), severe (eGFR <30) (1 and 2 points, respectively)	C statistic before/after addition to the CHA_2DS_2-VASc score: 0.62 (0.59-0.64) / 0.61 (0.58-0.64)
History of gout attack		
Chao *et al.* [177]	History of a gout attack	Hazard ratio 1.19 (1.05-1.36)
History of falls		
Banerjee *et al.*[180]	History of falls based on clinical history or medical records	Overall: Hazard ratio 1.71 (1.04-2.83) Anticoagulation users: Hazard ratio 5.19 (2.1-12.6) Anticoagulation non-users: Hazard ratios 0.88 (0.38-2.01)

Table 4 - continued			
Psoriasis			
Ahlehoff *et al.*[182]	Psoriasis identified by discharge diagnosis and drug prescription claims:	Incidence rate ratios:	Event rate per 100 person-years in CHA_2DS_2-VASc=0:
	No psoriasis [reference]	1	0.9 (0.8-1.0)
	Mild psoriasis	0.99 (0.87-1.11)	1.0 (0.5-2.1)
	Severe psoriasis	1.27 (1.02-1.57)	2.3 (0.9-6.1)
Thyroid dysfunction			
Bruere *et al.*[223]	Thyroid disorders in three categories:	Odds ratios by CHA_2DS_2-VASc score level	
		Score level	Hyperthyroidism
	No thyroid disorder [reference]	0-1	-
	Hyperthyroidism	2-3	0.57 (0.18-1.76)
	Hypothyroidism	4-5	1.58 (0.86-2.93)
		>6	0.87 (0.30-2.47)
		Score level	Hypothyroidism
		0-1	1.82 (0.53-6.31)
		2-3	0.69 (0.39-1.23)
		4-5	1.12 (0.81-1.56)
		>6	1.04 (0.70-1.54)
LIFESTYLE FACTORS			
Body mass index			
Overvad *et al.* [186]	Body mass index (kg/m^2):	Hazard ratios:	
	Normal 18.5-25 [ref]	1	
	Overweight 25-30	1.14 (0.83-1.57)	
	Obesity >30	0.98 (0.67-1.42)	
Alcohol intake			
Overvad *et al.* [187]	Alcohol (drinks per week) in sex-specific categories	Hazard ratios for men	Hazard ratios for women
	Men / Women		
	Abstainers / Abstainers	1.19 (0.43-3-28)	0.66 (0.16-2.79)
	<14 [ref] / <7 [ref]	1	1
	14-20 / 7-13	0.72 (0.39-1.33)	1.14 (0.61-2.13)
	21-27 / 13-20	1.08 (0.65-1.80)	0.77 (0.30-1.98)
	>27 / >20	1.02 (0.68-1.54)	1.71 (0.81-3.60)
Smoking			
Albertsen *et al.* [188]	Smoking habits in four categories	Hazard ratios for men	Hazard ratios for women
	Never [ref]	1	1
	Former	0.64 (0.41-0.99)	1.38 (0.74-2.59)
	≤25 grams/day	1.13 (0.73-1.74)	2.06 (1.14-3.72)
	>25 grams/day	1.21 (0.66-2.21)	1.15 (0.15-8.66)
Nakagawa *et al.* [199]	History of smoking vs. no history of smoking	Hazard ratio 4.7 (1.0-22.3)	

Table 4 - continued				
BIOMARKERS				
Hijazi *et al.* [205]	Cardiac troponin I (µg/L)	N-terminal pro-B-type natriuretic peptide (ng/L)	Hazard ratios for cardiac troponin I	Hazard ratios for N-terminal pro-B-type natriuretic peptide
	<0.010	Quartile 1	1 [ref]	1 [ref]
	0.010-0.019	Quartile 2	1.92 (1.33-2.76)	1.28 (0.80-2.06)
	0.020-0.039	Quartile 3	2.17 (1.43-3.30)	1.19 (0.74-1.91)
	≥0.040	Quartile 4	2.23 (1.33-3.74)	2.12 (1.38-3.26)
Wallentin *et al.* [208]	Growth differentiation factor 15		C statistic before/after addition to the CHA_2DS_2-VASc score: 0.667/0.670	
Roldán *et al.* [207]	N-terminal pro-B-type natriuretic peptide (≥822 pg/mL)		Hazard ratio above versus below the cut off: 2.71 (1.54-4.75) C statistic before/after addition to the CHA_2DS_2-VASc score: 0.62 (0.59-0.65) / 0.68 (0.56-0.71)	
Pignatelli *et al.* [209]	8-iso prostaglandin $F_{2\alpha}$ in tertiles		C statistic before/after addition to the CHA_2DS_2-VASc score: 0.67 (0.61-0.74) / 0.72 (0.67-0.78)	

4.2. REFINING THE EXISTING COMPONENTS

The sections below cover the literature aiming to refine stroke risk stratification in atrial fibrillation by breaking down the existing CHA_2DS_2-VASc components, which is also summarised in Table 5.

Heart failure

Patients with heart failure often present with very varying degrees of disease severity, as reflected by differences in ejection fraction and symptomatic status. Attempts to make use of these traditional categorisations for refined stroke risk stratification in atrial fibrillation has been investigated.

An analysis of patients with heart failure and atrial fibrillation not on anticoagulation from the Loire Valley Atrial Fibrillation Project found no clear stroke risk pattern when patients were subdivided according to left ventricular ejection fraction.[224] In another study, heart failure patients not randomised to oral anticoagulation in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trials, left ventricular ejection fraction did not provide additional value to stroke risk estimation.[225] When stratified according to New York Heart Association class, which categorises patients according to symptom level, indications of a lower risk of stroke, transient ischaemic attack, or systemic embolism with higher symptom class was observed.[225]

Table 5. Overview of studies aiming to refine stroke risk stratification using the CHA_2DS_2-VASc score by subdividing the existing components.

Risk factor	Definition of subdivision	Results (95% confidence interval)*	
Heart failure			
Banerjee *et al.*[224]	Left ventricular ejection fraction:	Hazard ratios:	
	≥50%	1 [ref]	
	35-49%	1.27 (0.83-1.93)	
	<35%	0.75 (0.44-1.30)	
	1% drop (continuous variable)	1.05 (0.97-1.13)	
Sandhu *et al.*[225]	Left ventricular ejection fraction <50%	Hazard ratio 1.10 (0.87-1.39)	
	New York Heart Association Class	Hazard ratios:	
	I	1 [ref]	
	II	0.88 (0.68-1.13)	
	III or IV	0.73 (0.53-1.01)	
Age			
Chao *et al.*[226]	Patients with CHA_2DS_2-VASc score 0 (men) and 1 (women) aged <65 years divided into subgroups:	Hazard ratios	Event rate per 100-person years
	Age 20—39	1 [ref]	0.32
	Age 40—49	2.29 (1.76-2.97)	0.73
	Age 50—54	4.11 (3.16-5.32)	1.29
	Age 55—59	4.89 (3.80-6.30)	1.56
	Age 60—64	7.60 (5.98-9.66)	2.42
Diabetes mellitus			
Saliba *et al.* [227]	Glycated haemoglobin (%) in quartiles in patients with diabetes mellitus	Hazard ratios	
	No diabetes mellitus	1 [ref]	
	Quartile 1 (<6.35)	1.04 (0.83-1.30)	
	Quartile 2 (6.35-6.90)	1.14 (0.92-1.42)	
	Quartile 3 (>6.90-7.70)	1.46 (1.19-1.79)	
	Quartile 4 (>7.70)	1.63 (1.33-2.00)	
Overvad *et al.* [228]	Diabetes mellitus duration in 5-year categories:	Hazard ratios	
	No diabetes mellitus [ref]	1 [ref]	
	Diabetes duration 0-4 years	1.11 (1.03–1.20)	
	Diabetes duration 5-9 years	1.32 (1.20–1.44)	
	Diabetes duration 10-14 years	1.28 (1.13–1.45)	
	Diabetes duration ≥15 years	1.48 (1.29–1.70)	
Previous stroke, systemic embolism, or transient ischaemic attack			
Li *et al.* [229]	Stroke severity by National Institutes of Health Stroke Scale (NIHSS) score	C statistic before/after addition to the CHA_2DS_2-VASc score: 0.55 / 0.58	
Ntaios *et al.* [230]	Leukoaraiosis defined as hypodensity on CT or hyperintensity on T2-weighted MRI in periventricular or subcortical regions, or in the pons.	Hazard ratio 0.99 (0.61–1.60) C statistic before/after addition to the CHA_2DS_2-VASc score: 0.64 / 0.64	

Age

Using data from a large, Taiwanese administrative database, Chao *et al.* investigated whether subdividing patients aged <65 years with low CHA_2DS_2-VASc scores (0 in men and 1 in women) into several age categories would refine stroke risk stratification.[226] They found that for Taiwanese patients, an age cut-off of 50 years might be more a more appropriate treatment threshold to apply than the current cut-off of 65 years suggested by the CHA_2DS_2-VASc score.

Diabetes mellitus

Patients with diabetes mellitus are a very heterogeneous group consisting of some patients with type 1 diabetes and some with type 2 diabetes, two aetiologically distinct diseases. Furthermore, patients exhibit varying degrees of diabetic complications, duration of disease, and level of glycaemic control. Assuming that the risk of stroke is uniform in such a diverse population is indeed simplistic, but diabetes mellitus is currently dichotomised in the CHA_2DS_2-VASc score.[52] Two published studies have investigated simple ways of subdividing diabetes mellitus using duration of the disease measured as time since diagnosis, or by levels of haemoglobin A1c (HbA1c).[227,228]

*** PAPER 4 ***

In **Paper 4**, we subdivided patients with atrial fibrillation and diabetes according to the duration of their diabetes disease, and investigated their risk of ischaemic stroke or systemic embolism in a Cox proportional hazards model with adjustment for CHA_2DS_2-VASc components and antithrombotic treatment during follow-up.[228] Patients with diabetes were identified in nationwide administrative registries, and duration of disease was calculated as time from first diagnosis in the National Patient Register or first claimed prescription of a glucose-lowering drug.[228,231,232] Compared with patients with atrial fibrillation and without diabetes, the risk of ischaemic stroke or systemic embolism was higher in all patients with diabetes mellitus, irrespective of diabetes duration category. However, duration of diabetes exhibited a clear linear dose-response relationship with risk of ischaemic stroke. Duration of diabetes mellitus was not positively associated with risk of bleeding in patients on anticoagulant treatment, adding additional weight to using diabetes duration to refine stroke risk in atrial fibrillation.[228]

A large register-based study from Israel investigated the risk of incident stroke in patients with atrial fibrillation and diabetes according to the degree of glycaemic control as measured by HbA1c.[227] HbA1c in quartiles exhibited a clear dose-response relationship with stroke risk after adjustment for CHA_2DS_2-VASc components. Patients in the first quartile had an incident stroke risk almost similar to that of patients without diabetes (hazard ratio 1.04, 95% CI 0.83–1.30), indicating that patients with good glycaemic control should perhaps not be attributed one point due to diabetes in the CHA_2DS_2-VASc score.[227]

Both duration of diabetes mellitus and HbA1c are easily obtainable patient characteristics in everyday clinical practice. Whether duration of diabetes and levels of glycated haemoglobin provide refinement of stroke risk independent of each other is uncertain, as they are likely to be correlated (to some extend both reflecting severity of diabetes). Nonetheless, both studies revoke the simplistic assumption that all patients with diabetes mellitus carry equal stroke risk once diagnosed with atrial fibrillation. Whether using established diabetic complications as stroke risk markers will provide even more accurate risk stratification warrants further investigation.

Previous thromboembolism

The subgroup of patients with a previous stroke has also been subdivided in order to potentially refine stroke risk stratification in this category of patients. In a Chinese study evaluating the ability of the CHA_2DS_2-VASc score for predicting one-year self-reported recurrences of ischaemic stroke or transient ischaemic attack, it was tested whether addition of the baseline National Institutes of Health Stroke Scale (NIHSS) score would improve the performance of CHA_2DS_2-VASc.[229] The NIHSS score includes eleven items that rate the severity of a stroke event. Adding baseline NIHSS score to the CHA_2DS_2-VASc score improved the C statistic slightly from 0.55 to 0.58. In a Greek study, the presence of leukoaraiosis, determined either by computed tomography (CT) scan or magnetic resonance (MRI) scan, was added to the CHA_2DS_2-VASc score in atrial fibrillation patients with first ever ischaemic stroke.[230] After adjustment for pre-stroke CHA_2DS_2-VASc score, leukoaraiosis was not associated with stroke recurrence with a hazard ratio of 0.99 (95% CI 0.61–1.60). Consequently, the C statistic was also unaltered after addition of leukoaraiosis to the CHA_2DS_2-VASc score (see Table 5).

The clinical value of refining stroke risk stratification among patients that are unequivocally recommended anticoagulation by guidelines still remains to be defined.

Vascular disease

The current definition of vascular disease in the CHA_2DS_2-VASc score does not include asymptomatic atherosclerosis detected by ankle-brachial index. An Italian study found that the prevalence of vascular disease in patients with atrial fibrillation rose from 17.3% to 33% when including an ankle-brachial index <0.90 in the vascular disease definition.[233] Whether this change in definition would improve the prognostic value of the CHA_2DS_2-VASc score warrants future prospectively designed investigations with consideration of clinical outcomes.

In summary, some of the existing components of the CHA_2DS_2-VASc score could be subdivided to provide additional refinement of stroke risk stratification in atrial fibrillation, including age, diabetes and previous thromboembolism. No studies report important refinement among patients with heart failure, whereas

subdivision of other CHA_2DS_2-VASc components remains to be investigated. For example, a patient with well-treated hypertension is unlikely to carry a similar stroke risk than a patient with malignant, uncontrolled hypertension, but both patients have a similar indication for antithrombotic treatment in the CHA_2DS_2-VASc score.[52,127,234,235]

CHAPTER 5. METHODOLOGICAL CONSIDERATIONS

The vast majority of studies investigating stroke risk stratification in atrial fibrillation are prospective cohort studies. To best discuss overall methodological issues related to such prospective studies concerning risk stratification, **Paper 1-4** forming the basis for this thesis will be used for illustrative purposes.[144,186,187,228]
The internal validity of observational studies is threatened by bias, which may occur on the basis of issues with selection, information, or confounding.[236] These matters are discussed below followed by considerations of external validity. The studies forming the basis for this thesis all used information from national Danish registries. For those unfamiliar with the structure and content of these national registries, a short description of the relevant registries can be found in Text box 2.[237,238]

5.1. SELECTION ISSUES

Selection bias may occur if there is a systematic difference between exposure and outcome in those included in the study compared with those not included but otherwise eligible for the study, or from censoring due to differential loss to follow-up or competing risks (also known as informative censoring).[239] In other words, the total study loss, whether occurring at the time of study conception or during the study process, can introduce selection bias. It is, however, selection bias due to informative censoring that cohort studies are mainly prone to, as selection at entry into a cohort is only very rarely associated with outcome, since the outcome of interest has not (or at least should not have) occurred at the time of enrolment.[236,240] Selection criteria for a cohort study impact therefore mainly on the generalisability of the results. In **Paper 1-3,** the study population comprised of participants from the Diet, Cancer, and Health cohort. Of those invited into this cohort, only approximately 1/3 of those invited agreed to participate.[241] It has been demonstrated that non-responders carry a higher mortality risk than those participating, an excess risk consistent also within levels of socioeconomic status, suggesting that important differences in lifestyle and other environmental factors are likely to exist between responders and non-responders in epidemiological cohorts.[242] However, this would not necessarily bias effect estimates on a relative scale, since this would require the associations between, e.g., alcohol and body mass index and risk of stroke to be systematically different between identified and non-identified participants with atrial fibrillation, which is a different and more unlikely scenario.[243] Conversely, had the aim been to quantify the absolute stroke risk among atrial fibrillation patients according to body mass index, the higher risk

in non-responders would underestimate the absolute risk associated with body mass index, but this is an issue of generalisability or representativeness, and not selection bias.[244]

In **Paper 1 and 2** investigating BMI and alcohol intake as potential candidates for refining stroke risk stratification in patients with atrial fibrillation, a composite endpoint comprising ischaemic stroke, systemic embolism, or death was chosen as the primary outcome.[186,187] This was done in part because death may be a competing event in the relationship between exposure and risk of ischaemic stroke, which is the outcome of primary interest with regards to anticoagulant treatment. When patients who drink heavily or have a high BMI die, and if those who die were more likely to suffer a subsequent ischaemic stroke than those retained in the study, competing risks from death may bias the results by underestimating the association between exposure and outcome. Formally, competing risk from death may result in selection bias, which can be avoided by use of a composite endpoint including the competing event.[245] However, it comes at the cost of a different interpretation of the results, as they no longer solely reflect the outcome of primary interest (that is, ischaemic stroke). Nonetheless, some deaths are also likely to be due to undiagnosed/unregistered stroke and therefore not captured by using ischaemic stroke alone as the outcome measure.

Nationwide Danish registries provided the outcome information used in **Paper 1-4**.[231,246] With the exception of very few patients who emigrated during the study period, this allowed for virtually complete follow-up for vital status as well as registration of thromboembolic events in patients admitted to a hospital. The potential selection bias arising from informative censoring due to loss to follow-up was therefore negligible.[240] Data were analysed using a Cox proportional hazards model, which is a convenient method for time-to-event analysis.[247] The method takes into account time to censoring (time-to-non-event), which occurs not only if patients emigrate, but also at end of study when patients have not experienced the event of primary interest, and the method also allows for concomitant adjustment for covariates.[248,249]

5.2. INFORMATION ISSUES

Is the baseline and outcome information obtained in an epidemiological study reliable? Unreliable information in epidemiological studies may bias the results.[236]

In **Paper 1-4**, [144,186,187,228] the study populations were defined by patients with a first time hospital-based diagnosis of atrial fibrillation, who were identified based on data from the Danish National Patient Register.[231] A diagnosis of atrial fibrillation in the National Patient Register is considered highly valid with a positive predictive value >90%, which is unlikely to be associated with the exposures in **Paper 1-4**.[250]

With some exceptions (e.g., sex category), it is a task of the authors to decide how to define and categorise exposure. In risk prediction research, it is advised to investigate the factor under investigation in arbitrary categories as well as in a continuous manner (if possible) in order to maximise the predictive value of a given factor.[251,252] In **Paper 1, 2 and 4**, the exposures BMI, alcohol intake, and duration of diabetes mellitus were all investigated according to such recommendations.[186,187,228] For example, BMI was categorised arbitrarily according to the World Health Organisation categorisation of normal weight (BMI 18.5-25), overweight (BMI 25-30), and obesity (BMI ≥30), but the results from graphically presented continuous analyses stratified by sex revealed that the risk of stroke, thromboembolism, or death was J-shaped for men and U-shaped for women, with the lowest risk of outcome among normal weight men and overweight women.[186] Information about sex, BMI, and diabetes duration was objectively measured, whereas alcohol intake was self-reported. Information based on self-report is generally more unreliable, but that is nonetheless the only possible way to assess a patient's alcohol intake.

The validity of the outcome under study is another critical information aspect. The positive predictive value of a diagnosis of ischaemic stroke in the Danish National Patient Register is high (approximately 90%), while a discharge diagnosis of unspecified stroke, which was also included in the studies, represents an ischaemic event in approximately 2/3 of the cases.[253,254] Hence, ischaemic stroke event rates can only be estimated with some uncertainty from registries. However, in comparative studies, which often report the primary outcome measure on a relative scale (e.g., relative risk of hazard ratios), this would not spuriously create a positive association, as long as the positive predictive value for stroke is equally good (or bad) among exposed and non-exposed. Where it may cause concern is when trying to accurately estimate event rates.

5.3. ESTIMATING EVENT RATES USING ADMINISTRATIVE REGISTRIES

The problems with estimating stroke rates using administrative registries are designated an entire section here, since such reported rates from register-based observational studies have had a major impact on guideline recommendations for use of antithrombotic treatment in patients with atrial fibrillation.[53,72,85,86,155,255,256] The magnitude of stroke risk within levels of the CHA_2DS_2-VASc score has often been quantified by stroke event rates. Specifically, the event rates observed among patients with CHA_2DS_2-VASc=1 are of special interest, since it is for such patients that there is the largest disagreement about which and whether antithrombotic treatment should be offered. The problems with estimating the absolute risk of stroke using administrative registries involve issues with both selection and information (see Figure 2).

How do you estimate the 'true' stroke rates from a non-anticoagulated population meant for comparison with the suggested treatment 'tipping point'? Should it include ischaemic stroke or cardioembolic stroke only, and perhaps systemic embolisms and transient ischaemic attacks? Unsurprisingly, event rates for lower risk patients vary greatly depending on the specific outcome definition used.[155] For example, event rates reported in Danish nationwide registry studies have had a strong influence on current international guideline recommendations.[53,85] These Danish event rates are among the highest reported from Western populations in the atrial fibrillation literature,[82] and the validity of these high rates is currently being debated.[55,105,155,257] Nonetheless, different ways of defining the study population may impact on the magnitude of the event rates. For example, analyses from the nationwide Swedish patient register suggested that stroke rates among patients with low CHA_2DS_2-VASc scores were much lower than those reported in Danish studies, hereby raising concerns about whether such patients will actually benefit from anticoagulant treatment.[155,258] However, they defined a baseline untreated population by including only patients who did not initiate anticoagulant treatment during follow-up, a flawed methodological approach known as 'conditioning on the future'.[74,259] Such an approach may underestimate stroke risk, because the exclusion criterion, initiating anticoagulant therapy, is likely to identify patients who recently survived a thromboembolic event. Indeed, Nielsen *et al.* demonstrated that this baseline exclusion of patients based on future events yielded lower stroke rates than a more appropriate approach with right censoring at time of initiation of anticoagulant treatment.[260]

The validity of the outcome information is also critical when aiming to accurately assess stroke risk. For example, many CHA_2DS_2-VASc validation studies aiming to accurately estimate stroke rates have been using administrative registries to identify stroke outcomes.[85,86,155,156] Ideally, stroke diagnoses based on register data should be 100% sensitive with a positive predictive value also of 100%. This is, inevitably, not the case.[261] While perhaps reasonably sensitive, some patients with atrial fibrillation also have fatal strokes and are therefore never admitted to a hospital, which underestimates the number of stroke events. Attempts have been made to overcome this issue by also including deaths recorded as being due to a thromboembolic event in the outcome definitions, for example by using data from the Danish Register of Causes of Death.[53,85,262] However, less than 10% of deceased have an autopsy performed in Denmark, inevitably hampering the validity of such data,[262] and only approximately 10% of deaths among patients hospitalised with atrial fibrillation are assumed to be attributed to stroke.[263] Another important validity aspect is the positive predictive value of a stroke diagnosis, which in a systematic review including 77 studies from various countries has been reported to be approximately 80% for ischaemic stroke alone,[261] slightly lower than reports from Danish validation studies.[253,254] This indicates that estimating stroke event rates based on administrative databases may overestimate the 'true' event rate by up to 25%. Secondary discharge diagnoses, which have also been used in previous

key literature, may be even less valid, as they are likely in some cased to represent recoding of previous events.[85] Also, stroke rates associated with atrial fibrillation may vary over time, and event rates calculated from historical cohorts, accurately estimated or not, cannot necessarily be extrapolated to present and future patient populations.[264]

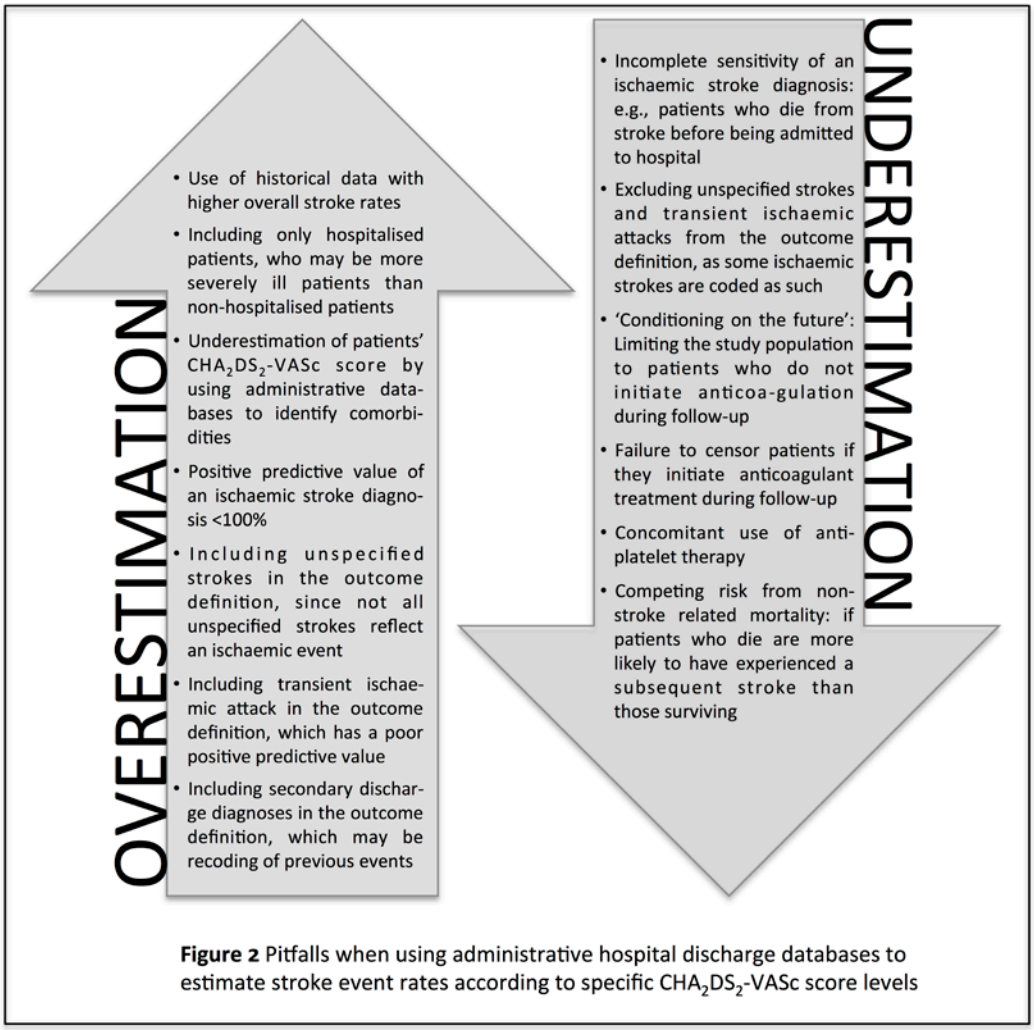

Figure 2 Pitfalls when using administrative hospital discharge databases to estimate stroke event rates according to specific CHA_2DS_2-VASc score levels

Another critical aspect is whether we can be certain that a patient with CHA_2DS_2-VASc=1 would not have had a higher score, if we evaluated him or her in clinical practice instead of just by using administrative registries, that is, misclassification of the risk score level. Assuming that higher CHA_2DS_2-VASc score also equates to higher stroke risk, this could potentially overestimate the event rates related to CHA_2DS_2-VASc=1 and hereby give a false impression that such patients are 'high-

risk' patients. Clearly, some components can be reliable estimated from registries, including age and sex, but comorbidities such as heart failure, hypertension, diabetes, and vascular disease may not have been completely registered. For example, in patients admitted to hospital, a heart failure diagnosis in the Danish National Patient Register is relatively accurate (positive predictive value of 81%) but very incomplete (sensitivity of 29%), indicating severe underregistration.[265]

In short, although administrative registries have the advantage of very limited loss to follow-up, there are also important pitfalls associated with their use, as summarised in Figure 2. In practice, it is impossible to assess the impact related to the sum of these potential sources of error on the magnitude of the observed stroke rate. Only one thing is certain, namely that no study reporting on stroke rates according to CHA_2DS_2-VASc score level is likely to have captured the 'true' stroke rate. Using administrative registries to accurately estimate stroke event rates warrants utmost caution.

5.4. CONFOUNDING

Confounding is a concept related to studies of causality. The CHA_2DS_2-VASc score is a tool used for stroke risk prediction, and it does therefore not reflect the causal structures of thromboembolic risk in patients with atrial fibrillation. Although some included components are known causes of stroke in the general population, they are included in the prediction model not necessarily for their causal relationship with stroke, but merely because they serve as easily obtainable patient characteristics that, from a risk stratification perspective, provide useful prognostic information in patients with atrial fibrillation, also independent of the other components in the model.

To illustrate this further, we investigated whether alcohol intake was associated with ischaemic stroke, systemic embolism, or death in patients with atrial fibrillation beyond what was already encompassed by the CHA_2DS_2-VASc score in **Paper 2**. Therefore, we adjusted for components of the CHA_2DS_2-VASc score. This was not an attempt to adjust for confounding and hereby explore the potential causal relationship between alcohol intake and stroke or death, but to elucidate the potential added value by alcohol intake to risk stratification in patients with atrial fibrillation. If this had been an attempt to study the effect of alcohol intake on stroke risk in patients with atrial fibrillation, smoking (among other factors) may have confounded the association, and this would need to be taken into account in the analysis. However, as smoking habits are not (explicitly) included in the CHA_2DS_2-VASc score, the confluence of alcohol and smoking habits was irrelevant to this particular question. Consequently, as studies with focus on prediction and risk stratification do (should) not attempt causal inferences, similarly do they not provide evidence or justify recommendations for a beneficial effect of lowering

alcohol intake on the future risk of a thromboembolic event once diagnosed with atrial fibrillation. Similar reasoning holds for the studies about BMI and diabetes duration.

As mentioned, some components of the CHA_2DS_2-VASc score may also be causally related to stroke risk in patients with atrial fibrillation. For example, female sex is included as a component in the CHA_2DS_2-VASc score. This is based on multiple observations of a higher risk of stroke in women versus men following a diagnosis of atrial fibrillation.[139] It has been speculated that such differences in stroke risk may pertain to actual physiological differences between men and women.[140,143] Some studies have attempted to answer this question by adjusting for potential confounding factors beyond what is included in the CHA_2DS_2-VASc score, but these studies have been register-based with an inevitable lack of information about anthropometric measures and lifestyle factors, which may confound the association between sex and stroke risk.[140–142] In an effort to dig deeper into the possibility of an intrinsic sex-related difference in stroke risk among patients with atrial fibrillation, we investigated this matter in **Paper 3** using data from the Diet, Cancer and Health cohort, which holds detailed information on lifestyle behaviour on approximately 3,000 patients with atrial fibrillation.[144] In our study, additional adjustment for potentially confounding factors such as smoking, alcohol, and anthropometric measures did not change the effect estimate (hazard ratio of 0.81 versus 0.77), indicating that differences in lifestyle and anthropometry are unlikely to explain the previously observed sex differences in stroke risk.[139,143]

In **Paper 1-4**, beginning of follow-up for the individual patient started at their respective time of a first diagnosis of atrial fibrillation as registered in the National Patient Register.[231] This design made the available follow-up period among patients highly variably. To take into account these differences in length of follow-up, which may impact on the estimated stroke risk, time since diagnosis of atrial fibrillation was modelled as the underlying time axis in the Cox proportional hazards models used in the studies, and was hereby closely controlled for.[247,266,267]

Large, unselected cohorts of patients with atrial fibrillation not treated with any kind of antithrombotic agents no longer exist. Consequently, the natural history between atrial fibrillation and stroke can no longer be studied, and researches investigating stroke risk predictors suitable for guiding antithrombotic treatment in patients with atrial fibrillation are required to choose between different approaches. One option is to define a cohort using only patients not treated with antithrombotic agents, and then censor patients once they initiate antithrombotic treatment, and settle with the lack of knowledge about why particularly these patients are untreated. This may impact on the generalisability of the results.[268] Another option is to include all patients with atrial fibrillation irrespective of antithrombotic treatment status during follow-up, and then subsequently adjust for such treatment differences in the analysis. In **Paper 1-4**, the latter approach was

chosen in an attempt to mimic a cohort not using antithrombotic treatment.[144,186,187,228] However, differences in antithrombotic treatment between exposed and non-exposed during follow-up may distort the associations if not taken into account. We performed adjustments for time-varying use of antithrombotic treatment during follow-up based on information from the Danish National Prescription Registry, which holds information on all claimed prescriptions from Danish pharmacies since 1994.[232] This allowed for more precise adjustment compared to using only baseline treatment information. Nonetheless, information about the degree of anticoagulant control, which has a major impact on the preventive effect of anticoagulant treatment, was not available.[269]

In summary, studies focusing on refining an established stroke prediction model, confounding by other known stroke risk factors associated with both exposure and outcome, but not included in the existing model, is therefore an issue of less concern. Careful considerations of how to deal with potential differences in anti-thrombotic treatment between exposed and non-exposed during follow-up requires careful consideration to avoid distortions of the observed associations.

5.5. GENERALISABILITY

Generalisability, also referred to as external validity or representativeness, concerns whether scientific findings can be extrapolated to other populations than the study population itself.[236] In aetiological research, where you attempt to isolate the effect of a single, potentially causal exposure, lack of representativeness is often a minor issue.[244] In such a case, scientific inference based on knowledge about the underlying biological mechanism is generally sufficient to evaluate whether the findings can be applied to other populations. In **Paper 1, 2 and 4**, our aim was to demonstrate whether BMI, alcohol intake, and diabetes duration could potentially improve the identification of patients with atrial fibrillation at high risk of stroke.[186,187,228] The primary outcome was measured on a relative scale, in order to reveal whether the risk was higher in the exposed versus unexposed individuals. We, therefore, did not specifically isolate the effect of these exposures, since we only took CHA_2DS_2-VASc components into account in the adjusted analysis. Nonetheless, something did cause the observed excess risk. For example, in the study of alcohol intake, the observed associations may be partially explained by a direct effect of alcohol, but also by other causes of stroke associated with high alcohol intake, e.g., smoking and sedentary lifestyle. In other populations, alcohol may be differently associated with such other known causes of stroke, for example due to cultural differences, and therefore yield different relative estimates. Also, excessive alcohol consumption is widespread among Danish citizens, and such ranges of alcohol consumption as well as (binge) drinking patterns may not be similar in other populations.[270] Indeed, drinking pattern, which is known to vary from country to country, may modify the effect of alcohol on stroke risk.[271,272]

Similar reasoning can be made for BMI and diabetes duration, which also theoretically may exhibit different associations in other populations (there are several ways to obtain a high BMI, and country-specific management of diabetes may influence the impact of longer duration). External validation of the findings in **Paper 1, 2 and 4** is therefore warranted.

Generalisability or representativeness is a more important issue when the purpose of a study is purely descriptive.[273] This is the case for studies evaluating the performance of CHA_2DS_2-VASc, which report on observed event rates according to different score levels. Here, external validation of the CHA_2DS_2-VASc score is essential to evaluate calibration, since stroke rates observed in one population may be different in other populations. For example, stroke rates in patients with atrial fibrillation are generally higher in Asian patients. Such issues concerning miscalibration may support the development of country or region-specific stroke risk models.

5.6. EVALUATING THE PERFORMANCE OF A RISK PREDICTION MODEL

So how should we evaluate whether a refined model improves stroke risk stratification? As previously discussed, the main focus on the predictive performance of the CHA_2DS_2-VASc score has been on how well calibrated the model is for patients with lower scores of 0, 1 and 2, i.e., how well does the predicted absolute risk align with the observed absolute risk, and does the observed risk lie consistently below or above the recommended antithrombotic treatment threshold.[274] Since the discriminatory properties of the score essentially do not influence treatment decisions, evaluating the potential improvement in predictive value of adding additional risk factors to the existing score by the C statistic has no immediate clinical implications and should perhaps be discouraged.[275] Also, even the addition of a highly clinically relevant risk component strongly associated with the outcome may yield no or only minor improvement in the C statistic, and may for this reason falsely be assumed to be of no clinical value.[276] Lack of improvement in the C statistic after addition of a novel component does not preclude that this new component may provide important refinement to calibration among patients with CHA_2DS_2-VASc scores surrounding the treatment decision threshold.[118]

Another way of evaluating the performance of a refined model is by means of reclassification, often calculated as the net reclassification improvement, which is a measure reflecting the sum of correct and incorrect reclassifications of cases and non-cases.[277] For cases, correct reclassification is to a higher risk score level, while reclassification to a lower risk score level is considered incorrect reclassification, and *vice versa* for non-cases. However, the clinical utility of such measures is also being discussed.[278,279] In short, depending on the choice of performance measure,

some indices for evaluating a prediction model may indicate no or little improvement in risk prediction when in practice it may advance clinical decision-making by improving calibration in important subgroups.[280]

In **Paper 1, 2 and 4** in this thesis, we focused on identifying potentially refining prognostic stroke risk factors beyond the CHA_2DS_2-VASc score, but we did not evaluate the performance of the refined model in terms of discrimination. This was not done in part due to the reasons listed above concerning the clinical utility of discriminatory measures, but also because these studies were the first to describe these associations in the context of risk stratification in atrial fibrillation, and replication in future studies is needed. Additionally, internal validation of a prediction model on the very same data that was used to derive the model will likely provide performance indices that are too optimistic.[281] Also for this reason is external validation of refined models paramount. When further studies have confirmed or refuted the potential value of the factors identified in the present review, future attempts to improve the CHA_2DS_2-VASc score should include careful considerations on how to evaluate the performance of the refined model, while keeping in mind the currently recommended treatment decision thresholds.[282]

CHAPTER 6. MOVING FORWARD

The above sections summarised the evidence aiming to refine stroke risk stratification in atrial fibrillation beyond the widely adopted CHA_2DS_2-VASc score. The following sections will discuss ways to move forward by taking into consideration additional prognostic factors for stroke in atrial fibrillation, as well as some other alternative ways to advance the current approach. Also, other on-going and unresolved issues related to stroke risk stratification will be addressed.

As previously discussed, one advantage of the CHA_2DS_2-VASc score over the older $CHADS_2$ score is the smaller proportion of patients categorised into intermediate risk categories.[53] Nonetheless, the CHA_2DS_2-VASc score still categorises a substantial proportion of patients, mainly those with a score of 1, whose risk level resides close to the cut-off for assumed benefit from anticoagulant treatment.[73] This still leaves some patients and treating physicians in doubt when weighing the risks and benefits of anticoagulant treatment, as also reflected by conflicting guideline recommendations. This uncertainty may partly explain the widespread and repeatedly established underuse of anticoagulation in patients with atrial fibrillation as otherwise recommended by guidelines.[81,283] The literature review in this thesis identified several studies aiming for identification of new prognostic factors for stroke in atrial fibrillation that may contribute to improved clinical decision-making regarding antithrombotic treatment.

6.1. INTERPRETING DIFFERENCES IN EVENT RATES ACROSS POPULATIONS

The CHA_2DS_2-VASc score has some limitations with regard to accurately predicting risk across populations.[69,74,284] As previously discussed, some of the differences in event rates may pertain to methodological differences, but actual differences across populations are also conceivable. This may be partially explained by the crude and reductionist design of CHA_2DS_2-VASc that does not allow for consideration of for example disease severity. For example, the Danish National Patient Register holds information on inpatient, outpatient as well as emergency department contacts.[231] A Danish nationwide analysis investigated whether thromboembolic event rates differed in patients with atrial fibrillation depending on in which hospital setting they were managed.[285] They found that thromboembolic event rates in patients not using anticoagulant treatment were highest in inpatients and lower in emergency department patients and outpatients, also within $CHADS_2$ score levels. This underlines that there are risk differences between populations that are not captured by risk stratifying patients by $CHADS_2$ only (and most likely also by CHA_2DS_2-VASc, given the substantial overlap of the two scores). This may explain some of the observed miscalibration of the CHA_2DS_2-

VASc score when applied to different patient populations, which may have varying degrees of disease severity as well as additional stroke risk factors that are not encompassed by CHA_2DS_2-VASc.

There are also regional or country-specific differences in overall stroke incidence that inevitably may entail miscalibration,[286] a circumstance that would impact on which treatment threshold should be applied. For example, in several Asian populations, the observed absolute stroke risk in patients categorised as CHA_2DS_2-VASc score 0 and 1 has proven to be markedly higher than the risk otherwise predicted by the model.[156,214,215,226] Recalibration of the model to the overall stroke incidence levels across populations would allow for more accurate stroke risk prediction.[287] It is possible, however, that applying the CHA_2DS_2-VASc score in Asian populations will then eventually fail to identify any patients at sufficiently low risk who can be safely left without antithrombotic treatment, and, therefore, for the specific clinical decision on whether or not to initiate oral anticoagulation, effectively make risk stratification with CHA_2DS_2-VASc redundant. The remaining option would then be the development of new population-specific models.[226] In short, deciding on a universal cut-off of a CHA_2DS_2-VASc score of 1 as the risk score level decisive for anticoagulant treatment is most likely inappropriate due to variations in overall stroke incidences. If stroke risk stratification will continue to be performed using the CHA_2DS_2-VASc score, various atrial fibrillation guideline committees should perhaps agree to disagree.

6.2. ANTIPLATELETS, ANTICOAGULANTS, OR BOTH?

Anticoagulants and aspirin exert their antithrombotic effects through different pathways. Anticoagulants inhibit, directly or indirectly, specific factors in the coagulation cascade, while aspirin is a platelet inhibitor.[288,289] These differential antithrombotic actions makes it theoretically tempting to combine these treatments to maximise prevention, but this is generally not recommended, as excess bleeding risk outweighs the potential added protective effect in most patients.[290–292] As previously noted, also aspirin monotherapy for stroke prevention in patients with atrial fibrillation is almost obsolete according to European guidelines, reserved only to those who refuse any form of anticoagulant treatment.[61,293] In contrast, American guidelines have left the door ajar for aspirin, allowing the option of recommending aspirin to patients with a CHA_2DS_2-VASc score of 1.[58] Canadian guidelines recommend a third approach, suggesting oral anticoagulants to all patients aged ≥65 and younger patients with congestive heart failure, hypertension, diabetes mellitus, or previous stroke, while men with a CHA_2DS_2-VASc score of 1 and women with a CHA_2DS_2-VASc score of 2 due to vascular disease and female sex are recommended aspirin, and women (in line with European recommendations) with female sex as their only risk factor can be left without any antithrombotic treatment, see Table 2.[60]

Indeed, oral anticoagulants are overall superior to aspirin for stroke prevention in atrial fibrillation,[39] but the overall higher effectiveness comes at the cost of a higher risk of bleeding with anticoagulants.[294] As also indicated by Canadian guidelines, this overall superiority cannot *per se* exclude the possibility that certain subgroups may benefit more from aspirin than oral anticoagulants, given the different antithrombotic effects and bleeding profiles of the drugs.[60,147]

That the superiority of VKAs over aspirin for cardiovascular prevention is mainly due to a specific protective effect against cardioembolic strokes is supported by a small, randomised pilot study, in which patients with paroxysmal atrial fibrillation with no evidence of atrial stasis or complex aortic plaques on echocardiography were randomized to aspirin or VKA.[295,296] The mean CHA_2DS_2-VASc score was 2.1, and the mean follow-up was 1.6 years. The hazard ratio comparing the aspirin arm with the VKA arm for a composite endpoint of all-cause mortality, stroke, major bleeding, acute coronary syndrome and systemic embolism was 0.54 (95% CI 0.16-1.85), suggestive of a potential net clinical benefit of aspirin over warfarin following stroke risk refinement using echocardiography. A larger trial with longer follow-up is needed to confirm these intriguing findings, but they support the theory that various cardiac imaging techniques may have the potential not only to improve risk stratification for ischaemic stroke overall, but also may allow for more accurate identification of patients at low and high risk of cardioembolic stroke specifically.[171,297,298] For example, N-terminal pro-B-type natriuretic peptide, morphology of the left atrial appendage, D-dimer, midregional proatrial natriuretic peptide, and soluble thrombomodulin may be related specifically to cardioembolic stroke.[299–302] This may further tailor antithrombotic regimens for the individual patient.

The CHA_2DS_2-VASc score is mainly used to guide anticoagulant treatment decisions, but despite this it has never been specifically validated for its ability to predict the events that are mainly prevented by such treatment, that is, cardioembolic stroke. This is somewhat intriguing, since several components in the score are associated with ischaemic strokes of non-cardioembolic origin. Nonetheless, pooled data from cross-sectional studies found a prevalence of left atrial appendage thrombus of 10% in patients with non-valvular atrial fibrillation, the presence of which was associated with age, female sex, hypertension, diabetes mellitus, and chronic heart failure, all components from the CHA_2DS_2-VASc score.[303] Further comprehensive prospective validation of the CHA_2DS_2-VASc score with consideration of ischaemic stroke subtypes may be warranted to verify that these observations also translate into future risk of actual cardioembolic stroke. Alternatively, a novel risk score incorporating risk components that have been validated for and are more specific for predicting cardioembolic stroke would perhaps be a more appropriate tool to guide anticoagulant treatment.

In short, there is an absence of randomised evidence for choice of antithrombotic agent in patients with low CHA_2DS_2-VASc scores, who balance on the edge of benefit from antithrombotic treatment. Exploring the distribution of ischaemic stroke subtypes across the CHA_2DS_2-VASc components would provide a more solid evidence-base for choosing one agent over another for use in such patients.

6.3. MAKING USE OF ADDITIONAL PROGNOSTIC FACTORS

Unsurprisingly, factors prognostic for stroke in atrial fibrillation are not confined to components of the CHA_2DS_2-VASc score, as highlighted in this review of additional risk predictors for stroke in atrial fibrillation. There are several additional factors to choose from when assessing a patient's risk of stroke following a diagnosis of atrial fibrillation. Potential promising candidates for refinement of stroke risk stratification include atrial fibrillation subtype, atrium electromechanical interval, chronic kidney disease, history of a gout attack, psoriasis, lifestyle factors including BMI, alcohol intake, and smoking, and biomarkers such as cardiac troponin and N-terminal pro-B-type natriuretic peptide. One approach would be to incorporate one or more of these additional components into the CHA_2DS_2-VASc score, either by adding extra components to the score, or substituting existing components with others with more clinical relevance. Importantly, though, the usefulness of many of these reported factors need confirmation in other studies, as most have been investigated only in a single population. Many of the presented studies therefore act mainly as preliminary reports that may serve as inspiration for future studies. Also, some prognostic factors were investigated in cohorts consisting solely of anticoagulated patients, and such results cannot automatically be extrapolated to non-anticoagulated cohorts. Many of the suggested additional factors frequently coexist. For example, people who drink excessively are often also smokers. Hence, inclusion of both smoking and alcohol habits would require additional analyses to establish whether they both contribute with valuable risk stratification independent of each other. Optimally, a study investigating the combined impact of all the 'novel' prognostic factors identified in this review would shed light on which additional variables would provide the biggest gain in the ability to risk stratify patients with atrial fibrillation according to future stroke risk.

CHA_2DS_2-VASc 2.0?

As illustrated in this review, there are many additional factors to take into consideration when aiming to risk stratify patients with atrial fibrillation. These could be used to refine the CHA_2DS_2-VASc score while preserving the widely adopted acronym.

Female sex is a component in the CHA_2DS_2-VASc score, but in current European guidelines, recommendations for anticoagulant therapy are similar for men and women, since anticoagulant treatment is not indicated in women with female sex

as their only risk factor (see Table 2). Effectively so, female sex does not inform treatment decisions regarding initiation of oral anticoagulation according to current European guidelines. The above review of the literature aiming to refine the CHA_2DS_2-VASc score identified two obvious potential candidates for replacing the female sex category component (Sc), which would also preserve the well-known and widely adopted acronym. The first is chronic kidney disease, as defined by creatinine clearance <60mL/min, which could be included as Serum creatinine.[88,175,304] Another option is adding information about a patient's smoking habits (Smoking category), for example in a tripartite manner as never, former, and current.[198] Both have been repeatedly investigated for their association with stroke in atrial fibrillation beyond CHA_2DS_2-VASc, and they are easily obtainable patient characteristics obtained during most routine clinical examinations. They are both likely to be superior to female sex in providing clinically relevant stroke risk stratification in patients with atrial fibrillation.

Another issue is the lack of uniform calibration across populations that may not be resolved by adding one or two additional variables. Observed event rates especially in the intermediate risk categories vary substantially depending on study setting. This may pertain in part to the simplicity of the CHA_2DS_2-VASc score, which includes mainly dichotomised components and does not include some other well-known stroke risk factors. Refining the CHA_2DS_2-VASc score within its own boundaries by breaking down the existing components into sub-categories would be one approach to improve the accuracy of the predicted absolute risk for the individual patient. As illustrated in this review, no convincing evidence exists for subdividing patients with heart failure.[305] Results from studies subdividing patients with diabetes mellitus are more promising, for example by duration of disease or level of glycaemic control. Also, using an age cut-off of 65 years as treatment threshold as in the CHA_2DS_2-VASc score has been challenged by data from an Asian population. Whether refinement of the age categorisations will provide clinically useful refinement to risk stratification also in Western civilisations merits further investigation.

Adding additional factors to or subdividing existing components of the CHA_2DS_2-VASc score will inevitably increase the complexity of the model. However, at present there are applications for mobile devices that can calculate the CHA_2DS_2-VASc score and the associated stroke risk in its current form. Refinement by subdividing the individual components of the score may provide more comprehensive and accurate risk predictions, and such a mobile device application could be easily extended with such detailed data, which would help limit the negative impact of the inevitable increase in model complexity. This may curtail scepticism regarding miscalibration and improve the clinical credibility and utility by providing more accurate risk calculations, while preserving the widely adopted CHA_2DS_2-VASc acronym.[284]

Developing an alternative model

A third and more drastic change of approach would be to abandon the CHA_2DS_2-VASc score, and replace it with a more complex risk score incorporating a mixture of comorbidities, biomarkers, and genetic factors, which have been validated specifically for their association with cardioembolic stroke. This would allow for a more tailored treatment approach that would rely on more accurately predicted risks for the individual patient.[306] Such a novel score could potentially identify a larger group of patients who could be safely left without antithrombotic treatment, which would temper the very inclusive approach that is provided within the current CHA_2DS_2-VASc framework. Indeed, this review demonstrates that several other factors beyond those included in the CHA_2DS_2-VASc score may serve as useful prognostic factors for stroke in atrial fibrillation. The first stroke risk model incorporating biomarkers was recently introduced, the ABC score, which includes age, biomarkers, and prior stroke, which was shown to outperform the CHA_2DS_2-VASc score when evaluated by C statistics.[307] However, future external validation studies will establish whether this score will also improve decision-making regarding antithrombotic treatment in atrial fibrillation.

Some guideline recommendations for antithrombotic treatment differ for men and women, recommendations that are based on the overall higher risk of stroke observed in women compared with men. However, several studies also report on patient characteristics that do not provide similar prognostic stroke information in men and women, including body mass index, alcohol intake and renal disease.[186,187,308] One way to accommodate these differences would be to develop sex-specific stroke risk stratification models.[309]

To retain, refine, or revolutionise?

Would the introduction of a more complex risk score, either by a refined CHA_2DS_2-VASc score or by introducing a new model, which could provide more reliable calibration, improve appropriate use of antithrombotic treatment in atrial fibrillation? It would likely increase the chances of convincing the scientific community to compose more uniform guideline recommendations, but would it also improve guideline adherence? Perhaps, but it is important to remember that even the currently recommended relatively simple approaches to stroke prevention based on the CHA_2DS_2-VASc score are not echoed in clinical practice.[310–313] Not only are anticoagulants not prescribed to patients with a established indication, they are also inappropriately prescribed to patients who are recommended no therapy by guidelines.[314] This could be an argument in favour of simply retaining risk stratification strategies to be performed using the CHA_2DS_2-VASc score, which physicians with time are likely to become increasingly familiar with. Indeed, it may turn out that the optimal approach to stroke prevention in atrial fibrillation is offering anticoagulation to men and women with CHA_2DS_2-VASc scores of ≥1 and ≥2, respectively. If so, the factors identified in the present review could form the basis for a toolbox, which could be used to 'reproach' patients who

initially refuse anticoagulation. This could help minimise the current gap between guideline recommendations and real-world usage.[313,314]

6.4. ALTERNATIVE WAYS TO MOVE FORWARD

Non-pharmacological approaches to stroke prevention have also been introduced, e.g., the Watchman device, which mechanically seals of the left atrial appendage, the main source of atrial thrombi.[315] This strategy has proven to be non-inferior to warfarin for stroke prevention.[316] However, its long-term effectiveness also with respect to device-related thrombus remains to be established,[317,318] and concerns have been raised about whether all thromboembolisms related to atrial fibrillation originate from the left atrial appendage.[319] Nonetheless, the Watchman device may prove to be an attractive alternative option for selected patients (and physicians!), who place great emphasis on bleeding risk.

One principal step towards resolving the disagreements of which antithrombotic agent (if any) should be offered to patients with a CHA_2DS_2-VASc score of 1 would be to conduct a series of randomised trials in patients with different factors contributing to their score of 1. In the United States, this could be done while adhering to current guideline recommendations, since they at present leave it to the physician and patient to choose between no treatment, aspirin, or anticoagulation. This would curtail the risk of confounding by indication, which real-world comparative effectiveness studies are inevitably prone to.[320] Nonetheless, such randomised trials are not on the horizon,[321] and observational 'net clinical benefit' comparative effectiveness research across various risk score categories are likely to retain an important role in the future directions for stroke prevention in atrial fibrillation.[70,72,322–329]

Guiding antithrombotic treatment using the CHA_2DS_2-VASc score surely has some limitations. Notwithstanding these imperfections, it is worth noting that no other available risk score has been demonstrated to convincingly outperform the CHA_2DS_2-VASc score. Whether the CHA_2DS_2-VASc score will be the preferred decision tool also in the future is uncertain. It is highly likely that anticoagulating the vast majority of patients with atrial fibrillation as defined by CHA_2DS_2-VASc indeed is a feasible approach. However, feasible does not necessarily mean optimal, and it is also likely that refined risk prediction models may entail more comprehensive risk stratification, which will allow for a more accurate and individualised approach to antithrombotic treatment. Future evidence will eventually revoke or justify the current approach.

CHAPTER 7. CONCLUDING REMARKS

Stroke risk stratification in patients with atrial fibrillation anno 2016 is mainly based on the CHA_2DS_2-VASc score, which is a simple and widely adopted risk stratification tool used to guide decisions about lifelong antithrombotic treatment. It provides a simple approach to stroke risk stratification that has several advantages as well as some important drawbacks, including simplicity and miscalibration, which is also reflected by conflicting guideline recommendations on use of the score. Despite some important drawbacks, the CHA_2DS_2-VASc score currently remains the preferred tool for risk stratification, mainly because there are no convincingly better tools available. Hence, stroke risk stratification strategies are likely to attract substantial attention especially in the near future. Potential avenues for improvement include adding novel prognostic markers as identified in the current review, including various electro- and echocardiographic features, additional comorbid conditions, lifestyle related factors, or biomarkers. Also, several studies have indicated that breaking down the existing CHA_2DS_2-VASc components may contribute to more exhaustive stroke risk stratification in patients with atrial fibrillation. In turn, the development of refined prognostic models could perhaps optimise our decision-making regarding antithrombotic treatment in patients with atrial fibrillation.

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APPENDICES

Appendix A. Paper 1

Appendix B. Paper 2

Appendix C. Paper 3

Appendix D. Paper 4

APPENDIX A. PAPER 1

CLINICAL RESEARCH STUDY

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Body Mass Index and Adverse Events in Patients with Incident Atrial Fibrillation

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ABSTRACT

BACKGROUND: Obesity is associated with the development of atrial fibrillation and may impact atrial fibrillation-related outcomes. To date, no anthropometric measure is included in any risk stratification scheme for stroke and death in atrial fibrillation patients.

METHODS: The prospective Danish Diet, Cancer and Health study is a cohort including 57,053 participants (27,178 men and 29,875 women) aged between 50 and 64 years. The study population for this study included the 3135 patients (2025 men and 1110 women) who developed incident atrial fibrillation during follow-up.

RESULTS: Of the subjects with atrial fibrillation, 1414 (45%) had a body mass index (BMI) in the overweight category (BMI 25 to <30 kg/m^2) and 767 (24%) were categorized as obese (BMI ≥ 30 kg/m^2). During a median follow-up of 4.9 years, 609 deaths and 216 thromboembolic events (98% ischemic strokes) occurred. Using normal-weight patients as reference, the risk of a composite end point of "ischemic stroke, thromboembolism, or death" was significantly higher in overweight (crude hazard ratio [HR] 1.31; 95% confidence interval [CI], 1.09-1.56) and obese patients (crude HR 1.55; 95% CI 1.27-1.90). After adjustment for $CHADS_2$ and CHA_2DS_2-VASc scores, the HRs for the composite end point were 1.21 (95% CI 1.02-1.45) and 1.31 (95% CI 1.10-1.56), respectively, for overweight and 1.25 (95% CI 1.03-1.53) and 1.36 (95% CI 1.11-1.65), respectively, for obese. Continuous analyses of BMI stratified by sex identified obese men and normal-weight women as the sex-specific "high-risk" categories.

CONCLUSION: Overweight and obesity are risk factors for "ischemic stroke, thromboembolism or death" in patients with atrial fibrillation, even after adjustment for $CHADS_2$ and CHA_2DS_2-VASc scores. The association between BMI and outcomes among atrial fibrillation patients may be modified by sex.

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KEYWORDS: Atrial fibrillation; Body mass index; Death; Obesity; Stroke; Thromboembolism

Atrial fibrillation is the most common sustained cardiac rhythm disorder. It affects 1%-1.5% of the population in the developed world,[1,2] and the prevalence is expected to increase due to an aging population and an increase in the prevalence of established risk factors for incident atrial fibrillation, for example, diabetes mellitus.[3] Atrial fibrillation entails a substantial risk of mortality and morbidity from often-fatal stroke and thromboembolism.[4,5] Furthermore, health care costs related to atrial fibrillation are increasing.[6]

The risk of stroke in atrial fibrillation is not homogeneous. Several well-established risk factors[7,8] have been used to formulate stroke risk-stratification schema, such as

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Authorship: All authors had access to the data and had a role in writing of the manuscript.

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the Cardiac failure, Hypertension, Age ≥75, Diabetes, Stroke [Doubled] ($CHADS_2$) score.[9] A refinement of the $CHADS_2$ score has since been introduced, the CHA_2DS_2-VASc score, which gives extra weight to age ≥75 years [doubled], and includes vascular disease, age 65-74 years, and female sex as risk factors.[10] Thus far, no anthropometric variable has been included in any clinical risk stratification schema for stroke in atrial fibrillation.

Obesity has reached pandemic proportions,[11] and body mass index (BMI), a proxy measure of obesity, is associated with higher overall mortality[12,13] and a higher risk of, especially, ischemic stroke.[14] In recent years, obesity has been established repeatedly as an independent predictor of incident atrial fibrillation,[15-18] including in the present cohort.[19] Despite the overwhelming amount of research linking obesity and the *development* of atrial fibrillation, the *prognostic impact* of obesity on outcomes among atrial fibrillation patients is sparsely investigated, and the studies thus far have revealed inconsistent results.[20-23]

As obesity often coexists with established risk factors for ischemic stroke among atrial fibrillation patients as well as the general population, we hypothesized that obesity would be associated with the risk of stroke and death among patients with atrial fibrillation. To test this hypothesis, we analyzed data from a large Danish prospective cohort—the Diet, Cancer and Health study—to assess the risk of ischemic stroke, thromboembolism, and death according to BMI among patients with incident atrial fibrillation.

CLINICAL SIGNIFICANCE

- Obesity and atrial fibrillation are common and often coexist, but the prognostic impact of obesity on outcomes among patients with atrial fibrillation is sparsely investigated.
- Several risk stratification schemes useful for predicting stroke and death among atrial fibrillation patients exist, but none include anthropometric measures.
- Overweight and obese represent "high-risk" atrial fibrillation patients, even after adjustments for $CHADS_2$ and CHA_2DS_2-VASc, but the associations are modified by sex.

METHODS

The Diet, Cancer and Health study cohort was established between 1993 and 1997. The study design has been reported in detail elsewhere.[24] The primary objective of this prospective study was to investigate the etiologic role of diet and lifestyle in the development of cancer, and 57,053 participants were enrolled (27,178 men and 29,875 women). The study participants were aged between 50 and 64 years and without a cancer diagnosis registered in the Danish Cancer Registry[25] at entry into the Diet, Cancer and Health cohort. Participants were, for this study, followed from time of first diagnosis of atrial fibrillation (not earlier than January 1995) until December 2009.

The cohort subjects were linked to the National Patient Register[25] using a unique, national identification number, which is part of the personal information stored in the Civil Registration System. Exclusion criteria are listed in **Figure 1**. Codes from the International Classification of Diseases (ICD-10) were used to extract hospital discharge admissions for atrial fibrillation. Atrial fibrillation and atrial flutter have one ICD-10 code (I48). Therefore, a small number of atrial flutter cases also would have been included.

Exposure Variable

The exposure variable studied was BMI. Anthropometric data were collected at the time of entry into the Diet, Cancer and Health cohort by trained laboratory technicians. Height

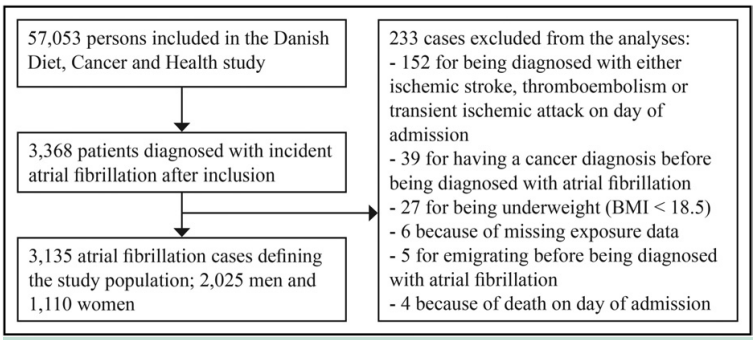

Figure 1 Flow diagram of how the study population was arrived at.

was measured without shoes and recorded to the nearest centimeter. Weight was measured by a digital scale with participants wearing either light clothing or underwear, and was recorded to the nearest 100 grams. BMI (kg/m^2) was categorized according to World Health Organization guidelines into the following groups: normal weight 18.5 to <25, overweight 25 to <30, and obesity ≥30. We excluded underweight subjects (n = 27) and cohort participants for whom anthropometric data were missing.

Comorbid Variables

To determine the different comorbid variables, a method used by Olesen et al,[26] who validated the $CHADS_2$ and CHA_2DS_2-VASc schemes in a large atrial fibrillation cohort using register-based data, was adapted. A history of congestive heart failure was defined as having a previous diagnosis of heart failure in the National Patient Register and treatment with a loop diuretic. Patients with hypertension were defined as so, if they were treated with at least 2 of the following antihypertensive medicaments: α-adrenergic blockers, nonloop diuretics, vasodilators, beta-blockers, calcium channel blockers, and renin-angiotensin system inhibitors. Confirmation of a diagnosis of previous ischemic stroke, thromboembolism, or transient ischemic attack; previous diagnosis of vascular disease, meaning a diagnosis of peripheral artery disease; previous myocardial infarction, or aortic plaque, was retrieved from the National Patient Register. A diagnosis of diabetes was obtained from either self-reported data, data from the National Patient Register, the National Diabetes Register,[25] or use of a glucose-lowering drug.

Medical treatment status was obtained by evaluating the prescription pattern obtained from the Danish National Prescription Registry, which was used to model vitamin K antagonist (VKA) treatment as a time-varying covariate.[27] ICD codes and Anatomical Therapeutic Chemical drug codes used for determining the comorbid variables are available in Supplemental Table 1, online.

Outcomes

We defined our primary outcome as the composite of "ischemic stroke, thromboembolism, or death" during follow-up. Secondary analyses were performed for the components of the primary composite end point, that is, "ischemic stroke or thromboembolism," and "death." Information on emigration and death was available from the National Civil Registration System, and occurrences of ischemic stroke using ICD-10 (I63.0-I63.9, I64.9) and arterial thromboembolism using ICD-10 (I74.0-I74.9) were found in the National Patient Register.

Statistical Methods

To describe the distribution at baseline (ie, at time of atrial fibrillation diagnosis) for the covariates, we used descriptive analysis with proportions for discrete covariates and medians with 10th and 90th percentiles for continuous covariates. Incidence rates (per 100 person-years) for the various outcomes were calculated for each exposure group. Cox proportional hazards models were used to estimate the hazard rate ratio for the end point using normal-weight BMI category as reference. In all analyses, VKA treatment was considered a confounder and thus, controlled for. Data were analyzed as crude (ie, adjusted for VKA treatment only), and adjusted for both VKA treatment and stroke risk-stratification scores ($CHADS_2$ and CHA_2DS_2-VASc). VKA treatment was modeled as a time-varying covariate. The association of BMI considered as a continuous variable was analyzed using fractional polynomials; again all analyses were adjusted for VKA treatment, but stratified by sex, as men and women might have a high BMI due to different body compositions. A P-value <.05 was considered as statistically significant. Data were analyzed using Stata 12 (StataCorp LP, College Station, Tex).

RESULTS

Of 57,053 subjects in the cohort, we identified 3368 patients with incident atrial fibrillation during follow-up. Of those, 233 were excluded from the final analysis, leaving a study population of 3135 incident atrial fibrillation cases (**Figure 1**).

Clinical characteristics of the study population, in total and according to BMI, are shown in Table 1. The mean age was 66.9 years, and 35% were female. Of this cohort, 1414 (45.1%) subjects met the BMI criteria for overweight (25 to <30 kg/m^2) and 767 (24.5%) subjects met the BMI criteria for obesity (≥30 kg/m^2). The prevalence of congestive heart failure, hypertension, diabetes, and myocardial infarction increased with higher BMI category from normal weight to overweight to obese, with the highest prevalence among subjects with BMI ≥30 (**Table 1**). Obese BMI subjects were treated most frequently with VKA. Clinical characteristics for men and women separately are available in Supplemental Table 2, online.

During the 17,243 person-years of follow-up (median 4.9 years), 609 (19.4%) patients died and 216 (6.9%) had an ischemic stroke or thromboembolism. Crude incidence rates for the entire cohort and men and women separately are shown in **Table 2**.

Hazard ratios (HR) using normal-weight patients as reference after 1-year follow up and after full follow-up are shown in **Table 3**. At full follow-up, crude HRs for the BMI categories overweight and obese were both higher for the composite endpoint (HR 1.31; 95% confidence interval [CI], 1.09-1.56, and HR 1.55; 95% CI, 1.27-1.90, respectively), and attenuated but remained significant after adjusting for $CHADS_2$ and CHA_2DS_2-VASc scores. These HRs were largely driven by a difference in mortality.

Fractional polynomials of the association between BMI and the composite end point at full follow-up for men and women separately are shown in **Figure 2**. Crude analysis, that is, adjusted for VKA treatment, of BMI resulted in a J-shaped curve for men. The lowest risk was observed for BMI around 23 kg/m^2. When adjusted for $CHADS_2$ and

Table 1 Clinical Characteristics of 3135 Incident Atrial Fibrillation Cases According to Body Mass Index (kg/m^2)

		Body Mass Index		
	Entire Cohort	18.5 to <25	25 to <30	≥30
Subjects, n	3135 (100.0%)	954 (30.4%)	1414 (45.1%)	767 (24.5%)
Age, years	67.0	67.2	67.0	66.9
Median (10%; 90%)	(59.3; 74.2)	(59.5; 74.4)	(59.5; 74.3)	(58.7; 73.5)
Age ≥75 years (%)	7.5	8.6	8.1	4.7
Age 65-74 years (%)	56.0	56.2	55.9	55.9
Years of follow-up, median (10%; 90%)	4.8 (1.0; 11.1)	4.7 (0.8; 10.8)	4.9 (1.0; 11.4)	5.0 (1.1; 11.1)
Female sex (%)	35.4	47.4	26.2	37.6
Body mass index, median (10%; 90%)	26.8 (22.3; 33.5)	23.2 (20.5; 24.6)	27.1 (25.4; 29.3)	32.5 (30.4; 39.1)
Congestive heart failure (%)	7.2	4.7	6.4	11.6
Hypertension (%)	28.9	20.1	28.5	40.4
Diabetes (%)	14.3	6.9	12.9	26.0
Previous (%)				
Transient ischemic attack	3.2	3.8	3.0	2.9
Thromboembolism	0.5	0.4	0.5	0.8
Ischemic stroke	6.2	5.9	5.8	7.4
Peripheral artery disease (%)	3.8	3.3	3.8	4.6
Previous MI (%)	10.9	7.6	11.8	13.3
Aortic plaque (%)	0.4	0.2	0.6	0.3
VKA treated (%)	21.8	18.6	22.8	24.4
$CHADS_2 = 0$ (%)	54.2	63.2	55.8	40.2
CHA_2DS_2-VASc = 0 (%)	15.8	14.1	18.8	12.3

MI = myocardial infarction; VKA = vitamin K antagonist.
Congestive heart failure covers both heart failure and left ventricular dysfunction.

CHA_2DS_2-VASc scores, the association attenuated slightly, but the J-shape remained. Among women, BMI showed a U-shaped relationship, with those with a BMI around 26 kg/m^2 carrying the lowest risk. When adjusted for $CHADS_2$ and CHA_2DS_2-VASc scores, the positive association for large BMI and the composite end point disappeared, whereas the positive association for normal-weight women persisted.

Table 2 Hazard Ratios (95% CI) for Ischemic Stroke, Thromboembolism, or Death among 3135 Subjects after Incident Atrial Fibrillation

	1-Year Follow-up			Full Follow-up*		
Entire Cohort	Crude	Adjustment 1	Adjustment 2	Crude	Adjustment 1	Adjustment 2
Ischemic stroke, TE or death						
BMI 18.5 to <25	1	1	1	1	1	1
BMI 25 to <30	1.33 (1.09-1.74)†	1.25 (0.95-1.64)	1.34 (1.02-1.76)†	1.31 (1.09-1.56)†	1.21 (1.02-1.45)†	1.31 (1.10-1.56)†
BMI ≥30	1.44 (1.05-1.96)†	1.19 (0.87-1.63)	1.27 (0.93-1.73)	1.55 (1.27-1.90)†	1.25 (1.03-1.53)†	1.36 (1.11-1.65)†
Ischemic stroke or TE						
BMI 18.5 to <25	1	1	1	1	1	1
BMI 25 to <30	1.39 (0.79-2.46)	1.25 (0.71-2.21)	1.40 (0.79-2.47)	1.15 (0.84-1.59)	1.06 (0.77-1.46)	1.14 (0.83-1.57)
BMI ≥30	1.66 (0.88-3.10)	1.20 (0.64-2.24)	0.93 (0.58-1.47)	1.16 (0.80-1.68)	0.91 (0.63-1.33)	0.98 (0.67-1.42)
Death						
BMI 18.5 to <25	1	1	1	1	1	1
BMI 25 to <30	1.29 (0.95-1.76)	1.24 (0.91-1.68)	1.32 (0.97-1.78)	1.30 (1.06-1.59)†	1.20 (0.99-1.47)	1.31 (1.07-1.59)†
BMI ≥30	1.39 (0.98-1.97)	1.21 (0.85-1.72)	1.26 (0.89-1.79)	1.60 (1.29-2.00)†	1.31 (1.05-1.63)†	1.41 (1.13-1.75)†

BMI = body mass index (kg/m^2); CI = confidence interval; TE = thromboembolism.
Crude: With time from atrial fibrillation diagnosis as time axis and adjusted for VKA treatment.
*Median follow-up 4.9 years.
†Indicates $P < .05$.

Adjustment 1: Same as crude + adjusted for $CHADS_2$ score.
Adjustment 2: Same as crude + adjusted for CHA_2DS_2-VASc score.

Table 3 Incidence Rates per 100 Person-years (95% CI) for 3135 Patients with Incident Atrial Fibrillation According to Body Mass Index

	Body Mass Index(kg/m^2)		
	18.5 to <25	25 to <30	≥30
Entire cohort (n = 3135)			
1-year follow-up			
Ischemic stroke, TE or death	9.16 (7.38-11.38)	10.90 (9.25-12.84)	11.21 (9.00-13.96)
Ischemic stroke or TE	2.01 (1.26-3.19)	2.74 (1.98-3.80)	3.22 (2.14-4.85)
Death	7.39 (5.82-9.39)	8.33 (6.92-10.04)	8.39 (6.53-10.79)
Full follow-up*			
Ischemic stroke, TE or death	4.50 (3.91-5.18)	5.38 (4.84-5.97)	6.22 (5.44-7.11)
Ischemic stroke or TE	1.41 (1.09-1.81)	1.57 (1.29-1.91)	1.67 (1.20-2.05)
Death	3.51 (3.00-4.10)	4.07 (3.62-4.57)	4.90 (4.22-5.68)
Men (n = 2025)			
1-year follow-up			
Ischemic stroke, TE or death	9.60 (7.16-12.85)	11.72 (9.74-14.09)	12.65 (9.73-16.43)
Ischemic stroke or TE	2.35 (1.30-4.24)	2.70 (1.84-3.96)	4.06 (2.56-6.45)
Death	7.56 (5.45-10.48)	9.19 (4.48-11.30)	9.06 (6.67-12.30)
Full follow-up†			
Ischemic stroke, TE or death	4.98 (4.13-6.02)	5.73 (5.09-6.44)	6.97 (5.94-8.18)
Ischemic stroke or TE	1.52 (1.08-2.14)	1.66 (1.33-2.07)	1.62 (1.16-2.25)
Death	3.96 (3.21-4.87)	4.29 (3.76-4.90)	5.69 (4.79-6.77)
Women (n = 1110)			
1-year follow-up			
Ischemic stroke, TE or death	8.68 (6.29-11.99)	8.64 (6.04-12.36)	8.86 (5.94-13.22)
Ischemic stroke or TE	1.64 (0.78-3.45)	2.88 (1.55-5.35)	1.85 (0.77-4.44)
Death	7.20 (5.06-10.24)	5.95 (3.88-9.13)	7.31 (4.72-11.33)
Full follow-up‡			
Ischemic stroke, TE or death	4.00 (3.23-4.95)	4.37 (3.48-5.50)	4.95 (3.86-6.33)
Ischemic stroke or TE	1.29 (0.88-1.87)	1.32 (0.87-2.00)	1.49 (0.95-2.34)
Death	3.04 (2.39-3.87)	3.40 (2.64-4.39)	3.56 (2.69-4.73)

CI = confidence interval; TE = thromboembolism.
*Median 4.9 years.
†Median 4.9 years.
‡Median 4.7 years.

DISCUSSION

In this large prospective cohort, we have demonstrated that both overweight and obesity, according to BMI, are associated with a significantly higher short- and long-term risk of the composite end point of "ischemic stroke, thromboembolism, or death" among atrial fibrillation patients. The association attenuated but remained significant at full follow-up, even after controlling for $CHADS_2$ and CHA_2DS_2-VASc scores, and was driven primarily by a difference in mortality. Our hypothesis of obese atrial fibrillation patients representing a high-risk category was hereby confirmed, although this association was influenced by sex.

Strengths and Limitations

The Diet, Cancer and Health study population is a selected population in which only about 35% of those invited agreed to participate, and only an unknown proportion of participants with atrial fibrillation was identified, that is, we relied on hospital discharge diagnoses. It is, however, unlikely that the association between BMI and ischemic stroke or death is systematically different between identified and nonidentified participants with atrial fibrillation. The participants were followed in national registries with very limited loss to follow-up. The study is therefore most likely not subject to selection bias. Validation studies indicated a positive predictive value of more than 92% for atrial fibrillation diagnoses.[19,28] Changes in BMI may have occurred during follow-up, and this was not taken into account, but BMI tends to be fairly stable over time, especially in older adults.[29,30] Follow-up for vital status was almost complete, and the predictive value for stroke diagnoses is more than 80% and most likely not associated with anthropometric measures obtained at entry into the Diet, Cancer and Health cohort. Information bias is thus not a likely explanation of the study results.

In the crude analyses, only VKA treatment was taken into account. The time axis was time from the diagnosis of atrial fibrillation and thus, closely controlled for. We did not differentiate between subtypes of atrial fibrillation, but current strategies for consideration of oral anticoagulation are

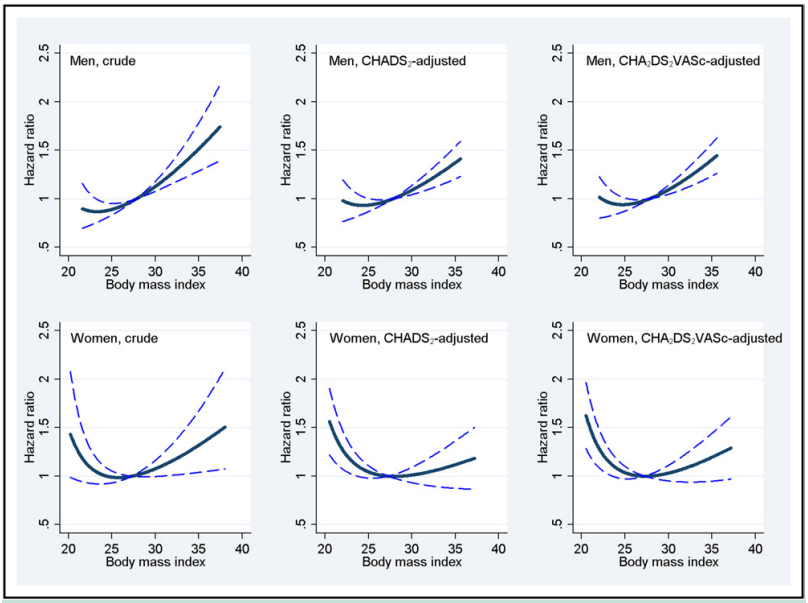

Figure 2 Body mass index and the risk of ischemic stroke, thromboembolism, or death among men (top row) and women (bottom row) at full follow-up.
Fractional polynomials of the 5th to 95th percentile of body mass index. Dashed lines indicate 95% confidence intervals. All analyses adjusted for vitamin K antagonist treatment.

irrespective of atrial fibrillation subtype.[31] As we focused on a possible added value compared with use of traditional risk scores, $CHADS_2$ and CHA_2DS_2-VASc scores also were controlled for in multivariate analyses. Anthropometry also is most likely associated with other lifestyle risk factors for ischemic stroke, thromboembolism, and death. These risk factors would have been potential confounders if the aim had been to specify the independent association for anthropometry, but not in this study concerning a possible added value to the risk scores. Confounding by other known stroke risk factors is thus not an issue of concern.

The impact of obesity on atrial fibrillation outcomes is sparsely investigated, and our study is the first to investigate this matter prospectively in a population-based cohort. A cross-sectional study by Novo et al[23] found no association between obesity and risk of thromboembolic events in a study of 480 atrial fibrillation patients where 26.6% suffered a thromboembolic event. Interestingly, a prospective study by Badheka et al[20] investigated the effect of BMI on mortality among atrial fibrillation patients using data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) randomized trial cohort. After a mean follow-up of 3 years, they found that being overweight or obese was associated with a significantly lower risk of all-cause mortality, and concluded that an obesity paradox might exist among atrial fibrillation patients. As they focused on the actual effect of body mass index, this is a different biological scenario and their study is not directly comparable to the present analysis with focus on risk-prediction models. Nonetheless, the lack of a positive association regarding mortality found in the mentioned study remains conspicuous, but only 62% of the participants in the AFFIRM cohort had information about BMI, and this may have influenced the results. Of note, another study investigated the effect of BMI on outcomes among atrial fibrillation patients using the exact same AFFIRM dataset, which yielded slightly different results due to differences in the multivariate analyses.[21,32]

Several other studies support our findings of obesity being associated with a worse prognosis among atrial fibrillation patients. Obesity among atrial fibrillation patients has been associated with increased risk of progression from paroxysmal to permanent atrial fibrillation,[33] an increased rate of recurrence of atrial fibrillation,[34] a higher prevalence of a left atrial/left atrial appendage thrombus,[22] and to be an independent predictor of procedural failure after catheter ablation.[35] Furthermore, obesity has been associated with a "prothrombotic state," meaning a higher presence of thrombotic cofactors.[36] Also, obese atrial fibrillation patients have a higher number of follow-up visits compared with normal-weight patients.[34]

The observed higher risk among overweight and obese atrial fibrillation patients in our study may partly be due to unhealthy lifestyle and unmeasured comorbidity not encompassed in the $CHADS_2$ and CHA_2DS_2-VASc-scores, and not weight status per se. For example, obstructive sleep

apnea, a condition related to obesity, also has been associated with a higher risk of stroke.[37]

To our knowledge, our study is the first to demonstrate a positive association between weight status and adverse outcomes among atrial fibrillation patients. It is important to keep in mind that the other similar larger-scale studies found no such positive association.[20,21] Further studies are needed to clarify this. Importantly, our study does not provide evidence that weight loss will improve the prognosis among overweight and obese atrial fibrillation patients.

Our analysis further reveals that a high BMI seems to be worse for men than for women, whereas normal-weight women appeared to be at highest risk. The reason for this intriguing finding is unknown, but could be due to differences in body composition between men and women. Further investigations with focus on different anthropometric measures such as waist and hip circumference are necessary to clarify this. Because our cohort was predominantly white and relatively young (median age 67.0 years), further studies investigating different ethnicities and older atrial fibrillation populations are needed. Also, as we excluded the few subjects with a BMI <18.5, the impact of being underweight is unknown.

Clinical Implications

This study shows that even after risk scoring a patient with either $CHADS_2$ or CHA_2DS_2-VASc, overweight and obese patients still represent "high-risk" categories. We have chosen a composite end point including the main outcomes that are affected by intervention, that is, oral anticoagulation therapy significantly reduces stroke/thromboembolism (by 64%) and death (by 26%), compared with placebo/control in patients with atrial fibrillation.[38] Importantly, some deaths in our study are likely to be due to undiagnosed stroke due to the register-based nature of the dataset. Further, the $CHADS_2$ and CHA_2DS_2-VASc are useful for predicting both stroke and death in atrial fibrillation patients.[39,40] Proper risk prediction calculations such as C-statistics and net reclassification improvement should be undertaken when the associations between obesity and stroke and death among atrial fibrillation patients have been repeatedly established. If so, BMI might play a future role in improving risk-prediction models for stroke and death among patients with atrial fibrillation by means of sex-specific alternative BMI categorizations.

In conclusion, this study shows that overweight and obese patients with atrial fibrillation represent a "high-risk" population, even after adjustments for $CHADS_2$ and CHA_2DS_2-VASc scores. The association between BMI and adverse outcomes among patients with atrial fibrillation may be modified by sex.

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APPENDIX B. PAPER 2

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ORIGINAL ARTICLE

Alcohol intake and prognosis of atrial fibrillation

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ABSTRACT

Objective To assess alcohol intake as a risk factor for adverse events among patients with incident atrial fibrillation (AF).

Design Prospective cohort study.

Setting Population based cohort study and nationwide Danish registries.

Patients The Danish Diet, Cancer and Health study included 57 053 participants (27 178 men and 29 875 women) aged between 50 and 64 years. The study population for this study included the 3107 participants (1999 men, 1108 women) who developed incident AF after inclusion.

Main outcome measures A composite of thromboembolism or death.

Results During a median follow-up of 4.9 years 608 deaths and 211 thromboembolic events occurred. Of those who developed AF, 690 (35%) men and 233 (21%) women had a high intake of alcohol (>20 drinks/week for men and >13 drinks/week for women). After adjustment for use of oral anticoagulation and components of the CHA_2DS_2-VASc score, men with an intake of >27 drinks/week had a higher risk for thromboembolism or death (hazard ratio (HR) 1.33, 95% CI 1.08 to 1.63) than men with an intake of <14 drinks/week. Women with an intake of >20 drinks/week also had a higher risk (HR 1.23, 95% CI 0.78 to 1.96) than women in the low intake category. The higher risk among men was primarily driven by mortality (HR 1.51, 95% CI 1.20 to 1.89), whereas the risk found among women was driven by thromboembolism (HR 1.71, 95% CI 0.81 to 3.60).

Conclusions High alcohol intake predicts thromboembolism or death, even after adjustment for established clinical risk factors, and may help identify high risk AF patients who could be targeted for stroke and cardiovascular prevention strategies.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and is associated with a substantial risk of mortality and morbidity from ischaemic stroke and arterial thromboembolism. A variety of clinical risk stratification schemes aiming to identify high risk patients suitable for oral anticoagulation exist, the most widely used being the $CHADS_2$ and CHA_2DS_2-VASc scores.[1 2]

Alcohol has been estimated to account for 3.8% of all deaths and 4.6% of all diseases and injuries worldwide.[3] The intake of alcohol in light to moderate amounts is, however, associated with a lower risk of cardiovascular as well as all cause mortality, whereas heavier use is associated with a higher risk.[4] The same pattern has been observed with alcohol intake and risk of stroke.[5 6] A recent meta-analysis concluded that moderate to high alcohol intake is associated with a greater risk of developing AF, whereas the impact of light drinking remains uncertain.[7]

Alcohol use or abuse has not been determined as a risk factor for ischaemic stroke and mortality in AF patients. In contrast, alcohol abuse has been considered a contraindication to oral anticoagulation with the vitamin K antagonist (VKA) class of drugs (eg, warfarin), and alcohol intake—even in moderate amounts (eg, from >8 drinks per week)—has been implemented in some clinical risk scores for bleeding risk assessment among AF patients.[8–10]

Previous studies of the association between alcohol intake and adverse events among AF patients have been restricted to dichotomous analyses from randomised trial cohorts,[11 12] or has been limited by few subjects with a heavy intake.[13] Thus, the relationship between the full range of alcohol intake on outcomes has not been investigated prospectively with long term follow-up in a large non-selected AF cohort.

The objective of this study was to assess prospectively the associations of alcohol intake and the long term risk of thromboembolism and death among AF patients, by analysing data from the large Danish Diet, Cancer, and Health cohort study. We hypothesised that the relationship between alcohol intake and the risk of thromboembolic events and death would be either J or U shaped, with the highest risk among heavy users.

METHODS

The Diet, Cancer and Health cohort was established between 1993 and 1997, originally enrolling 57 053 participants (27 178 men and 29 875 women). The study design has been reported in detail elsewhere.[14] Cross linkage between the cohort participants and the National Civil Registration system together with the National Patient Register[15] provided detailed information on incident AF, thromboembolism, and death and specific information about censoring from emigration and death during follow-up.

Incident cases of AF

The cohort subjects were linked to the National Patient Register, dating back to 1977, using the Danish Personal Identification number. This is a

unique and national identification number, which is part of the personal information stored in the Civil Registration System. The study population in the present study included participants who developed incident AF during follow-up.

Codes from the International Classification of Diseases, 10th revision (ICD-10) were used to extract admissions for AF. This includes all patients diagnosed with AF in hospital or ambulatories, but not from general practice. AF and atrial flutter have one common ICD-10 code (I48). Therefore, some atrial flutter cases have been included in the present study.

Alcohol intake and drinking pattern

All participants filled in a detailed semiquantitative food and drink frequency questionnaire at entry and 5 years after entry into the cohort, which has been described and validated previously.[16 17] Exposure data were extracted from the questionnaire closest to but before the first diagnosis of AF. Participants reported detailed information on both frequency of intake and type of alcohol beverages consumed within the last year. The number of standard drinks per week (12 g of ethanol) was calculated on the basis of the assumed alcohol content in the different alcoholic beverages. People who reported no alcohol intake during the last year in both questionnaires were categorised as abstainers. These details were used to generate an exposure variable describing the weekly alcohol intake into five categories for women: abstainers, <7, 7–13, 13–20 and >20 drinks; and five categories for men: abstainers, <14, 14–20, 21–27 and >27 drinks.

Comorbid variables

To determine the different comorbid variables a method used by Olesen *et al*[18] was adapted. ICD codes and ATC (Anatomical Therapeutic Chemical) drug codes used for determining the comorbid variables are available in online web-only table 1.

Outcomes

We defined our primary outcome as the composite of 'thromboembolism or death', with thromboembolism comprising ischaemic stroke and arterial thromboembolism. Secondary analyses were performed for the components of the primary composite end point, that is, 'thromboembolism' and 'death'. Information on emigration or death was available from the National Civil Registration System, and incident cases of ischaemic stroke using ICD-10 (I63.0–I63.9, I64.9) and arterial thromboembolism using ICD-10 (I74.0–I74.9) were found in the National Patient Register.

Statistical methods

Association of reported alcohol intake on risk of event was reported in terms of incidence rates for the weekly intake groups and subsequently analysed by means of Cox proportional regression using time since AF as the underlying time scale. End of study (30 December 2009) or emigration was considered as outcome independent censoring. For the secondary outcome event thromboembolism, death was considered as a censoring event.

All analyses were stratified by sex. The associations are reported as a crude measure of association and after adjustment for the risk factors recommended in current stroke prevention guidelines, essentially the CHA_2DS_2-VASc components.[19–21] The risk factors were derived at time of AF diagnosis and assumed to be constant throughout time at risk. Both crude and adjusted analyses are adjusted for the effect of VKA treatment, incorporated as a time varying covariate. This was possible as all prescriptions handled in Danish pharmacies are reported to a common database. As there is no prior hypothesis on the associations of alcohol exposure in terms of the number of standard drinks per week, the effect was further modelled using a natural cubic spline and presented graphically. Data were analysed using Stata V.12 (Stata Corporation, College Station, Texas, USA). A value of $p<0.05$ was considered statistically significant.

RESULTS

We identified 3366 patients with incident AF during follow-up. Of those, 259 (7.7%) patients were excluded from the final analyses (figure 1), leaving a study population of 3107 cases: 1999 men and 1108 women.

Baseline characteristics according to weekly alcohol intake are presented in table 1 for men and table 2 for women. Men had a median age of 66.5 years, with a median follow-up of 4.9 years, and a median weekly alcohol intake of 12.5 drinks (10th–90th centile, 2.1–40.7) (table 1). Only 43 (2%) males reported being abstainers and 690 (35%) patients had a weekly alcohol intake above the Danish recommended male maximum of 21 drinks per week. Around 25% had a CHA_2DS_2-VASc score of 0.

Women had a median age of 67.8 years, with a median follow-up of 4.7 years and a median weekly alcohol intake of 5.6 drinks per week (10th–90th centile, 0.7–21.7) (table 2). Only 45 (4%) females reported being abstainers and 233 (21%) reported having a weekly alcohol intake above the Danish recommended female maximum of 14 drinks per week. Around 21% had a CHA_2DS_2-VASc score of 1 (women cannot score 0).

Follow-up

During 17 089 person years of follow-up, 608 patients died and 211 had a thromboembolic event. Crude incidence rates for men and women are available in online web-only table 2. Hazard ratios (HRs) at full follow-up are presented in table 3 for men

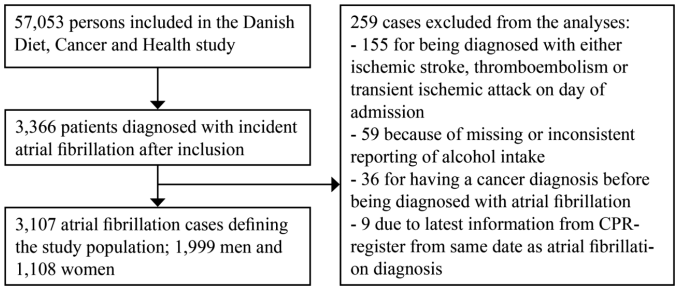

Figure 1 Inclusion of the study population. CPR (unique and national identification number).

Table 1 Clinical characteristics of men according to weekly alcohol intake

	Alcohol intake, drinks* per week					
	All men	**Abstainer**	**<14**	**14–20**	**21–27**	**>27**
Subjects, n	1999	43	1025	241	234	456
Drinks per week (median, (10%; 90%))	12.5 (2.1–40.7)	N/A	6.9 (1.5–11.9)	18.4 (14.9–20.7)	23.8 (21.4–26.3)	38.8 (28.6–64.7)
Years of follow-up (median (10%; 90%))	4.9 (1.0–11.3)	5.3 (1.8–11.5)	5.0 (1.0–11.2)	4.7 (1.0–11.2)	4.9 (0.9–11.6)	4.8 (1.1–11.4)
Age, years (median (10%; 90%))	66.5 (58.8–73.9)	66.8 (60.0–73.3)	66.7 (59.1–74.4)	66.5 (58.8–73.7)	66.5 (58.8–73.8)	66.4 (58.5–73.5)
Age ≥75 years	6.7	4.9	7.7	6.6	6.0	5.0
Age 65–74 years	53.4	62.8	52.7	52.7	54.3	53.9
Heart failure	7.5	11.6	8.1	6.2	5.6	7.2
Hypertension	27.7	20.9	29.1	27.8	25.6	26.1
Diabetes	15.3	18.6	15.0	17.4	11.5	16.4
Previous						
Ischaemic stroke	6.4	7.0	7.0	5.8	6.8	5.0
Transient ischaemic attack	3.0	0.0	3.3	2.6	4.3	2.2
Arterial thromboembolism	0.6	2.3	0.7	0.0	0.0	0.9
Haemorrhagic stroke	1.0	0.0	0.5	1.7	0.9	1.5
Vascular disease						
Previous myocardial infarction	13.3	18.6	15.1	11.6	9.4	11.4
Aortic plaque	0.4	2.3	0.4	0.4	0.0	0.2
Peripheral artery disease	4.6	7.0	3.5	5.0	4.7	6.4
VKA treated	21.7	23.3	21.2	22.8	20.5	22.8
$CHADS_2$ (mean)	0.83	0.81	0.86	0.82	0.74	0.81
0	50.5	44.1	49.3	49.4	57.7	50.4
1	28.0	34.9	28.2	31.1	22.2	28.3
≥2	21.5	20.9	22.4	19.5	20.1	21.3
CHA_2DS_2-VASc=0	24.9	20.9	24.8	23.2	26.1	25.9

Data are percentages unless otherwise stated.
*One drink corresponds to 12 g of pure alcohol.
VKA, vitamin K antagonist.

and table 4 for women. Results for the entire cohort without stratification for sex are shown in online web-only table 3.

Among men, the group with an intake of <14 drinks per week was used as reference. After multivariate analysis the highest risk of 'thromboembolism or death' among men was found among abstainers (HR 1.62, 95% CI 0.99 to 2.66). Men with an intake of >27 drinks per week also had a significantly higher risk after multivariate adjustment (HR 1.33, 95% CI 1.08 to 1.63). This higher risk was primarily driven by a difference in mortality (HR 1.51, 95% CI 1.20 to 1.89). Further adjustment for frequency of intake did not influence the results for men.

Among women, subjects with a weekly intake of <7 drinks was used as reference. After multivariate analysis a trend for the highest risk of 'thromboembolism or death' was found among women with an intake of 14–20 drinks per week (HR 1.25, 95% CI 0.82 to 1.92), which was very similar to the risk found among women in the highest intake category of >20 drinks per week (HR 1.23, 95% CI 0.78 to 1.96). Abstainers had the lowest risk (HR 0.76, 95% CI 0.38 to 1.50). The higher risk seen among women with an intake of 14–20 drinks per week was driven by a difference in mortality, whereas the higher risk seen among women with an intake of ≥20 drinks per week was driven mainly by a difference in risk of thromboembolism, which was significant when adjusted for frequency of intake (HR 2.78, 95% CI 1.02 to 7.60).

An analysis of the low risk subgroup of men with CHA_2DS_2-VASc=0 and women with CHA_2DS_2-VASc=1 according to alcohol intake is presented in online web-only table 4. The higher risk of thromboembolism and death was also evident in men with CHA_2DS_2-VASc=0 and an intake of >27 drinks per week (HR 1.88, 95% CI 1.18 to 2.99). A higher risk was again seen among the nine male abstainers, but the HR should be interpreted with caution given the small numbers. A non-significant trend was seen among the small numbers of women with CHA_2DS_2-VASc=1 and an intake of >14 drinks per week.

In figure 2 the number of drinks per week are modelled as cubic splines. For men (figure 2A), the risk of the composite end point of thromboembolism or death was greater with higher intake of alcohol. For both secondary outcomes of 'thromboembolism' and 'death' separately, roughly similar curves were seen, although the association was stronger for death than for thromboembolism.

For women (figure 2B), the risk for the composite end point was higher with higher intake of alcohol until a peak at around 30 drinks weekly, after which the curve declined slightly. Analyses of the secondary end points of thromboembolism and death revealed that women had a higher risk for 'thromboembolism' with higher intake of alcohol in a dose–response matter, whereas the curve for 'death' rose until around 20 drinks weekly and thereafter declined to a level below one for the highest number of drinks per week.

To investigate whether the higher risk of mortality observed among men was caused by fatal bleeding events, we censored all patients with a major bleeding (see online web-only table 1 for ICD codes) followed by death within 30 days, and this did not attenuate the association (data not shown). As alcohol is also related to the development of cancer, we censored all patients who were given a cancer diagnosis during follow-up in a

Table 2 Clinical characteristics of women according to weekly alcohol intake

	Alcohol intake, drinks* per week					
	All women	Abstainer	<7	7–13	14–20	>20
Subjects, n	1108	45	601	229	110	123
Drinks per week (median, (10%; 90%))	5.6 (0.7–21.7)	N/A	2.3 (0.6–6.2)	9.3 (7.4–12.2)	18.8 (15.0–20.2)	26.5 (21.7–40.9)
Years of follow-up (median (10%; 90%))	4.7 (1.0–10.8)	4.2 (1.1–11.4)	4.8 (1.0–11.0)	4.9 (0.9–11.0)	5.3 (1.4–10.5)	3.1 (0.7–9.5)
Age, years (median (10%; 90%))	67.8 (60.2–74.6)	68.7 (61.4–73.6)	67.8 (59.6–74.5)	67.2 (60.3–75.1)	68.2 (60.5–74.2)	68.9 (60.2–74.6)
Age ≥75 years	9.1	8.9	8.7	10.5	7.3	10.6
Age 65–74 years	59.4	57.8	59.9	56.3	60.9	61.8
Heart failure	5.6	8.9	8.8	3.1	5.5	1.6
Hypertension	28.0	33.3	29.6	23.6	25.5	28.5
Diabetes	11.4	26.7	12.1	9.6	3.6	12.2
Previous						
Ischaemic stroke	6.0	6.7	5.5	7.9	5.5	4.9
TIA	3.6	8.9	4.0	1.3	2.7	4.9
Arterial thromboembolism	0.4	0.0	0.2	1.3	0.9	0.0
Haemorrhagic stroke	1.4	0.0	1.7	1.7	0.9	0.0
Vascular disease:						
Previous MI	6.5	4.4	8.0	5.2	7.3	1.6
Aortic plaque	0.5	2.2	0.5	0.0	0.0	0.8
Peripheral artery disease	2.7	2.2	3.0	1.3	3.6	3.3
VKA treated	14.4	6.7	15.5	10.0	14.5	20.3
$CHADS_2$ (mean)	0.81	1.16	0.82	0.79	0.64	0.78
0	50.8	37.8	51.1	52.0	54.5	48.8
1	29.0	31.1	27.0	29.7	33.6	32.5
≥2	20.2	31.1	22.0	18.3	11.8	18.7
CHA_2DS_2-VASc=1	21.3	17.8	21.1	22.7	20.9	21.1

Data are percentages unless otherwise stated.
*One drink corresponds to 12 g of pure alcohol.
MI, myocardial infarction; TIA, transient ischaemic attack; VKA, vitamin K antagonist

sensitivity analysis. The associations between alcohol intake and thromboembolism and death were still present (data not shown).

DISCUSSION

In this study we found that among men with AF, abstainers and heavy users (>27 drinks per week) of alcohol had the highest risk of 'thromboembolism or death', even after adjustment for well known stroke risk factors used in current guidelines. Among women, subjects with an intake above 14 drinks per week had the highest risk of thromboembolism or death after adjustment for known stroke risk factors, whereas abstainers were not at higher risk. Our hypothesis of abstainers and heavy users having the highest risk was hereby confirmed, except abstaining women did not have a higher risk. Generally, the higher risk seen among men was mainly driven by death, whereas the higher risk among female heavy alcohol users was driven by thromboembolism. The higher risk of death found among men was not explained by either cancer or fatal bleeding. Further adjustment for frequency of intake indicated that drinking pattern was of more importance for women, as the measures of association changed for women but not for men.

Strengths and limitations

The Diet, Cancer and Health study population is a selected population where only about 35% of those invited agreed to participate. Also, we relied on hospital discharge diagnoses to diagnose AF. It is, however, unlikely that the association between alcohol intake and thromboembolism or death is systematically different between identified and non-identified participants with AF. A validation study indicated a positive predictive value of >92% for AF diagnoses.[22] The participants were followed in national registries with very limited loss to follow-up, and thus the study is unlikely to be subject to selection bias.

It is important to realise that this is not a study of the actual *effect* of alcohol per se but merely of the associations between reported alcohol intake and risk of outcomes. Due to the self-reported nature of alcohol intake, some AF patients might have been misclassified. However, this only mirrors the 'real life' clinical situation in which a physician would retrieve information about a patient's alcohol intake in a clinical history—that is, self-reported. Nonetheless, changes in drinking pattern may have occurred during follow-up, and this was not taken into account. However, we minimised this risk by assessing alcohol intake closest to, but before, first diagnosis of AF. Follow-up for vital status was almost complete, and the predictive values for stroke diagnoses is >80% and most likely not associated with reported alcohol intake obtained from questionnaires. Information bias is thus not a likely explanation of the study results.

In the first analyses VKA treatment was taken into account, but we had no information on international normalised ratio (INR) values. The time axis was time from the diagnosis of AF and thus closely controlled for. We did not differentiate between subtypes of AF, which may have differed among alcohol subgroups. We focused on the possible added value compared to use of current guidelines,[19–21] and components of the CHA_2DS_2-VASc risk score were therefore included in multivariate analyses. Heavy alcohol users are most likely also associated with other lifestyle risk factors for thromboembolism and

Table 3 Hazard ratios (95% CI) for thromboembolism and death according to weekly alcohol intake for men with incident atrial fibrillation

	Alcohol intake, drinks* per week				
	Abstainers	**<14 (reference)**	**14–20**	**21–27**	**>27**
Subjects, n	43	1025	241	234	456
Thromboembolism or death					
VKA adjusted†	**1.82 (1.11 to 2.97)**	1	0.92 (0.69 to 1.24)	1.02 (0.76 to 1.36)	**1.36 (1.11 to 1.66)**
Multi adjusted‡	1.62 (0.99 to 2.66)	1	0.99 (0.74 to 1.32)	1.11 (0.83 to 1.47)	**1.33 (1.08 to 1.63)**
Frequency adjusted§	1.28 (0.75 to 2.18)	1	0.97 (0.70 to 1.33)	1.07 (0.77 to 1.47)	1.26 (0.98 to 1.63)
Thromboembolism					
VKA adjusted	1.30 (0.47 to 3.56)	1	0.65 (0.36 to 1.20)	1.03 (0.61 to 1.71)	0.99 (0.66 to 1.49)
Multi adjusted	1.19 (0.43 to 3.28)	1	0.72 (0.39 to 1.33)	1.08 (0.65 to 1.80)	1.02 (0.68 to 1.54)
Frequency adjusted	0.95 (0.32 to 2.79)	1	0.75 (0.39 to 1.44)	1.10 (0.62 to 1.98)	1.04 (0.62 to 1.73)
Death					
VKA adjusted	1.16 (0.64 to 2.12)	1	1.03 (0.72 to 1.47)	1.03 (0.71 to 1.48)	**1.45 (1.09 to 1.94)**
Multi adjusted	1.60 (0.91 to 2.81)	1	1.08 (0.79 to 1.49)	1.10 (0.80 to 1.52)	**1.51 (1.20 to 1.89)**
Frequency adjusted	1.25 (0.69 to 2.29)	1	1.05 (0.74 to 1.49)	1.04 (0.73 to 1.49)	**1.40 (1.06 to 1.86)**

Thromboembolism: includes ischaemic stroke or peripheral arterial thromboembolism. Measures of association in bold indicate statistical significance.
*One drink equates to 12 g of pure alcohol.
†Calculated using Cox's regression with time since atrial fibrillation diagnosis as underlying time variable and adjusted for VKA treatment.
‡Further adjustment for CHA_2DS_2-VASc components.
§Also adjusted for frequency of intake (not weekly, non-daily or daily).
VKA, vitamin K antagonist.

death. These risk factors would have been potential confounders if the aim had been to specify the independent association for alcohol, but not in this study concerning a possible added value to existing risk stratification strategies. Confounding by other known stroke risk factors is therefore not an issue of concern.

Few studies have investigated the associations between reported alcohol intake and risk of thromboembolism and death in AF patients. An analysis of 2012 participants from the SPAF (Stroke Prevention in Atrial Fibrillation) I–III trials found incidence rates for ischaemic stroke to be lower with higher reported alcohol intake, and that users of alcohol had a lower risk than non-users (HR 0.4, p=0.04).[12] However, dichotomisation is not discriminatory enough, and non-users may include previous users who have stopped drinking due to health issues. Thus, using 'non-users' as reference could therefore give a biased image of the true associations, and is therefore not optimal when trying to identify high risk subjects.[23] Similarly, data from the anticoagulated arms of the SPORTIF (Stroke Prevention Using Oral Thrombin Inhibitor In Atrial Fibrillation) III and IV trials found users of alcohol to have a lower risk of stroke or systemic embolism than non-users (HR 0.69, 95% CI 0.51 to 0.93).[11] In our sex stratified analysis, only abstaining men had a higher risk, whereas abstaining women were not at higher risk. This may reflect the fact that abstaining men could be previous heavy users of alcohol. Nonetheless, our cohort had few abstainers and change might have influenced these results. We also observed other differences between men and women, as the higher risk among heavy drinkers in men

Table 4 Hazard ratios (95% CI) for thromboembolism and death according to weekly alcohol intake for women with incident atrial fibrillation

	Alcohol intake, drinks* per week				
	Abstainers	**<7 (reference)**	**7 to 13**	**14 to 20**	**>20**
Subjects, n	45	601	229	110	123
Thromboembolism or death					
VKA adjusted†	0.90 (0.46 to 1.76)	1	0.94 (0.67 to 1.32)	1.20 (0.78 to 1.83)	1.08 (0.68 to 1.70)
Multi adjusted‡	0.76 (0.38 to 1.50)	1	1.06 (0.74 to 1.50)	1.25 (0.82 to 1.92)	1.23 (0.78 to 1.96)
Frequency adjusted§	0.70 (0.35 to 1.40)	1	1.30 (0.85 to 2.01)	1.66 (0.96 to 2.86)	1.71 (0.93 to 3.14)
Thromboembolism					
VKA adjusted	0.75 (0.18 to 3.13)	1	1.03 (0.56 to 1.91)	0.77 (0.30 to 1.97)	1.53 (0.73 to 3.17)
Multi adjusted	0.66 (0.16 to 2.79)	1	1.14 (0.61 to 2.13)	0.77 (0.301.98) to	1.71 (0.81 to 3.60)
Frequency adjusted	0.68 (0.16 to 2.94)	1	1.45 (0.68 to 3.11)	1.11 (0.37 to 3.28)	**2.78 (1.02 to 7.60)**
Death					
VKA adjusted	0.84 (0.39 to 1.81)	1	0.93 (0.63 to 1.37)	1.24 (0.77 to 1.98)	0.97 (0.57 to 1.64)
Multi adjusted	0.72 (0.33 to 1.55)	1	1.06 (0.72 to 1.57)	1.29 (0.80 to 2.08)	1.10 (0.64 to 1.89)
Frequency adjusted	0.65 (0.30 to 1.42)	1	1.29 (0.79 to 2.10)	1.65 (0.89 to 3.03)	1.44 (0.72 to 2.87)

Thromboembolism: includes ischaemic stroke or peripheral arterial thromboembolism. Measures of association in bold indicates statistical significance.
*One drink equates to 12 g of pure alcohol.
†Calculated using Cox's regression with time since atrial fibrillation diagnosis as underlying time variable and adjusted for VKA treatment.
‡Further adjustment for CHA_2DS_2-VASc components.
§Also adjusted for frequency of intake (not weekly, non-daily or daily).
VKA, vitamin K antagonist.

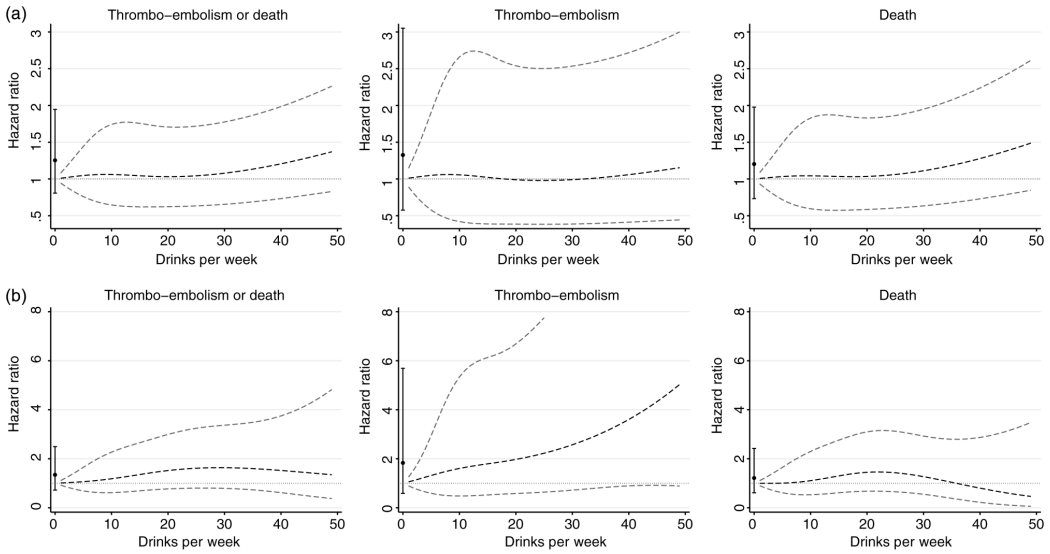

Figure 2 Continuous analysis of alcohol intake and the risk for thromboembolism and death. All analyses adjusted for vitamin K antagonist treatment and CHA_2DS_2-VASc components. Black dots indicate hazard ratio with 95% CI for abstainers. (a) Men. (b) Women.

was driven by mortality in contrast to thromboembolism in women. On a general population level heavy alcohol intake is associated with stroke and death among both men and women.[6] Considering this is not a study of the *effect* of alcohol, these differences might pertain to differences in lifestyle between sexes that were not taken into account in the present analyses.

In the Cardiovascular Health Study, Mukamal and colleagues investigated the relationship between reported alcohol intake and mortality among 1232 AF patients.[13] After multivariate analysis, including adjustment for concurrent warfarin treatment, all groups of alcohol users had a lower risk of death compared with never drinkers, with the highest intake category defined as ≥14 drinks per week. Thus, they mainly studied the associations for moderate alcohol intake, as the average intake among incident AF cases was quite low (2.6 drinks per week against 15.0 drinks per week in the present analysis).

Clinical implications

We have chosen a composite end point including the outcomes affected by intervention with oral anticoagulation, since VKA use prevents both thromboembolism *and* death in AF patients.[24] Importantly, some deaths in our study are likely to be due to undiagnosed ischaemic stroke caused by the register based nature of the dataset. The two most widely used stroke risk stratification schemes, $CHADS_2$ and CHA_2DS_2-VASc, are capable of predicting both stroke *and* death among AF patients.[25]

In recent years, two new oral anticoagulants have gained approval for stroke prevention in AF patients, with one additional drug nearing approval.[26–28] Each has fundamentally different pharmacokinetic properties than the VKAs, and their anticoagulant effects are not directly affected by high intake of alcohol. The role of alcohol as a risk factor for bleeding in anticoagulated patients will thus potentially diminish, as the new oral anticoagulants will become more widely used. Reported alcohol intake may then help to identify subjects at high risk for ischaemic events without worrying about alcohol interfering with the anticoagulant effect of these new and safer agents. Importantly, we found indications that even among those considered low risk subjects (men with CHA_2DS_2-VASc=0 and women with CHA_2DS_2-VASc=1) alcohol intake might help to differentiate them into low risk and high risk patients, but due to small numbers further studies are needed to confirm this.

Further studies are also needed to confirm our results in an AF cohort with older participants and other ethnic groups, as our cohort was relatively young and predominantly white. If confirmed, self-reported alcohol intake may help identify subjects potentially at high risk of thromboembolic events and death once diagnosed with incident AF.

CONCLUSION

High alcohol intake predicts 'thromboembolism or death', even after taking into account clinical risk factors recommended by current guidelines. High alcohol consumption may help identify AF patients with a higher risk for 'thromboembolism or death', who could be targeted for stroke and cardiovascular prevention strategies.

Contributors All authors contributed to the study design, data analysis, manuscript writing, reviewing and editing.

Competing interests DAL and GYHL are co-authors of the original CHA_2DS_2-VASc study. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim and Sanofi Aventis. DAL has received an investigator initiated educational grant from Bayer Healthcare and honoraria from Boehringer Ingelheim, Bayer Healthcare, Bristol Myers Squibb, Sanofi Aventis and Pfizer. In addition, DAL is a panellist on the 9th edition of the American College of Chest Physicians guidelines on antithrombotic therapy in AF. TBL and LHR have served as speakers for Bayer, BMS/Pfizer and Boehringer Ingelheim. TFO, FS, IEA and KO have no potential conflicts of interest to declare.

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APPENDIX C. PAPER 3

Female sex as a risk factor for thromboembolism and death in patients with incident atrial fibrillation

The prospective Danish Diet, Cancer and Health study

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Summary

Several studies have demonstrated sex differences in risk of thromboembolism and death among patients with atrial fibrillation, but it is unclear to what extent these associations relate to actual physiological differences. To date, no study has investigated sex differences with concomitant control for lifestyle related factors known to influence stroke risk. We used data from the Danish Diet, Cancer and Health study, including 57,053 participants (52% female) aged 50–64 years. The study population for this study included the 2,895 patients (36% female) with incident atrial fibrillation after inclusion. Data were linked to outcomes identified using nationwide registries. Risk of thromboembolism and death according to female sex were analysed using Cox proportional hazards models. After a median follow-up of 5.0 years, 137 men and 62 women suffered a thromboembolic event, and 349 men and 151 women died. In a crude analysis, female sex was associated with a non-significant lower risk of thromboembolism (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.61–1.11). Adjustment for differences in antithrombotic therapy, relevant comorbidities and lifestyle did not change this association (HR 0.77, 95% CI 0.55–1.13). In the final model, female sex was associated with a lower risk of death (HR 0.65, 95% CI 0.51–0.84). The associations were similar in a sensitivity analysis of women not taking hormone replacement therapy, and the effect of hormone replacement therapy use within females was non-significant for both endpoints of thromboembolism and death. In conclusion, in a relatively young population of patients with atrial fibrillation, female sex was associated with a lower risk of thromboembolism and death.

Keywords

Atrial fibrillation, sex differences, thromboembolism, stroke, death, epidemiology

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Introduction

Atrial fibrillation is the most common cardiac arrhythmia and is associated with a substantial risk for thromboembolic events such as ischaemic stroke and peripheral arterial embolism (1). Several risk stratification schemes for stroke among atrial fibrillation (AF) patients have been developed, some of which have incorporated female sex as a component (2, 3).

As the CHA_2DS_2-VASc score, which includes female sex as a risk factor, is recommended as a risk stratification tools for AF patients in both European (4) and American guidelines (5, 6) the question of whether female sex is justified as a risk predictor has undergone extensive validation (7). Large nationwide register based studies have investigated whether female sex was associated with risk of thromboembolic events after control for comorbidity encompassed in the CHA_2DS_2-VASc score (8–10). All studies found significantly higher risks for thromboembolic events among female AF patients, but this higher risk was primarily driven by a higher risk among older patients ≥65 years – these patients who irrespective of sex should be considered for oral anticoagulation according to existing guidelines (4–6).

The register-based studies also made further investigation into whether female sex was *intrinsically* associated with thromboembolism by adjusting for additional comorbidity. Due to the reg-

ister-based nature of these datasets their results may have been confounded by differences in lifestyle between sexes – information that was inevitably unavailable from those registries. Additionally, the evidence of hormone replacement therapy as a risk modifier of thromboembolic events among women with AF has provided conflicting results (11).

The aim of this study was to further investigate the impact of female sex on risk of thromboembolism and death among AF patients with concomitant control for confounding from lifestyle-related factors and other known comorbidities known to influence risk of thromboembolism, for example smoking, alcohol, sedentary lifestyle, obesity and hormone replacement therapy (HRT) (12). To do this, we analysed data from the large prospective Danish Diet, Cancer and Health study, which holds detailed information on demographics and lifestyle factors.

Materials and methods

The Diet, Cancer and Health cohort was established between 1993 and 1997. The study design has been reported in detail elsewhere (13). The primary objective of this prospective study was to investigate the etiologic role of diet and lifestyle in the development of cancer, and 57, 053 participants were enrolled (27, 178 men and 29, 876 women). The study participants were aged 50 to 64 years, living in the urban areas of Copenhagen or Aarhus, and without a cancer diagnosis registered in the Danish Cancer Registry (14) at baseline. Participants were, for this study, followed from time of first diagnosis of AF until December 2009. The Diet, Cancer and Health cohort has detailed information on demographics, existing co-morbidities, and individual risk factors. Cross linkage between the cohort participants and the National Patient Register (14) provided detailed information on incident AF, thromboembolism and death and specific information about potential censoring from emigration and death during follow-up.

Case finding

The cohort subjects were linked to the National Patient Register, dating back to 1977, using the Danish Personal Identification number. This is a unique national identification number, which is part of the personal information stored in the Civil Registration System. The study population in the present study included participants who developed incident AF during follow-up, but not earlier than April 1995. Incident cases of AF not habitually residing in Denmark were excluded, as were cases diagnosed simultaneously with thromboembolism or transient ischaemic attack or patients who died on the same day they were diagnosed with AF. Codes from the International Classification of Diseases (ICD) 10 were used to extract admissions for AF. AF and atrial flutter have a common ICD-10 code (I48). Therefore, some atrial flutter cases were included in the present study (15).

Confounding factors

All participants filled in a background questionnaire as well as a detailed semi-quantitative food-frequency questionnaire at entry and five years after entry into the Diet, Cancer and Health study, which has been described and validated previously (16, 17). Lifestyle data were extracted from the questionnaire closest to but prior to the first diagnosis of AF. We extracted information about educational level, smoking and alcohol habits. At inclusion, trained laboratory assistants obtained information about body mass index and waist circumference, whereas anthropometric measures obtained from the follow-up questionnaire were self-reported.

Information about known risk factors included in the CHA_2DS_2-VASc score was determined at the time of AF diagnosis using ICD-8 and ICD-10 codes (in combination with Anatomical Therapeutic Chemical [ATC] Classification System drug codes). This included information about heart failure, hypertension, diabetes mellitus, vascular diseases and previous ischaemic stroke, peripheral arterial thromboembolism or transient ischaemic attack. Due to small numbers we excluded people with a diagnosis of anaemia, platelet or coagulation defects, moderate/severe renal disease and moderate/severe liver disease, as the specific risk associated with these disease was not the primary objective of this study. Information about use of warfarin, acetylsalicylic acid, clopidogrel and HRT was obtained from the National Prescription Registry using ATC drug codes. ICD and ATC codes used in this study are listed in Suppl. Table 1 (available online at www.thrombosis-online.com).

For the purpose of assessing sex differences in mortality, we obtained additional information about major chronic diseases using the Charlson Comorbidity Index (18). This is a method of classifying comorbidity with an estimated impact on subsequent risk of death. The predictive values of these components from the Danish National Patient Register have been validated (19). This includes information about myocardial infarction, congestive heart failure, hypertension, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, renal disease, diabetes mellitus, hemiplegia, cancer and AIDS. The ICD codes used to determine the Charlson Comorbidity Index are presented in Suppl. Table 2 (available online at www.thrombosis-online.com).

Outcomes

We defined our primary outcome as 'thromboembolism' comprising ischaemic stroke and arterial thromboembolism. All-cause mortality was considered a secondary outcome. Information on emigration or death was available from the National Civil Registration System, and incident cases of ischaemic stroke using ICD-10 (I63.0 – I63.9, I64.9) and arterial thromboembolism using ICD-10 (I74.0 – I74.9) were found in the National Patient Register.

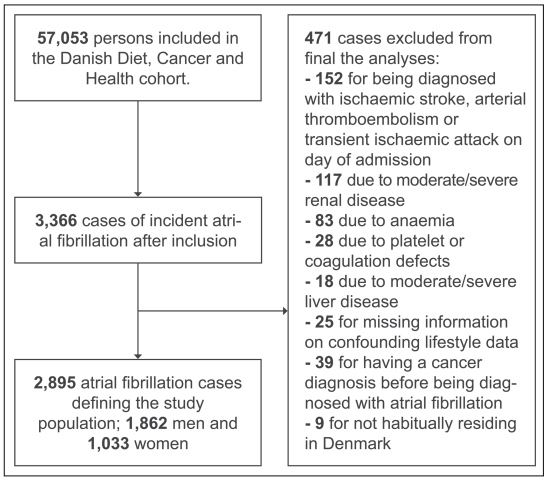

Figure 1: Flow chart with details of how the study population was defined.

Statistical analysis

Incidence rates for thromboembolism and death were calculated according to sex and age group. Overall incidence rates by sex were age-adjusted by direct standardisation. Associations between sex and risk of thromboembolism and death were analysed using Cox proportional regression with time since AF as the underlying time scale. End of follow-up (December 30, 2009) or emigration was considered as outcome independent censoring. For the primary outcome thromboembolism, death was considered a censoring event. The associations are reported as crude and after adjustment for antithrombotic treatment, risk factors for thromboembolism recommended in current guidelines and socioeconomic and lifestyle factors. Continuous confounding factors were modelled as cubic splines. A supplementary analysis on the potential modification by HRT was performed analogously by subdividing the sex factor level: 'female' according to baseline HRT status. Data were analysed using Stata version 12 (Stata Corporation, College Station, TX, USA). Results are reported with 95% confidence intervals (CI).

Results

We identified 3, 366 cohort participants diagnosed with incident AF during follow-up. Of those, 471 were excluded from the final analyses, leaving a study population of 2, 895 incident AF cases: 1, 862 men and 1, 033 women (►Figure 1).

Clinical baseline characteristics of men and women are shown in ►Table 1. Compared with men, women had a lower prevalence of congestive heart failure, diabetes mellitus, previous myocardial infarction and peripheral artery disease, a lower intake of alcohol,

Table 1: Baseline characteristics of 2,895 men and women with incident atrial fibrillation.

	Men	Women
Subjects – no. (%)	1,862 (64.3)	1,033 (35.7)
Years of follow-up	5.1 (1.0–11.5)	4.9 (1.0–10.8)
Current guideline identified risk factors – no. (%)		
Age, years -≥75 -65–74 -<65	66.5 (58.8–73.8) 120 (6.4) 986 (53.0) 756 (40.6)	67.6 (60.2–74.3) 88 (8.5) 617 (59.7) 328 (31.8)
Congestive heart failure	120 (6.4)	49 (4.7)
Hypertension	501 (26.9)	288 (27.9)
Diabetes mellitus	271 (14.6)	117 (11.3)
Previous: -Ischaemic stroke -Systemic arterial embolism -Transient ischaemic attack	 119 (6.4) 8 (0.4) 52 (2.8)	 61 (5.9) 4 (0.4) 36 (3.5)
Peripheral artery disease	77 (4.1)	23 (2.2)
Previous myocardial infarction	233 (12.5)	64 (6.2)
Aortic plaque	6 (0.3)	4 (0.4)
Other relevant comorbidity – no. (%)		
Haemorrhagic stroke	16 (0.9)	14 (1.4)
Charlson Comorbidity Index >2	233 (12.5)	110 (10.6)
Lifestyle and socioeconomic		
Educational level – no. (% with only basic schooling)	226 (12.1)	231 (22.4)
Body mass index – kg/m^2	27.0 (23.0–32.7)	25.9 (20.7–34.2)
Waist circumference – cm	100.0 (88.0–115.0)	89.0 (74.0–110.0)
Alcohol intake – drinks/week	12.3 (2.1–39.5)	5.7 (0.7–21.8)
Alcohol intake above recommended maximum – no. (%)	861 (46.2)	118 (11.4)
Smoking status – no. (%) -Never -Former -Current	 472 (25.3) 758 (40.7) 632 (33.9)	 413 (40.0) 302 (29.2) 318 (30.8)
Medication at time of atrial fibrillation diagnosis – no. (%)		
Hormone replacement therapy	-	221 (21.4)
Acetylsalicylic acid	525 (28.2)	268 (25.9)
Clopidogrel	41 (2.2)	21 (2.0)
Vitamin K antagonist	396 (21.3)	139 (13.5)
Stroke risk score level		
$CHADS_2$ -Mean -Score=0 – no. (%)	 0.71 1,060 (56.9)	 0.70 573 (55.5)
CHA_2DS_2-VASc -Mean -Score=0/1* – no. (%)	 1.47 484 (26.0)	 2.46 226 (21.9)

Data presented as figures followed by ranges are medians with 10th to 90th percentiles. * Percentage of patients with a score=0 for men and score=1 for women.

	Thromboembolism*		Death	
	Men (n=1,862)	Women (n=1,033)	Men (n=1,862)	Women (n=1,033)
Overall				
	1.70 (1.43–2.02)	1.21 (0.91–1.61)	4.22 (3.80–4.68)	3.13 (2.67–3.68)
Stratified by age (years)				
<65	1.05 (0.80–1.38)	0.67 (0.40–1.11)	2.64 (2.23–3.12)	2.17 (1.65–2.86)
65–74	2.22 (1.79–2.76)	1.88 (1.41–2.52)	4.99 (4.34–5.75)	3.38 (2.74–4.17)
≥75	2.56 (0.96–6.82)	0.85 (0.12–6.06)	13.1 (8.54–20.1)	11.7 (6.93–19.8)

* Thromboembolism includes ischemic stroke and systemic arterial thromboembolism. Overall incidence rates are age-adjusted.

Table 2: Overall and age-stratified incidence rates per 100 person-years for thromboembolism and death among men and women with incident atrial fibrillation.

Table 3: Hazard ratios (95% confidence intervals) for thromboembolism and death according to female sex in patients with incident atrial fibrillation.

	Thromboembolism*	Death
	Hazard ratio	Hazard ratio
All women in cohort		
Crude	0.82 (0.61–1.11)	0.79 (0.65–0.96)
Treatment adjusted	0.80 (0.59–1.08)	0.68 (0.56–0.83)
Multivariate model 1	0.74 (0.55–1.01)	0.66 (0.54–0.80)
Multivariate model 2	0.77 (0.52–1.13)	N/A
Multivariate model 3	N/A	0.65 (0.51–0.84)
Women not using hormone replacement therapy		
Crude	0.77 (0.55–1.08)	0.87 (0.71–1.07)
Treatment adjusted	0.75 (0.53–1.06)	0.78 (0.63–0.95)
Multivariate model 1	0.69 (0.49–0.98)	0.72 (0.58–0.88)
Multivariate model 2	0.71 (0.47–1.08)	N/A
Multivariate model 3	N/A	0.69 (0.53–0.89)
Women using hormone replacement therapy		
Crude	0.97 (0.60–1.60)	0.53 (0.35–0.79)
Treatment adjusted	0.93 (0.57–1.53)	0.43 (0.28–0.64)
Multivariate model 1	0.92 (0.56–1.52)	0.47 (0.31–0.70)
Multivariate model 2	0.99 (0.56–1.76)	N/A
Multivariate model 3	N/A	0.52 (0.33–0.81)

* Thromboembolism includes ischaemic stroke and systemic arterial thromboembolism. **Treatment adjusted:** Adjusted for the use of warfarin, acetylsalicylic acid and clopidogrel modelled as time-varying covariates. **Multivariate 1:** Additional adjustment for components of the CHA_2DS_2-VASc score, i.e. heart failure, hypertension, diabetes mellitus, previous ischaemic stroke/peripheral arterial thromboembolism/transient ischaemic attack, vascular disease and age (spline). **Multivariate 2:** Additional adjustment for educational level (short, medium, long), body mass index (spline), waist circumference (spline), smoking (never, former, light, heavy), and alcohol intake. **Multivariate 3:** Same model as in multivariate 2 with additional adjustment for Charlson Comorbidity Index (none, 1 or 2, >2). **N/A:** Not applicable.

were less educated and less likely to be started on antithrombotic medication at time of diagnosis of AF.

During follow-up, 137 men and 62 women were diagnosed with a thromboembolic event, and 349 men and 151 women died. Among both men and women, >95% of the thromboembolic events were strokes (134 and 59 events, respectively). Incidence rates stratified by sex and age group for thromboembolism and death are shown in ▶Table 2. Females had the lowest rates of thromboembolism and death in both the overall and age-stratified categories.

Hazard ratios (HRs) for thromboembolism and death after a median follow-up of 5.0 years are shown in ▶Table 3. In the crude analysis, women had a non-significantly lower risk of thromboembolism than men (HR 0.82, 95% CI 0.61–1.11). This estimate was fundamentally unchanged after stepwise adjustment for antithrombotic treatment during follow-up (HR 0.80, 95% CI 0.59–1.08), components of the CHA_2DS_2-VASc score (HR 0.74, 95% CI 0.55–1.01) and further adjustment for socioeconomic and lifestyle factors (HR 0.77, 95% CI 0.52–1.13). In the crude analysis using all cause mortality as an outcome, female sex was significantly associated with a lower risk than male sex (HR 0.79, 95% CI 0.65–0.96). Further adjustment for antithrombotic therapy during follow up, components of the CHA_2DS_2-VASc score, socioeconomic factors, lifestyle factors and Charlson Comorbidity Index slightly strengthened the association with all-cause mortality (fully adjusted HR 0.65, 95% CI 0.51–0.84).

In a sensitivity analysis, similar associations for thromboembolism and death were found also in the subset of women who were not using HRT at baseline (see ▶Table 3). For both endpoints of thromboembolism and death the effect of HRT use within females was statistically non-significant (p>0.35 in both interaction analyses).

Discussion

In this study we found that women had lower incidence rates of thromboembolism and death than men after being diagnosed with incident AF. In Cox proportional hazards models female sex was

Table 4: Hazard ratios with 95% confidence intervals from studies comparing risk of a thromboembolic event according to female sex in patients with atrial fibrillation.

Study	AF cases, n (% women)	Overall* Hazard ratio	Age <65 Hazard ratio	Age 65–74 Hazard ratio	Age ≥75 Hazard ratio
Mikkelsen, 2012	87,202 (51)	1.04 (1.01–1.08)	0.86 (0.76–0.98)	0.98 (0.90–1.07)	1.10 (1.05–1.15)
Tsadok, 2012	83,513 (53)	1.14 (1.07–1.22)	-	-	-
Friberg, 2012	100,802 (50)	1.18 (1.12–1.24)	1.10 (0.86–1.41)	1.11 (0.97–1.27)	1.23 (1.17–1.30)
Current study	2,895 (36)	0.77 (0.52–1.13)	0.57 (0.30–1.08)	0.86 (0.56–1.33)	0.39 (0.04–3.56)

* All results presented are from the multivariate analyses. Interpretation of the results in the ≥75 category from the current study warrants caution due to very few outcomes, as also reflected by the very wide confidence interval.

associated with a lower risk of thromboembolism and death compared with male sex. The associations were similar in a sensitivity analysis of women not taking hormone replacement therapy, and the effect of HRT use within females was statistically non-significant for both endpoints of thromboembolism and death.

Three large-scale studies have been conducted aimed solely at analysing sex differences in stroke risk among AF patients. All were population based studies using national registers from Denmark (8), Sweden (10) and Canada (9). They all found women to be at significantly higher risk of thromboembolic events even after adjustment for individual components of the CHA_2DS_2-VASc score (see ▶Table 4). These three studies have clearly established the role of female sex as a risk predictor, namely that female sex alone should not justify initiation of anticoagulant therapy (4–6), which is also supported by the current results. Whether female sex is intrinsically associated with thromboembolic events in AF patients remains controversial, as interpreting associations as causal based on register-based data alone requires utmost caution (20). None of the register-based studies had information about lifestyle factors such as smoking, alcohol and obesity. All of these are factors that have been associated with ischaemic stroke in the general population (12), and therefore may affect the risk of thromboembolic events among AF patients (21–23). Importantly, additional adjustment for lifestyle-related factors in the current study did not alter the association between female sex and risk of thromboembolism. This particular finding complements the large register-based CHA_2DS_2-VASc validation studies, supporting the possiblity that their findings might be contributable to intrinsic sex-related differences in stroke risk in AF.

The study by Mikkelsen et al. investigated female sex as a risk factor for stroke in a nationwide Danish cohort of AF patients not treated with warfarin at baseline (8). As they included all patients from Denmark with an incident diagnosis of AF obtained during hospitalisation, there is an inevitable overlap of AF cases between our study and the register-based nationwide study. As mentioned, they found an overall higher risk of thromboembolism among women. When dividing their population into three arbitrary age strata they found only women aged ≥75 years to have a higher risk of thromboembolism, whereas younger women had similar or even lower risks of stroke than age matched men (see ▶Table 4). Therefore, it is likely that the relatively young age of our population (median age 66.9 years) explains why we did not find a higher overall risk among women. Of note, although most data indicate that older women (≥75 years) account for much of the higher risk observed according to female sex (7–10, 24), an analysis of elderly AF patients aged ≥75 years not taking warfarin from the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, did not find female sex to be a risk factor for ischaemic stroke after adjustment for $CHADS_2$ components, angina and valve disease (25).

AF is associated with significantly worse ischaemic strokes than those occurring in the general population with regards to morbidity and mortality (26, 27). We analysed death as a secondary outcome with the expectation to find a reflection of the association found for thromboembolism, as some deaths are also likely to be caused by undiagnosed stroke due to the register-based nature of the data. This was confirmed as women remained at lower risk of death than men also in the final model. Interestingly, an analysis from the Framingham Heart Study developed risk stratification schemes separately for 'stroke' and 'stroke or death' among AF patients, and they found female sex to be a significant risk predictor in their model for stroke, but not in the model for stroke or death (3).

A recent review elucidates potential biological pathways explaining the observed sex differences in risk of thromboembolic events in patients with AF, including the role of HRT, concluding that the evidence describing the role of HRT is sparse and inconclusive (11). In our study, the effect of HRT use within females was statistically non-significant for both endpoints of thromboembolism and death. The Anticoagulation and Risk Factors in Atrial fibrillation (ATRIA) study, use of oral estrogen therapy was not associated with thromboembolism (28) whereas in an analysis from the SPAF I-III trials HRT was significantly associated with ischaemic stroke (29). Also, meta-analyses of randomised trials conducted on non-AF patients have found HRT to be associated with higher risk of stroke (30, 31). However, a Danish randomised trial of the effect of HRT on risk of cardiovascular events in recently post-menopausal women found indications of a lower risk of stroke in the treatment group (32). Further studies may be warranted to investigate the role of 'hormone use' (e.g. as HRT) in patients with AF and why female sex may be associated with lower risk of thromboembolic events and death among younger patients with AF.

Strenghts and limitations

The Diet, Cancer and Health study is a selected population where only 35% of those invited agreed to participate. It is however unlikely that the association between sex and risk of thromboembolic event is systematically different between participants and non-participants. The participants were followed in national registries with very limited loss to follow-up. The study is therefore not subject to selection bias. We relied on hospital discharge diagnosis for identification of AF cases, and cases solely handled outside of hospital where therefore not included. Information about potential confounding factors where questionnaires was the source of information were not obtained at exact time of AF diagnosis, but we used information from the questionnaires closest to, but prior to AF diagnosis in order to minimise potential misclassification. The validity of the diagnoses of AF and ischaemic stroke from the National Patient Register have been verified (15, 33). We did not investigate causes of death, as the validity of specific causation data from the Danish Register of Causes of Death is limited (34).

Stroke rates may be related to subtype of AF (35), and as we were unable to differentiate between subtypes (i.e. paroxysmal, persistent and permanent) we were unable to investigate the potential impact of subtype on sex differences in risk.

Ideally, risk factors for thromboembolic events in AF patients should be investigated in non-selected, non-anticoagulated cohorts, but such have not been accesible since the introduction of oral anticoagulation for prevention of thromboembolic events. We chose to include all patients irrespective of antithrombotic therapy with subsequent adjustment for differences in treatment, as choosing only non-anticoagulated patients would leave us with no information about why these patients were not anticoagulated. We have carefully included anti-thrombotic therapy as a time-varying covariate in the multivariate analysis in order to take into account potential differences in treatment during follow-up. This study is not powered to investigate the interaction between sex and anticoagulant therapy on risk of thromboembolic events. Importantly, we had no information about the quality of antithrombotic therapy such as time in therapeutic range (which has a major impact on the efficacy and safety of VKA treatment [36]), and one study has indicated that anticoagulated women with AF spend less time in therapeutic range than anticoagulated men (37), but this would not explain the lower risk associated with female sex in this study. Bleeding was also not an outcome in our study, as the specific focus was the associations between female sex and risk of thromboembolic events.

Due to small numbers we excluded patients with concomitant illnessess that may affect stroke risk (coagulation defects, anaemia, liver and renal disease). However, one study indicated that renal dysfunction may impact on the observed sex differences in risk of stroke and death in AF patients (38).

What is known about this topic?

- Several studies have demonstrated sex-differences in risk of thromboembolism and death among patients with atrial fibrillation (AF), but it is unclear to what extent these associations relate to actual physiological differences.
- To date, no study has investigated sex-differences with concomitant control for lifestyle related factors known to influence stroke risk.

What does this paper add?

- Amongst subjects with AF, female sex was associated with a non-significant lower risk of thromboembolism, after adjustment for differences in antithrombotic therapy, relevant comorbidities and lifestyle (HR 0.77, 95% CI 0.55–1.13).
- In the final model, female sex was also associated with a lower risk of death (HR 0.65, 95% CI 0.51–0.84).
- The associations were similar in a sensitivity analysis of women not taking hormone replacement therapy, and the effect of hormone replacement therapy use within females was non-significant for both endpoints of thromboembolism and death.

Conclusion

In a relatively young population-based AF cohort, female sex was associated with a significant lower risk of death and non-significantly lower risk of thromboembolism, after careful adjustments for antithrombotic therapy, comorbidity and differences in lifestyle. The effect of HRT use within females was non-significant for both endpoints of thromboembolism and death.

Conflicts of interest

Prof. Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi Aventis. Dr. Lane has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and served as a speaker for Boehringer Ingelheim, Bayer Healthcare, BMS/Pfizer. In addition, Dr. Lane is on the Steering Committee of a Phase IV apixaban study (AEGEAN). Both Prof. Lip and Dr. Lane have participated in various clinical trials of stroke prevention in atrial fibrillation. Associate Prof. Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim. Associate Prof. Larsen and Prof. Rasmussen have been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics and Boehringer Ingelheim. The other authors declare no conflicts of interest.

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APPENDIX D. PAPER 4

Duration of Diabetes Mellitus and Risk of Thromboembolism and Bleeding in Atrial Fibrillation

Nationwide Cohort Study

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Background and Purpose—Guidelines advocate anticoagulant treatment to all patients with atrial fibrillation and concomitant diabetes mellitus. The potential refinement to thromboembolic risk stratification that may spring from subdividing diabetes mellitus is unexplored. The purpose was to investigate duration of diabetes mellitus as a predictor of thromboembolism and anticoagulant-related bleeding in patients with atrial fibrillation.

Methods—Using nationwide Danish registries, we identified all patients discharged from hospital with an incident diagnosis of atrial fibrillation from 2000 to 2011. Hazard ratios with 95% confidence intervals for thromboembolism and bleeding according to years of diabetes mellitus duration in categories (0–4, 5–9, 10–14, and ≥15) and as a continuous variable using cubic splines were calculated by Cox regression.

Results—The study population comprised 137 222 patients with atrial fibrillation, of which 12.4% had diabetes mellitus. Compared with patients without diabetes mellitus and after adjustment for anticoagulant treatment and CHA_2DS_2-VASc components (congestive heart failure, hypertension, age, previous stroke, vascular disease, and sex), the risk of thromboembolism was lowest in the 0 to 4 years duration category (hazard ratio, 1.11; 95% confidence interval, 1.03–1.20), and highest in the longest duration category of ≥15 years (hazard ratio, 1.48; 95% confidence interval, 1.29–1.70). When analyzed as a continuous variable, duration of diabetes mellitus was associated with risk of thromboembolism in a dose-response-dependent manner, but not with a higher risk of bleeding during anticoagulant treatment.

Conclusions—In patients with atrial fibrillation, longer duration of diabetes mellitus was associated with a higher risk of thromboembolism, but not with a higher risk of anticoagulant-related bleeding. Considering the critical balance between preventing thromboembolism and avoiding bleeding, longer duration of diabetes mellitus may favor initiation of anticoagulant therapy. **(*Stroke*. 2015;46:2168-2174. DOI: 10.1161/STROKEAHA.115.009371.)**

Key Words: atrial fibrillation ■ diabetes mellitus ■ epidemiology ■ stroke ■ thromboembolism

Atrial fibrillation is the most commonly encountered cardiac arrhythmia and it is reaching epidemic proportions.[1] It is a frequent cause of thromboembolic events, such as ischemic stroke.[2] The cause of atrial fibrillation is multifactorial. One important contributor to the increasingly higher prevalence of atrial fibrillation is diabetes mellitus, as the prevalence of diabetes mellitus has risen in the general population.[3,4] The confluence of diabetes mellitus and atrial fibrillation infers that ≈1 in 5 patients with atrial fibrillation have concurrent diabetes mellitus.[5] Furthermore, in patients with atrial fibrillation, diabetes mellitus is a risk factor for thromboembolic events.[6,7]

International guidelines for management of patients with atrial fibrillation recommend using the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age, diabetes mellitus, stroke [doubled], vascular disease, age, and sex category [female])[6] to identify patients at sufficiently low risk to be in need of no antithrombotic treatment, whereas all others with 1 risk factor from the score should be considered for oral anticoagulant therapy, except women where female sex is their only risk factor.[8,9] Because diabetes mellitus is a component in the CHA_2DS_2-VASc score, this risk factor-based approach means that all patients with diabetes mellitus should be considered for anticoagulant treatment. Despite these clear recommendations, a widespread underuse of anticoagulant treatment is reported, which underlines a need for a continuous advancement into the epidemiology of thromboembolic risk in patients with atrial fibrillation.[10]

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There is a paucity of research investigating the potential benefit that may spring from subdividing diabetes mellitus in relation to thromboembolic risk stratification in patients with atrial fibrillation. Patients who have had diabetes mellitus for a long period of time have a heavier burden of diabetic complications such as vascular disease, ischemic stroke, autonomic neuropathy, and retinopathy than newly diagnosed patients.[11,12] These complications have been associated with stroke risk beyond the risk encompassed by diabetes mellitus itself,[12–16] as well as with episodes of atrial fibrillation.[17]

The aim of this cohort study was to investigate the duration of diabetes mellitus and the risk of thromboembolic events in patients with an incident hospital-based diagnosis of atrial fibrillation. Given the association between diabetes mellitus duration and diabetic complications, we hypothesized that longer duration of diabetes mellitus would serve as an important predictive marker of higher thromboembolic risk in the setting of atrial fibrillation.

Materials and Methods

Study Design and Data Sources

The study was designed as a nationwide, register-based cohort study. The unique national identification number given to all Danish residents was used to link individual-level data from several nationwide Danish registries.[18] Data were obtained from 3 registries, such as the Civil Registration System, the National Patient Register, and the National Prescription Registry.[19–21] In Denmark, the *International Classification of Diseases* (ICD)-Eigth Revision was used until 1994 and hereafter replaced by ICD-10. For all extracted variables, both primary and secondary diagnoses were obtained. The National Prescription Registry holds individual-level information on all claimed prescriptions from Danish pharmacies since 1995. Information about emigration or death was available from the National Civil Registration system.[19] All ICD codes and Anatomical Therapeutic Chemical (ATC) Classification System drug codes used in this study are available in Table I in the online-only Data Supplement.

Study Population

The study population consisted of all inpatients and outpatients discharged from hospital with an incident diagnosis of nonvalvular atrial fibrillation from 2000 through 2011 as registered in the National Patient Register.[22] Incident cases of atrial fibrillation not habitually residing in Denmark were excluded, as were patients with a previous diagnosis of cancer and patients who died or were diagnosed with thromboembolism or transient ischemic attack on the day of admission (Figure 1).

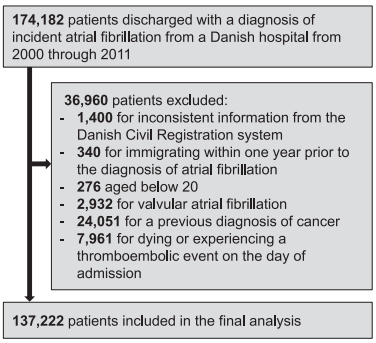

Figure 1. Flowchart explaining the patient selection process.

Exposure Variable

Diabetes mellitus was identified using ICD codes or a claimed prescription of a glucose-lowering drug.[23] Duration of diabetes mellitus was calculated from first diagnosis with an ICD code, or from the first claimed prescription of a glucose-lowering drug, whichever came first, until the time of discharge with a diagnosis of atrial fibrillation.

Outcomes

The primary outcome was thromboembolism, defined as a diagnosis of stroke (ischemic or unspecified, as the majority of unspecified strokes are of ischemic origin[24]) or systemic arterial embolism in the National Patient Register.[25] All-cause mortality and the combined end point of thromboembolism or death were considered secondary outcomes. Risk of bleeding during treatment with a vitamin K antagonist was also investigated in the subset of patients using vitamin K antagonists at baseline. Bleeding was defined as the occurrence of an intracranial, gastrointestinal, urinary tract, or airway bleeding (see Table I in the online-only Data Supplement for ICD codes).

Covariates

Components of the CHA_2DS_2-VASc score, the current guideline-recommended thromboembolic risk score,[8,9] were defined at the time of atrial fibrillation diagnosis using a combination of ICD and ATC codes. This included information about heart failure, hypertension, vascular disease, previous ischemic stroke, systemic arterial embolism, and transient ischemic attack. Age was determined from the Civil Registration System.[19] Components of a slightly modified HAS-BLED score, the current guideline-recommended bleeding risk score,[8,9] were likewise identified using a combination of ICD and ATC codes.[26] This included information about hypertension, abnormal renal/liver function, previous stroke, bleeding history/predisposition, age (>65 years), and drugs/alcohol concomitantly (information about control of blood pressure and time in therapeutic range was not available from the registries). Individual-level information about anticoagulant treatment during the entire follow-up period was available from the National Prescription Registry[21] (see Supplemental Table I in the online-only Data Supplement for ICD and ATC codes).

Statistical Analyses

Incidence rates for thromboembolism, death, and bleeding were calculated according to status of diabetes mellitus duration. Duration of diabetes mellitus was arbitrarily divided into the following categories: 0 to 4 years, 5 to 9 years, 10 to 14 years, and ≥15 years, and also analyzed as a continuous variable modeled as a natural cubic spline with knots at 5, 10, 15, and 20 years of duration, and presented graphically along with the best-fitted straight line. Associations between exposure and risk of outcome were analyzed using Cox proportional regression with time since atrial fibrillation as the underlying time scale. The associations between duration of diabetes mellitus and risk of thromboembolism and death are reported at 5-year follow-up as crude values and, to assess the potential refinement to current thromboembolic risk stratification strategies, also after adjustment for use of oral anticoagulants modeled as a time-varying covariate and components of the CHA_2DS_2-VASc risk score. Age was modeled as a continuous covariate using a natural cubic spline. End of follow-up (June 30, 2013) or emigration was considered as outcome-independent censoring. Death was considered a censoring event for the primary outcome, thromboembolism, and the secondary outcome, bleeding. The risk of bleeding was analyzed using only patients who were treated with a vitamin K antagonist at the time of discharge from hospital, or who were initiated on such treatment within 30 days after discharge. All such patients were considered baseline users of vitamin K antagonists. In the bleeding analysis, patients were censored at first occurrence of death, emigration or cessation of oral anticoagulant therapy, and adjustment was made for components of the HAS-BLED score

(age as continuous covariate). Data were analyzed using Stata version 13 (Stata Corporation, College Station, TX). Results are reported with 95% confidence intervals (CIs).

Results

We identified 174 182 patients discharged from a Danish hospital with an incident diagnosis of atrial fibrillation from 2000 through 2011. Of those, 36 960 patients were excluded, the majority because of a previous diagnosis of cancer (n=24 051) or from dying or because they suffered a thromboembolic event on the day of admission (n=7961; Figure 1).

The patients' baseline characteristics are presented in Table 1. In this cohort, 17 018 patients (12.4%) were classified as having diabetes mellitus. At the time of discharge from hospital, 85% of those where identified using an ICD code, 15% using an ATC code only, and 66% had both an ICD code and a history of claimed glucose-lowering drug prescription. A history of congestive heart failure, hypertension, ischemic stroke, peripheral artery disease, myocardial infarction, and bleeding was more frequent among patients with diabetes mellitus than patients without diabetes mellitus. Among patients with diabetes mellitus, longer duration of diabetes mellitus was associated with a progressively higher baseline prevalence of these comorbidities. The median available follow-up time was 4.0 years.

Crude incidence rates per 100 person-years are shown in Table II in the online-only Data Supplement. Patients with diabetes mellitus had higher rates of both thromboembolism and death than patients with nondiabetes, and displayed a trend of higher rates with longer duration.

Table 2 shows hazard ratios (HRs) for risk of thromboembolism and death using patients without diabetes as mellitus reference after 5 years of follow-up. When categorizing duration of diabetes mellitus, patients with diabetes mellitus with

Table 1. Baseline Characteristics of Patients With Atrial Fibrillation According to Duration of Diabetes Mellitus

			Patients With Diabetes Mellitus, Duration			
	Entire Cohort	No Diabetes Mellitus	0–4 y	5–9 y	10–14 y	≥15 y
Baseline characteristic						
Subjects, n (%)	137 222 (100)	120 204 (87.6)	7922 (5.8)	4781 (3.5)	2435 (1.8)	1880 (1.4)
Years of follow-up, median (10th–90th percentile)	4.0 (0.2–10.1)	4.1 (0.2–10.3)	3.4 (0.2–9.3)	3.0 (0.1–8.4)	2.7 (0.1–6.8)	2.4 (0.1–7.4)
Duration of diabetes mellitus, y	N/A	N/A	1.6 (0.0–4.3)	7.1 (5.4–9.4)	12.1 (10.4–14.3)	20.0 (15.6–27.5)
Current guideline identified risk factors (%)						
Age, median (10th–90th percentile)	72.9 (54.4–88.1)	72.8 (53.7–88.2)	72.5 (57.4–86.3)	73.9 (57.1–85.0)	74.6 (60.9–90.0)	73.3 (57.9–85.3)
≥75	47.3	47.4	43.6	49.1	51.0	46.5
65–74	25.1	24.4	30.6	29.9	30.3	29.9
<65	27.6	28.2	25.8	21.0	18.7	23.6
Congestive heart failure	18.2	16.9	25.6	28.8	31.1	31.3
Hypertension	21.4	18.9	34.9	38.8	46.7	48.1
Diabetes mellitus	12.4	0.0	100.0	100.0	100.0	100.0
Previous						
Ischemic stroke	7.7	7.1	9.5	11.9	14.6	15.9
Systemic embolism	0.7	0.6	1.0	0.9	0.7	1.1
Transient ischemic attack	4.9	4.8	5.3	5.5	6.7	6.9
Peripheral artery disease	7.4	6.6	10.4	13.2	17.0	21.8
Previous myocardial infarction	13.1	12.1	17.7	20.1	23.8	25.1
Female sex	46.7	47.2	41.0	43.7	44.9	46.8
Previous bleeding	10.1	9.6	12.7	14.4	14.6	14.4
Baseline antithrombotic therapy (%)*						
Vitamin K antagonist	14.8	14.5	17.7	15.9	17.0	12.6
Platelet inhibitor	55.5	53.5	66.4	72.2	72.4	71.9
Dabigatran	0.0	0.0	0.0	0.0	0.0	0.1
Stroke and bleeding risk score level—mean (SD)						
$CHADS_2$	1.3 (1.2)	1.1 (1.1)	2.4 (1.1)	2.6 (1.1)	2.8 (1.2)	2.8 (1.2)
CHA_2DS_2-VASc	2.8 (1.7)	2.6 (1.7)	3.9 (1.6)	4.2 (1.6)	4.5 (1.7)	4.5 (1.7)
HAS-BLED	2.0 (1.2)	2.0 (1.2)	2.4 (1.2)	2.7 (1.1)	2.8 (1.1)	2.9 (1.3)

$CHADS_2$ indicates congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke (doubled); CHA_2DS_2-VASc, gives extra weight to age ≥75 [doubled] and includes additional risk factors; vascular disease, age 65–74, and sex category (female); and HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history/predisposition, labile international normalized ratio, elderly (>65 y), drugs/alcohol concomitantly.

*Proportion of patients already using the specified agent at baseline and, therefore, not reflective of the antithrombotic treatment during follow-up.

the shortest duration (0–4 years) were at the lowest risk of thromboembolism in both the crude analysis and after adjustment for vitamin K antagonist treatment and components of the CHA_2DS_2-VASc score, with an adjusted HR of 1.11; 95% CI, 1.03 to 1.20. Patients with diabetes mellitus with the longest duration (≥15 years) appeared to be the category at the highest risk of thromboembolism (adjusted HR, 1.48; 95% CI, 1.29–1.70). The results were essentially similar in the analyses, where death was included as an outcome. All measures of associations were weakened by adjustment for CHA_2DS_2-VASc components. Results were unchanged after adjustment for baseline use of aspirin and clopidogrel (data not shown).

Figure 2 shows the HRs associated with duration of diabetes mellitus modeled as continuous variable using a cubic spline for the outcomes of thromboembolism and death after adjustment for anticoagulant treatment and components of the CHA_2DS_2-VASc score. Patients with atrial fibrillation but without diabetes mellitus were used as reference. These analyses confirmed an approximately linear dose–response relationship between the duration of diabetes mellitus and the risk of thromboembolism and death. In the linear model, a 5-year increase in duration of diabetes mellitus was associated with an adjusted HR for thromboembolism of 1.06; 95% CI, 1.02 to 1.10.

In an analysis restricted to patients using vitamin K antagonist at baseline, diabetes mellitus was associated with a crude HR for bleeding of 1.23 (95% CI, 1.03–1.48). The association attenuated after adjustment for components of the HAS-BLED bleeding risk score (HR, 1.06; 95% CI, 0.88–1.28). Figure 3 shows that longer duration of diabetes mellitus was not associated with a higher risk of bleeding both before and after adjustment for components of the HAS-BLED bleeding risk score, when compared with patients with atrial fibrillation but without diabetes mellitus. Incidence rates and HRs for bleeding according to categories of diabetes mellitus duration are shown in Table III in the online-only Data Supplement.

All associations about thromboembolism, death, and bleeding were fundamentally unchanged when including patients with a previous diagnosis of cancer and also when limiting the identification of patients with diabetes mellitus and the calculation of duration of diabetes mellitus to be based on ICD codes only (data not shown).

Discussion

In this cohort study, we investigated the potential for refining risk stratification in patients with an incident diagnosis of atrial fibrillation using duration of diabetes mellitus as a predictive marker of risk. Compared with patients without diabetes mellitus, we found that patients with diabetes mellitus were at higher risk of thromboembolism and death, and that longer duration of diabetes mellitus was associated with a progressively higher risk of thromboembolic events, also after careful adjustment for age and remaining components of the guideline-recommended CHA_2DS_2-VASc score. Longer duration of diabetes mellitus was not associated with a higher risk of bleeding in patients treated with a vitamin K antagonist.

Strengths and Limitations

The large sample size curtailed the risk of random error. We relied on hospital diagnoses to identify patients with atrial fibrillation, but the validity of this register-based diagnosis is high.[22] Similarly, the positive predictive value of a first diagnosis of diabetes mellitus is high (>95%).[23] We restricted our follow-up period to 5 years, as duration of diabetes mellitus inherently increases during follow-up. The use of nationwide administrative registries to identify outcomes allowed for virtually complete follow-up. Duration of diabetes mellitus was associated with both thromboembolism and death. Censoring by death from causes other than thromboembolism may, therefore, have caused a slight underestimation of the association between diabetes mellitus duration and risk of thromboembolism. Hence, selection bias is not a likely explanation for the study results. The positive predictive value of a diagnosis of stroke from the Danish National Patient Register is high

Table 2. Duration of Diabetes Mellitus and Hazard Ratios (95% Confidence Interval) for Thromboembolism and Death in Patients With Atrial Fibrillation

	No Diabetes Mellitus (Reference)	Patients With Diabetes Mellitus, Duration			
		0–4 y	5–9 y	10–14 y	≥15 y
Hazard ratios at 5-y follow-up					
Thromboembolism (no. of events)	9608	695	503	258	210
Crude	1	1.17 (1.08–1.26)	1.50 (1.37–1.64)	1.59 (1.41–1.80)	1.78 (1.56–2.04)
Adjusted*	1	1.11 (1.03–1.20)	1.32 (1.20–1.44)	1.28 (1.13–1.45)	1.48 (1.29–1.70)
Death (no. of events)	42 784	3 369	2399	1288	1037
Crude	1	1.26 (1.22–1.31)	1.59 (1.52–1.65)	1.77 (1.67–1.87)	1.94 (1.82–2.06)
Adjusted*	1	1.26 (1.22–1.31)	1.45 (1.39–1.51)	1.49 (1.41–1.58)	1.76 (1.66–1.87)
Thromboembolism or death (no. of events)	47 316	3690	2604	1385	1123
Crude	1	1.26 (1.22–1.30)	1.57 (1.51–1.64)	1.73 (1.64–1.83)	1.92 (1.81–2.04)
Adjusted*	1	1.24 (1.20–1.29)	1.42 (1.37–1.48)	1.45 (1.37–1.53)	1.72 (1.62–1.82)

Time since atrial fibrillation was the underlying time scale. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke (doubled), vascular disease, age, and sex category (female).

*Adjusted for CHA_2DS_2-VASc components (congestive heart failure, hypertension, age [continuous covariate], previous stroke, vascular disease, and sex) and vitamin K antagonist treatment modeled as a time-varying covariate.

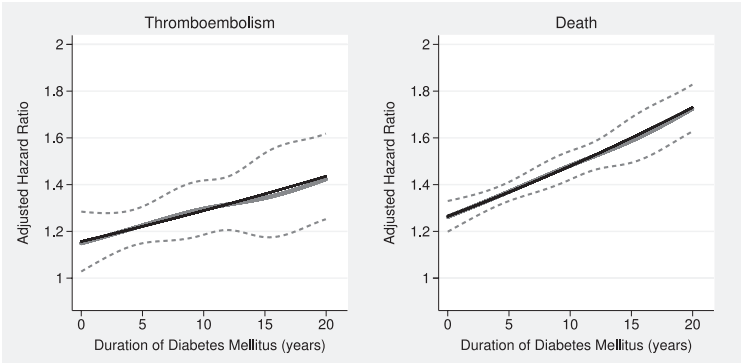

Figure 2. Duration of diabetes mellitus and hazard ratios for thromboembolism and death in patients with atrial fibrillation. Patients without diabetes mellitus are used as reference. Curves represent hazard ratios adjusted for vitamin K antagonist treatment and CHA_2DS_2-VASc components (congestive heart failure, hypertension, age, previous stroke, vascular disease, and sex). Solid gray lines are flexible cubic spline curves and solid black lines the best-fitted linear models. Dashed gray lines are 95% confidence intervals for the spline curves.

(≈80%), and, more importantly, it is most likely not associated with duration of diabetes mellitus.[25] The study results are, therefore, most likely not attributable to information bias. However, the use of only administrative registries to identify the covariates may have underestimated the prevalence of the comorbidities.

Diabetes mellitus may be involved in the pathogenesis of atrial fibrillation.[3] As a consequence, patients with diabetes mellitus may have atrial fibrillation because of different reasons than patients without diabetes mellitus. We made adjustment for components of the CHA_2DS_2-VASc score to unveil the potential refinement made by adding information about diabetes mellitus duration to the currently guideline-recommended risk stratification strategy (which suggests using the CHA_2DS_2-VASc score).[8,9] The focus was on duration of diabetes mellitus as a risk predictor, not a potential cause. Confounding by other causes of atrial fibrillation and simultaneously possible stroke risk factors is, therefore, not an issue of concern in this study.

Patients with diabetes mellitus without a hospital-based diagnosis of diabetes mellitus and treated only nonpharmacologically were not identified in this study, but the inclusion of some patients with diabetes mellitus in the nondiabetes reference group would only draw the association against the null. Moreover, the hospitalization-based identification of the study population assured that all patients with diabetes mellitus potentially could have obtained a diagnosis in the National Patient Register.

To eliminate the impact of the strong and inherent association between diabetes mellitus duration and age, we chose to model age as a continuous variable despite age being arbitrarily categorized in the CHA_2DS_2-VASc and HAS-BLED scores.

We calculated the duration of diabetes mellitus as the time since diagnosis. Actual onset of disease in type 2 diabetes mellitus occurs years before the clinical diagnosis,[27] so this study essentially investigates the potential, predictive value of using time since diagnosis of diabetes mellitus to refine risk stratification in patients with atrial fibrillation. Nonetheless, the delay in diagnosing type 2 diabetes mellitus is most likely universal, and does therefore in all probability not detract from the generalizability of the study results.

Interpretation and Clinical Perspective

In this study, patients with diabetes mellitus were at higher risk of thromboembolic events than patients without diabetes mellitus, and most importantly, the risk was higher the longer the duration of the disease.

A meta-analysis of studies reporting risk predictors for stroke in patients with atrial fibrillation found a higher risk associated with diabetes mellitus.[7] These findings have been supplemented by other large, register-based studies, which have confirmed the role of diabetes mellitus as a risk predictor.[28,29] Diabetes mellitus is also included in the widely recommended CHA_2DS_2-VASc risk stratification tool.[6] No studies have investigated the duration of diabetes mellitus and the risk of thromboembolic events in patients with incident atrial

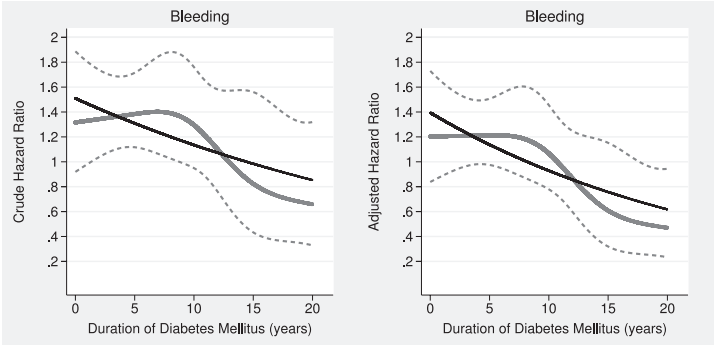

Figure 3. Duration of diabetes mellitus and hazard ratios for bleeding in patients with atrial fibrillation treated with a vitamin K antagonist at baseline. Patients without diabetes mellitus are used as reference. Left graph is crude. Right graph adjusted for components of the HAS-BLED score (hypertension, liver/renal disease, previous stroke, bleeding history/predisposition, age, and drugs/alcohol concomitantly). Solid gray lines are flexible cubic spline curves and solid black lines the best-fitted linear models. Dashed gray lines are 95% confidence intervals for the spline curves.

fibrillation. However, a population-based study of patients with diabetes mellitus found a dose–response relationship between the duration of diabetes mellitus and the risk of incident ischemic stroke.[12] In addition, duration of diabetes mellitus has been associated with cardiovascular diseases, such as coronary heart disease,[30] left ventricular diastolic dysfunction,[31] and cardiovascular mortality.[32]

Although this study explores risk prediction and not causality, some potential factors explaining the association between diabetes mellitus duration and thromboembolic events deserve mention. Longer duration of diabetes mellitus infers a higher burden of diabetic complications. One potential mediator is vascular disease, but this is already encompassed in the CHA_2DS_2-VASc score and, therefore, controlled for in our analysis. The persisting association may, therefore, be partly explained by diabetic complications, such as autonomic neuropathy, retinopathy, and nephropathy; all complications that have been associated with risk of stroke beyond the risk encompassed by diabetes mellitus itself.[13,15,16] Furthermore, autonomic neuropathy may induce additional episodes of atrial fibrillation,[17] thus influencing the subtype of atrial fibrillation, a factor also important for determining stroke risk in patients with atrial fibrillation.[33]

The balance between preventing thromboembolism and avoiding anticoagulation-related bleeding in patients with atrial fibrillation is critical. Despite clear recommendations for initiation of oral anticoagulant therapy, a worldwide pattern of underuse is reported.[10] Patient preferences are an important determinant of whether to treat, and formal thromboembolic and bleeding risk assessment is crucial to guide patients toward the most beneficial line of treatment.[34] The results from previous studies of diabetes mellitus as a bleeding risk predictor are inconsistent.[35,36] In this study, among patients receiving treatment with a vitamin K antagonist, no clear association between diabetes mellitus and bleeding risk was observed before nor after adjustment for components of the HAS-BLED score, a widely recommended bleeding risk score not including diabetes mellitus.[9,26] We even found indications of a lower bleeding risk with longer duration of diabetes mellitus. We are unable to provide any plausible explanations for this observation, but a study of patients with type 1 diabetes mellitus (patients with early debut of diabetes mellitus and, therefore, with longer duration of their disease in this study) found duration of diabetes mellitus to be a risk predictor for ischemic stroke, but not hemorrhagic stroke.[37] Considering some limitations of the present bleeding analysis (few bleeding events in the longer duration category, and use of claimed prescriptions and not actual verified usage of vitamin K antagonists to identify treatment periods, making it impossible to evaluate the impact of noncompliance), further studies investigating this matter are needed. However, these results suggest that when considering commencement of anticoagulant treatment, special emphasis may be directed toward patients with longer duration of diabetes mellitus. Of note, whether similar bleeding associations hold true for the nonvitamin K oral anticoagulants is unknown.

Suggestions for Future Research

Subsequent studies should explore whether the association between diabetes mellitus duration and the risk of thromboembolic events is mediated by specific diabetic complications.[38] Also, the potential impact of differentiating between degree of glycemic control as well as subtypes of diabetes mellitus (type 1 versus type 2) calls for investigation. As the Danish population is predominantly white, these findings also need confirmation in populations of different ethnicities.

Summary

In patients with atrial fibrillation, patients with diabetes mellitus with a longer duration of diabetes mellitus had a higher risk of thromboembolic events than patients with diabetes mellitus and shorter diabetes duration. Longer duration of diabetes mellitus was not associated with a risk of bleeding in patients treated with vitamin K antagonists. Considering the critical balance between prevention of thromboembolic events and avoidance of bleeding complications, longer duration of diabetes mellitus may favor initiation of anticoagulant treatment.

Disclosures

Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Daiichi-Sankyo and Sanofi Aventis. Dr Lane has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and served as a speaker for Boehringer Ingelheim, Bayer Healthcare, and BMS/Pfizer. In addition, Dr Lane is on the Steering Committee of a Phase IV apixaban study (AEGEAN). Both Drs Lip and Lane have participated in various clinical trials of stroke prevention in atrial fibrillation. Dr Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim. Drs Larsen and Rasmussen have been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. The other authors report no conflicts.

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