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BY
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CV

I graduated from the University of Aalborg in 2013 with a master's degree in Medicine with Industrial Specialization which combines medicine, pharmacology, and research. During the last year of my master education, I did a research project about the age dependence of risk factors for stroke and death in young patients with atrial fibrillation in collaboration with the Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University. Here I gathered a strong interest in risk stratification and cardiovascular diseases which lead to my PhD project. I started as a PhD student at the Aalborg Thrombosis Research Unit in August 2013.

During my time as a PhD student, I have participated in several international conferences where I have presented my research work, e.g., at the ESC Congress in London in 2015 where I was selected as the winner of the Young Investigator Award Session within thrombosis. Additionally, I spent one month at the Centre for Cardiovascular Sciences, University of Birmingham, City Hospital, Birmingham, United Kingdom, where I collaborated with international experts within the field and was involved in the research environment. My dissertation is based on four papers.

ENGLISH SUMMARY

Heart failure represents a major and growing public health problem due to its high prevalence and mortality. With the aging of the general population, the public health impact of heart failure is expected to increase substantially in the coming years. The heart failure population carries a very high mortality risk, but heart failure also ranks second as a cause of cardiogenic stroke. Epidemiological and pathophysiological data link heart failure to an increased risk of blood clot formation, leading to ischemic stroke and thromboembolism. Patients with heart failure do not only have an increased risk of stroke but also of stroke-related mortality and morbidity, as well as impaired quality of life. Risk stratification using readily available clinical variables may help identify patients at low and high risk of ischemic stroke and thromboembolism. Simple clinical risk scores have been useful in other settings to identify subgroups with a high risk of thromboembolic events. However, the potential of stroke risk stratification has not been studied in the heart failure population, neither has high-risk subgroups within this population been identified in detail.

The CHA_2DS_2-VASc score is a widely used risk score for clinical stroke risk stratification in atrial fibrillation. The score gives points according to the presence of different clinical risk factors, including congestive heart failure, hypertension, diabetes mellitus, previous stroke/transient ischemic attack/systemic embolism, vascular disease, age 65-74 years, age ≥75 years, and female sex. Recent research has indicated that the CHA_2DS_2-VASc score may be useful for predicting ischemic stroke in populations other than atrial fibrillation, including patients with acute coronary syndrome or sinus node dysfunction. However, its potential in predicting ischemic stroke risk among heart failure patients has not yet been explored in spite of opportunities to optimize prevention of such events in this population if managed correctly.

To better characterize patients with a diagnosis of heart failure who are at increased risk of stroke and thromboembolism and to assess the usefulness of the CHA_2DS_2-VASc score in these patients, we have linked data from Danish national registries. As the CHA_2DS_2-VASc score was originally developed for use in populations with atrial fibrillation, the extent to which the specific risk components of the score relate to the risk of stroke and thromboembolism in a heart failure population is unexplored. Three of these individual components have been selected for in-depth investigations of their usefulness for stroke risk stratification purposes. These include female sex, diabetes mellitus, and vascular disease (peripheral artery disease or prior myocardial infarction).

In a Danish heart failure population without atrial fibrillation, we found an association between the CHA_2DS_2-VASc score and an increased risk of ischemic stroke. When examining the discriminatory properties of the CHA_2DS_2-VASc score, the predictive accuracy of the score was modest in the heart failure population without atrial fibrillation. When investigating some of the individual components of the score, we found an association between a diagnosis of peripheral artery disease and diabetes mellitus and higher risk of ischemic stroke when compared with patients without these comorbidities, whereas we did not find an association between prior myocardial infarction and increased risk. Contrary to observations from populations with atrial fibrillation, we found an inverse association between female sex and ischemic stroke which attenuated with increasing age.

The research contained in this PhD project has contributed to identifying the individual and collective importance of a number of risk factors for ischemic stroke and thromboembolism, as defined by the CHA_2DS_2-VASc score, in patients with heart failure and without atrial fibrillation. The identification of high-risk subgroups is an important first step towards providing a basis for evidence-based clinical risk stratification for preventing stroke and thromboembolism among heart failure patients without atrial fibrillation.

DANSK RESUME

Hjertesvigt er et betydende og voksende sundhedsproblem med høj prævalens og mortalitet. I takt med at den generelle befolkning bliver ældre, forventes betydningen af hjertesvigt i befolkningen at blive væsentlig større i fremtiden. Hjertesvigt er associeret med en høj mortalitet, men rangerer også som nummer to på listen over årsager til kardioembolisk apopleksi. Resultater fra epidemiologiske og patofysiologiske studier forbinder hjertesvigt med en øget risiko for trombedannelse og dermed iskæmisk apopleksi og tromboemboli. Patienter med hjertesvigt har således en øget risiko for apopleksi og for apopleksi-relateret mortalitet og morbiditet samt nedsat livskvalitet. Risikostratificering ved anvendelse af tilgængelige kliniske faktorer kan muligvis identificere patienter med lav og høj risiko for iskæmisk apopleksi og tromboemboli. I andre sygdoms-sammenhænge har simple kliniske risikoscoresystemer vist sig brugbare til at identificere patientgrupper med en høj risiko for tromboemboli. Potentialet for risikostratificering for apopleksi i hjertesvigtspopulationen er dog ikke blevet undersøgt, ligesom høj-risiko patientgrupper ikke er identificeret.

For klinisk at risikostratificere patienter med forkammerflimmer i forhold til apopleksi bruges i dag CHA_2DS_2-VASc-scoresystemet. Dette scoresystem giver point ud fra tilstedeværelsen af forskellige kliniske risikofaktorer såsom hjertesvigt, hypertension, diabetes mellitus, tidligere apopleksi/forbigående iskæmisk anfald/tromboemboli, vaskulær sygdom, alder 65-74 år, alder $\geq$75 år og kvindekøn. I de seneste år er anvendelse af CHA_2DS_2-VASc-scoresystemet til at risiko-stratificere og prædiktere iskæmisk apopleksi blevet udvidet til andre sygdomsgrupper end den oprindelige patientgruppe med forkammerflimmer, men scoresystemets anvendelighed i en hjertesvigtspopulation er uafklaret. Dette på trods af en potentiel mulighed for at forhindre hændelser i denne population ved bedre identifikation af høj-risiko individer.

For bedre at kunne identificere patienter med en hjertesvigtsdiagnose, som har en øget risiko for apopleksi og tromboemboli, samt for at vurdere anvendeligheden af CHA_2DS_2-VASc-scoresystemet på denne patientgruppe har vi koblet informationer fra de danske nationale registre. Da CHA_2DS_2-VASc-scoresystemet oprindeligt er udviklet til patienter med forkammerflimmer, er det ikke undersøgt, hvorvidt de specifikke komponenter i scoresystemet relaterer til risikoen for apopleksi og tromboemboli hos hjertesvigtspatienter. Tre af disse komponenter er derfor blevet udvalgt til dybdegående undersøgelse af deres anvendelighed ved risiko-stratificering for apopleksi i hjertesvigtspopulationen. Disse komponenter inkluderer kvindekøn, diabetes mellitus og vaskulær sygdom (perifer arteriesygdom eller tidligere myokardieinfarkt).

I hjertesvigtspopulationen uden forkammerflimmer fandt vi en sammenhæng mellem CHA_2DS_2-VASc-scoresystemet og risiko for iskæmisk apopleksi. Da vi undersøgte de diskriminerende egenskaber af CHA_2DS_2-VASc-scoresystemet, fandt vi en moderat prædiktiv præcision ved scoresystemet i hjertesvigtspopulation uden forkammerflimmer. Ved undersøgelse af de individuelle komponenter af CHA_2DS_2-VASc-scoresystemet fandt vi en sammenhæng mellem en diagnose for perifer arteriesygdom samt diabetes mellitus og en højere risiko for iskæmisk apopleksi, hvorimod vi ikke fandt denne sammenhæng mellem tidligere myokardieinfarkt og iskæmisk apopleksi. Modsat observationer fra populationer med forkammerflimmer fandt vi en invers sammenhæng mellem kvindekøn og iskæmisk apopleksi hos hjertesvigtspopulationen uden forkammerflimmer, som dog svækkedes ved højere alder.

Den opnåede viden fra dette ph.d.-projekt har bidraget til anerkendelse af den individuelle og kollektive betydning af en række risikofaktorer for iskæmisk apopleksi og tromboemboli, defineret ud fra CHA_2DS_2-VASc-scoresystemet, hos hjertesvigtspatienter uden forkammerflimmer. Identificeringen af høj-risiko patientgrupper er et vigtigt skridt i forhold til at standardisere klinisk risiko-stratificering af hjertesvigtspatienter uden forkammerflimmer som et led i forebyggelsen af iskæmisk apopleksi og tromboemboli.

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Line Melgaard

ACRONYMS AND ABBREVIATIONS

AF: atrial fibrillation

CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 (double), diabetes mellitus, previous stroke/transient ischemic attack/systemic embolism (double), vascular disease, age 65-74, sex category (female)

COPD: chronic obstructive pulmonary disease

ESC: European Society of Cardiology

HF: heart failure

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HR: hazard rate ratio

MI: myocardial infarction

NOAC: non-vitamin K antagonist oral anticoagulant

NYHA: New York Heart Association

PAD: peripheral artery disease

RR: relative risk

TE: thromboembolic event

TIA: transient ischemic attack

LIST OF PAPERS

Paper 1: Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA_2DS_2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. JAMA.2015;314:1030-1038.

Paper 2: Melgaard L, Gorst-Rasmussen A, Rasmussen LH, Lip GYH, Larsen TB. Female sex is associated with a lower risk of stroke in patients with heart failure. Am Heart J 2015;169:396-403.

Paper 3: Melgaard L, Gorst-Rasmussen A, Rasmussen LH, Lip GYH, Larsen TB. Vascular disease and risk stratification for ischemic stroke and all-cause death in heart failure patients without diagnosed atrial fibrillation: A nationwide cohort study. PLoS One. 2016 Feb. [Under review, resubmitted with minor revisions].

Paper 4: Melgaard L, Gorst-Rasmussen A, Søgaard P, Rasmussen LH, Lip GYH, Larsen TB. Diabetes mellitus and risk of ischemic stroke in patients with heart failure and no atrial fibrillation. Int J Cardiol. 2016 Feb 3. [Accepted for publication, article in press].

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CHAPTER 1. INTRODUCTION

1.1. THE HEART FAILURE EPIDEMIC

The European Society of Cardiology (ESC) defines heart failure (HF) as an abnormality of cardiac structure or function leading to failure of the heart to deliver sufficient oxygen to the metabolizing tissues[1]. In some situations, the heart delivers the necessary amount of oxygen but only at the expense of increased left ventricular filling pressure[1]. HF can be described as a clinical syndrome rather than a disease in which patients have typical symptoms (e.g., dyspnea, abnormal fluid accumulation, and fatigue) and signs (e.g., elevated jugular vein pressure, pulmonary crackles, and displaced apex beat) of HF resulting from an abnormality of cardiac structure or function[2,3]. The diagnosis of HF requires a clinical evaluation incorporating both elements of the clinical history and signs plus physical examination and testing[3]. Since many of the symptoms of HF are unspecific, the diagnosis of HF can be troublesome. Therefore, determining a plausible underlying cause of the failure of the heart is an important step when diagnosing HF[2,4].

HF is an important healthcare issue, and with the aging of the population, the impact of HF is expected to increase substantially[5]. HF has a major impact on mortality and health economics[6]. Although survival has improved during the last twenty years due to improved treatment options, the prognosis still remains poor with a 5-year case fatality proportion of approximately 50% and a very high hospital readmission rate[7,8]. Age is a very important risk factor for HF, and the prevalence and incidence of HF increase progressively with age, with the prevalence exceeding ≥10% among persons 70 years or older[9]. In Denmark, approximately 1.5-2% of the population has shown signs of chronic HF, with half of these persons definitely having HF[10]. The incidence rate of chronic HF is 1-1.5 per 1000 Danish subjects per year, and the mean age at onset is 75 years, where the incidence rate is 12-30 per 1000 subjects[10].

The cardiac cause of HF is often myocardial disease (e.g., coronary artery disease) leading to permanent injury and systolic ventricular dysfunction[11]. Other common causes of HF are atrial fibrillation (AF), hypertension, or abnormalities of the ventricular diastolic function, valves, pericardium, or endocardium[2,12]. In most patients with HF, abnormalities of systolic and diastolic dysfunction coexist, irrespective of ejection fraction[12]. The pathophysiological damages in patients with left ventricular systolic dysfunction lead to remodeling of the ventricle with dilatation, increased mass, and impaired contractility[4]. Once ventricular dysfunction occurs, a sequence of compensatory systemic mechanisms is triggered which leads to structural and neurohormonal adaptations, including activation of the

renin-angiotensin-aldosterone system and the sympathetic nervous system[11]. These systems have a detrimental effect on several body components and induce a pathophysiological "vicious cycle", which accounts for many of the clinical symptoms and signs of HF[11]. The treatment of HF aims at interrupting these processes[2,4]. The etiology of chronic HF in Denmark is mainly due to ischemic heart disease (50-60%), with unknown/idiopathic (20-15%), hypertension (10-15%), valvular disease (5-10%), AF (3-4%), and other causes (4-10%) accounting for the remaining cases[10].

In 2010, the mortality risk of hospitalized Danish patients with HF was reported to be 26% within the first six months after diagnosis[13]. Among patients with chronic HF, the 2-year mortality risk was 41%, and the 5-year mortality risk has been estimated to be between 50 and 75%[13]. The high mortality risk in Denmark is similar to that found in other HF cohorts in developed countries[7,14]. The mortality risk in patients with HF is not homogeneous, and several risk factors have been identified to help stratify HF patients into low and high risk[15]. However, both sudden death and death due to progressive HF may be caused by unrecognized atheroembolic events[16]. Besides death, the most feared major adverse outcome in patients with HF is stroke[17]; nonetheless, until now only minor attempts have been made to identify HF patients with a high risk of stroke.

1.2. STROKE AND THROMBOEMBOLISM IN HEART FAILURE

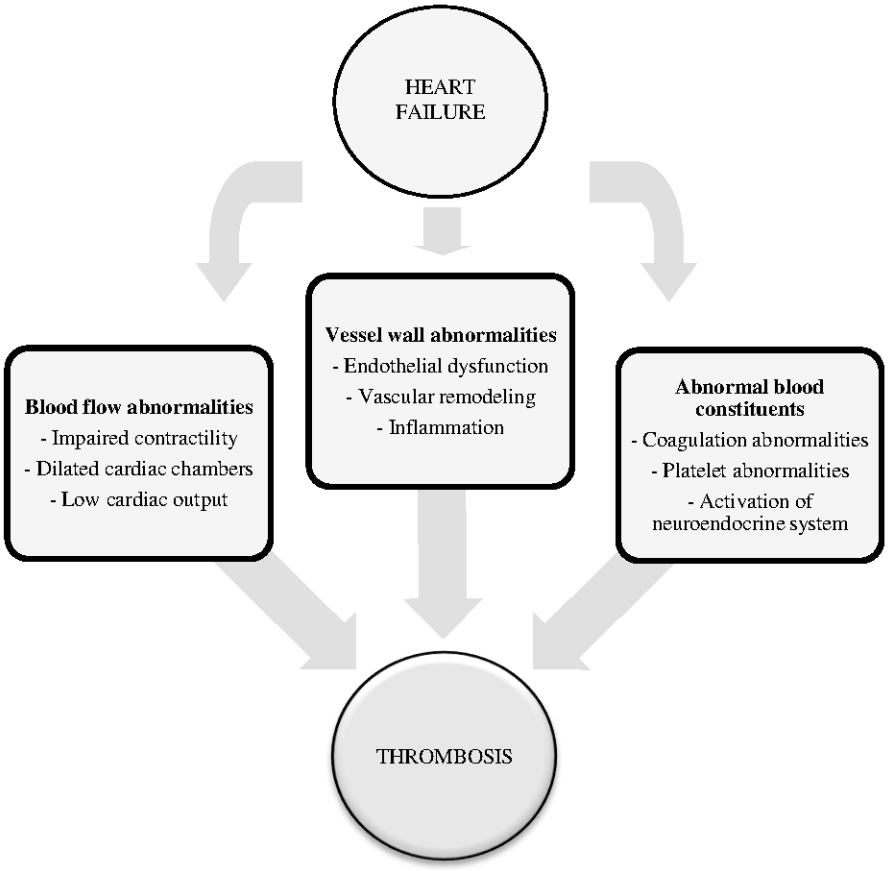
HF ranks second as a cause of cardiogenic stroke after AF[18]. HF does not only increase the risk of stroke, but also stroke-related mortality and morbidity, as well as impaired quality of life[19].

Despite the large number of patients with HF and the importance of stroke, little is known about the prevalence and incidence of this outcome in patients with HF who do not have AF, as most studies of patients with HF did not exclude patients with concomitant AF. For many years, AF has been subject to extensive research and is a known risk factor for stroke[20], but the focus on stroke in patients with HF and without AF is emerging.

Several studies have found an increased risk of stroke and thromboembolic events (TE) in patients with HF (summarized by Haeusler *et al*. in 2011)[17]. However, the long-term risk of stroke and its relationship to comorbidity in patients with HF and without AF is not well described[21]. In one study, the stroke risk in patients with HF was demonstrated to be higher especially within the first six months after a new HF diagnosis compared with persons without HF[22]. Compared with the general population, another study found a 17.4-fold increased risk of ischemic stroke during the first month after HF diagnosis and a persistently elevated risk

during the 5-year follow-up period[23]. However, none of these studies excluded patients with AF. The prevalence of "silent strokes" (ischemic brain lesions with no symptomatic presentation) is higher in patients with HF compared with subjects without HF (27-39% vs. 3.6%)[24]. This indicates that the prevalence of cerebrovascular disease may be higher in patients with HF than expected. Moreover, the risk of recurrent stroke is doubled in patients with HF and a prior stroke compared with patients without HF and a prior stroke[23]. A previous clinical diagnosis of HF has been demonstrated to be associated with a markedly higher mortality rate in patients with acute stroke compared with patients without HF[25,26], implying a poor prognosis of patients with HF who experience a stroke. Again, these studies did not exclude patients with AF.

Figure 1. Pathophysiology of thrombosis in heart failure (recreated from Eur J Heart Fail 2012;14: 681–695 with permission from Oxford University Press).



Several mechanisms have been associated with an increased risk of stroke and TE in patients with HF[27]. When AF is present, thrombus formation is frequently due to stasis in the left atrial appendages[19]. But patients with HF and without AF also have an increased risk of stroke events[28]. In general, three key characteristics have been associated with the formation of thrombi and contribute to a prothrombotic or hypercoagulable state; (1) blood flow abnormalities, (2) vessel wall abnormalities, and (3) abnormal blood constituents[29]. The pathophysiology of thrombogenesis in patients with HF may be explained through these multifactorial mechanisms[29], as illustrated in **Figure 1**. The etiology of HF may also impact on the mechanisms causing a stroke and on the clinical pattern of a stroke[30]. A study by Vemmos *et al*. showed that strokes in patients with HF are primarily of cardioembolic origin, especially if AF is present or in patients with HF with dilated cardiomyopathy or valvular diseases[31]. However, in patients with coronary artery disease or hypertension, strokes were predominantly atherosclerotic and lacunar, respectively. Especially, underlying atherosclerosis may play a dominant role in stroke occurrence, as many patients with HF have concomitant ischemic comorbidity. This diversity of stroke etiologies observed in the HF population reflects the fact that many predisposing factors for HF are also well-known causes of stroke even in the absence of HF.

1.3. STROKE RISK STRATIFICATION

Prediction models are increasingly used to complement clinical reasoning and decision making in modern medicine, in particular in the cardiovascular field[32–34]. Risk prediction models use predictors to estimate the absolute probability that a certain outcome will occur within a specific time period in an individual with a particular predictor profile (prognostic prediction model)[32]. Predictors may range from subject characteristics (e.g., age and sex), disease history, and physical examination results, to imaging, blood, urine, or genetic markers[32]. Prognostic prediction models are developed to guide healthcare professionals in their decision-making regarding further management such as initiating or withholding treatment and to inform individuals about their risk of developing a particular disease[34,35]. They are not meant to replace qualitative reasoning, but rather to supplement clinical decision-making by providing more objectively estimated probabilities[33,35].

Many cardiovascular disease risk scores have been developed using individuals from the general population or from more specific population subgroups, such as the AF population. In the latter population, simple clinical risk scores using readily available clinical variables have aided in the identification of patients at low and high risk of ischemic stroke and TE[36]. For example, the CHA_2DS_2-VASc score has been developed for stroke risk stratification in the AF population and is

recommended in current guidelines[37,38]. Based on the CHA_2DS_2-VASc score, patients are given 1 point for congestive HF, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease, and female sex and 2 points for age ≥75 years and previous stroke/transient ischemic attack (TIA)/systemic embolism; thus, 9 possible points (as age gives either 1 or 2 points), with higher scores indicating higher risk[20]. The score performs particularly well in identifying the patients with AF who are truly at low risk of TE[39,40].

In recent years, the use of the CHA_2DS_2-VASc score in predicting ischemic stroke and TE has extended beyond the original disease state for which it was proposed[41,42]. The CHA_2DS_2-VASc score has been applied to cohorts of patients without AF and has been reported to have modest predictive value for predicting ischemic stroke and TE in these cohorts[41,43–45]. For example, the CHA_2DS_2-VASc score can predict long-term outcomes in patients with acute ischemic stroke but without AF[43]. Indeed, in this study, patients with pre-stroke CHA_2DS_2-VASc scores of 0 had lower rates of mortality, stroke recurrence, and cardiovascular events compared with patients in the high-risk subgroups. Additionally, among patients with sinus node dysfunction and permanent pacemakers, the CHA_2DS_2-VASc score predicted a combined end point of stroke or death independent of a previous history of AF[44]. In patients with acute coronary syndrome but no AF, the CHA_2DS_2-VASc score predicted ischemic stroke/TIA events with an accuracy similar to that observed in historical populations with AF[42]. Furthermore, in a community study from Taiwan, the performance of the CHA_2DS_2-VASc score in predicting stroke was broadly similar in patients without and with AF[41].

The existing literature suggests that this simple clinical risk score, the CHA_2DS_2-VASc score, may provide a tool for easy clinical prognostic stroke risk stratification even among patients without AF[42–44]. To date, the use of stroke risk stratification in patients with HF has not been comprehensively studied. The prognostic weight of the individual risk factors of the CHA_2DS_2-VASc score may be different in patients with HF than that observed among patients with AF. Thus, besides assessing the performance of the CHA_2DS_2-VASc score in the HF population the next natural step is to examine each individual component of the score in the HF setting.

Stroke risk stratification has been useful in the AF population where the CHA_2DS_2-VASc score aids the decision whether or not to initiate anticoagulant therapy. The potential benefit of thromboprophylaxis in patients with HF and without AF is currently discussed in the literature[46–49]. However, it has been hypothesized that there is a rationale for using antithrombotic therapy as thromboprophylaxis in subgroups of patients with chronic HF and without AF[50]. Yet, information is lacking on the extent to which risk factors influence the prognosis among patients with HF and without AF. While studies of stroke risk stratification do not directly address the issue as to whether antithrombotic therapy is beneficial for HF patients,

they can nonetheless aid the clinician in assessing which patients could eventually be considered for thromboprophylactic management.

CHAPTER 2. AIMS AND HYPOTHESES

The aim of this PhD project was to contribute to the identification of risk factors for ischemic stroke and TE in patients with incident HF and without AF, thereby providing further knowledge of the disease burden associated with incident HF in combination with different comorbidities in order to potentially reduce the stroke burden in this population. The findings of this thesis may provide an important first step towards developing risk stratification methods for routine clinical use in HF patients, and thus, form the basis of evidence-based clinical risk stratification for preventing ischemic stroke and TE among HF patients without AF.

This thesis is based on four substudies. The first substudy assessed the properties of the CHA_2DS_2-VASc score for predicting ischemic stroke and TE risk in a population of patients with incident HF, with and without AF. The remaining three substudies evaluated selected components of the CHA_2DS_2-VASc score by examining the associations between sex, vascular disease, and diabetes and the risk of ischemic stroke and TE, respectively, in the context of the CHA_2DS_2-VASc score. The following list describes the specific aims and hypotheses of each substudy.

Substudy 1:

Aim: To assess the predictive properties of the CHA_2DS_2-VASc score in predicting ischemic stroke, TE, and all-cause death in a population with incident HF with and without diagnosed AF.

Hypothesis: The CHA_2DS_2-VASc score predicts ischemic stroke, TE, and all-cause death in incident HF patients without diagnosed AF similar to the performance observed among patients diagnosed with AF.

***Substudy 2*:**

Aim: To examine the association between sex, and the interaction between age and sex, and the risk of ischemic stroke, TE, and all-cause mortality in patients with incident HF without diagnosed AF.

Hypothesis: Female sex is associated with an increased risk of ischemic stroke, TE, and all-cause mortality in patients with incident HF without diagnosed AF, but age may affect this association.

***Substudy 3*:**

Aim: To examine the risk of ischemic stroke and all-cause mortality in patients with incident HF without diagnosed AF and with a previous diagnosis of vascular disease (peripheral artery disease (PAD) or prior myocardial infarction (MI)).

Hypothesis: A previous diagnosis of vascular disease is associated with an increased risk of ischemic stroke and all-cause mortality in patients with incident HF without diagnosed AF. However, PAD and prior MI may not confer the same risk.

***Substudy 4*:**

Aim: To examine the association between diabetes mellitus and the risk of ischemic stroke, TE, and all-cause mortality in patients with incident HF without diagnosed AF, and additionally, to explore the role of duration of diagnosed diabetes and risk of outcomes.

Hypothesis: A diagnosis of diabetes mellitus is associated with an increased risk of ischemic stroke, TE, and all-cause mortality in patients with incident HF without diagnosed AF, and longer duration is associated with a higher risk of each end point.

CHAPTER 3. REGISTER DATA SOURCES

In our four substudies, data from three Danish nationwide registries were linked using a unique person identification number (CPR number) which is used throughout all Danish national registries. The CPR is an abbreviation of "Central Person Register", which is the Danish name for the National Civil Registration System (described below)[51]. Once a person has been given a CPR number, this will follow the person forever[52]. Information from the Danish registries has been an important tool in health research and has resulted in numerous publications within different research fields[53]. The strengths of register-based research are the reduced time and cost that data collection would otherwise require, the large sample size, the representativeness, and the reduced risk of some common sources of bias (e.g., recall bias, non-response bias, or selection bias due to loss to follow-up)[54]. In the four substudies, all three registries were updated to December 31, 2013. A brief description of the three Danish national registries used in the four substudies is given below.

The National Civil Registration System

In Denmark, national registration of residents was done manually from 1924, but in 1968 the registration was recorded electronically in the National Civil Registration System[51]. This registry holds information on date of birth, vital status, date of death, and sex of all residents in Denmark[51,55]. Additionally, information about place of residence, citizenship, immigration/emigration, parents, and siblings, among other variables, is stored in the registry[52].

The Danish National Patient Registry

Risk factors and comorbidities within the study population were partly identified using the Danish National Patient Registry, which holds information on all hospital admissions along with diagnoses since 1977. Until 1994, all diagnoses were coded according to the 8th revision of the International Classification of Diseases (ICD-8). Subsequently, all diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD-10)[56–58]. In 1995, the Danish National Patient Registry extended to also include contacts to emergency rooms, specialist outpatient clinics, and psychiatric wards[58]. In 2003, all contacts to private hospitals were included; however, contacts to private hospitals account for only a very small proportion of all hospital contacts in the Danish health care

system[58]. The physician discharging the patient is responsible for determining the diagnostic codes related to the hospital stay. This registry was also used to identify the events of interest in our four substudies (death excluded which is registered in the National Civil Registration System).

The Danish National Prescription Registry

The Danish Registry of Medicinal Product Statistics collects individual-level data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System[57,59]. Individual-level over-the-counter medications are not included in this registry, but aggregated data on sales of over-the-counter drugs are included. For research purposes, an encrypted copy of this registry called the Danish National Prescription Registry became available in 2003, enabling linkage to an individual's prescription history using the CPR number[59]. This latter registry contains data from 1995 through present. Co-medication within the study population was identified using the Danish National Prescription Registry. Furthermore, this registry was used to ascertain the antithrombotic treatment status of each patient and, in some cases, used in combination with the Danish National Patient Registry to define comorbid conditions.

CHAPTER 4. STROKE RISK FACTORS IN HEART FAILURE

In the following sections, each substudy of the PhD thesis will be discussed. Due to the limited space in scientific papers, the following sections will provide additional information about each risk factor and critical deliberation of the results of each paper in a more general perspective. Furthermore, other putative stroke risk factors in the HF population will be evaluated together with the potential of stroke risk stratification in patients with HF. First of all, however, some methodological concerns, which are unavoidable when assessing stroke risk in a high-mortality population, will be outlined and discussed.

4.1. STROKE RISK ASSESSMENT IN A HIGH-MORTALITY POPULATION

Many cardiovascular studies use the time to a disease event as the primary outcome and thus, statistical methods developed for survival data are usually applied such as the Cox regression model[60,61]. When using the Cox regression model, hazard rates are compared. A hazard rate is a measure of the average frequency or "speed" with which an event occurs in a defined population in a defined time and answers the question: "if 100 persons were alive at some unspecified time point during follow-up, how many would we expect to experience the outcome during the next year"[60,62]. However, for risk stratification and prediction of an event for the individual patient, risks are more relevant from a clinical perspective[35]. A risk is the probability that an event will occur, e.g., that an individual will become ill or die within a stated period of time, and answers the question: "out of 100 persons at baseline, how many would we expect to experience the outcome during a specified follow-up period"[60,62]. In other words, rates are relative to a dynamic population (the at-risk population), whereas risks are relative to the baseline population.

In most cases, variables which are risk factors on the rate scale will also be risk factors on a risk scale[62]. In these cases, it is reasonable to use the (rate-based) Cox regression model to identify risk factors, which can be used in risk prediction and stratification. However, in some situations, the time to a specific event is of primary interest, but competing events may preclude its occurrence or greatly alter the chances to observe it[60,62]. In a population with a high mortality rate, such as the HF population, this is often the case. A patient who dies from any cause during follow-up is no longer at risk for any other event, such as ischemic stroke or TE[60,61]. In this situation, the one-to-one correspondence between risk factors on the rate scale and risk factors on the risk scale fails[62]. For example, a baseline

characteristic associated with a substantially higher stroke rate (i.e., the number of new strokes in the at-risk population) may have little influence on the absolute stroke risk if the characteristic is even more strongly associated with mortality; simply because patients die before developing a stroke. Risks and rates are two complementary ways of describing time-to-event data; and only when there are no competing risks and the outcome of interest is relatively rare can they be expected to be similar[62]. Competing risk from death may lead to bias by underestimating the association between exposure and outcome. When competing risk from death is present in a study, it is convenient to handle the issue of competing risks simply by studying a composite end point of mortality and a disease outcome[60]. On the other hand, this is a much less specific approach and cannot stand alone when risk prediction is used to support interventions which specifically target disease outcomes or if the frequency of each end point differs greatly[63]. Therefore, a better approach is to analyze the event of interest and take into account the competing risk[60].
In summary, these considerations underline two essential aspects: when the target is risk stratification, the experimenter should make statements about the behavior of risks, not rates; second, while statements about event rates can sometimes be directly translated to statements about absolute risk, this is not the case in a high-mortality population, such as the HF population. Both aspects can be readily dealt with by simply staying on an absolute risk scale from the offset[60].

Survival data and absolute risks: the pseudo-observations method

The primary reason why rate calculations and Cox regression models are most often used is that they are readily available in most statistical software. Oppositely, methods for risk calculation are less widely available. If we had complete follow-up, risk calculations would be easy because all observations would be categorized as either 0 or 1[61]. In that case, regression methods for binary data can be readily applied. For example, using a generalized linear model with a log link function would provide risk ratios. However, with survival data, observations are typically censored – so there is a subset of observations for which the status at the end of follow-up is unknown[60]. Simply discarding these observations disregards the information they contribute during the follow-up (i.e., the knowledge that the patients were event-free until censoring). A computationally convenient way to utilize this information is the pseudo-observations method[64]. Informally, the pseudo-observations method replaces unobserved survival status by an inputted pseudo-value. It can be shown that when the pseudo-values are inputted in a generalized linear model for binary data, associations on absolute risk scale are estimated correctly[65–67]. An advantage of the pseudo-value approach to assess associations on a risk scale is that it is easy to take competing risks into account [64]. In the substudies of this thesis, we used the pseudo-observations method to estimate the risk of the outcomes.

4.2. PAPER 1: PERFORMANCE OF THE CHA_2DS_2-VASC SCORE IN HEART FAILURE

As previously described, the use of the CHA_2DS_2-VASc score in predicting ischemic stroke and TE has extended beyond the original disease state for which it was proposed[41,42]. In patients with HF and without AF, it is unknown to date whether the risk of ischemic stroke increases with increasing CHA_2DS_2-VASc score in a similar fashion to that reported in patients with AF and, thus, whether the CHA_2DS_2-VASc score is a useful tool for stroke risk stratification in patients with HF.

In *substudy 1*[68], the risk of ischemic stroke, TE, and death was increasing with increasing CHA_2DS_2-VASc scores in patients without AF. At high CHA_2DS_2-VASc scores (≥4), the 1-year absolute risk of TE was relatively high, also in patients without AF (9.7%, 11.9%, and 18.0% for scores 4, 5, and 6, respectively). For the discriminatory properties of the CHA_2DS_2-VASc score, the score performed modestly in the HF population without AF (C-statistics: 0.63-0.69), but the performance depended on the choice of end point and the duration of follow-up. Our findings are consistent with another study, performed simultaneously with our study, where TE risk in patients with HF and without AF also increased with an increasing CHA_2DS_2-VASc score[69]. However, this concurrent study did not compare the properties of the CHA_2DS_2-VASc score and the event risk in HF patients with and without AF, which is an important comparison as HF patients with high scores may have an increased risk regardless of whether AF is present.

A good prediction model

Prognostic models are developed to provide objective estimates of outcome probabilities to complement clinical intuition and guidelines[35]. The underlying assumption is that accurately estimated probabilities improve clinicians' decision making and, consequently, improves patient outcome[70]. A good risk prediction model should exhibit good discrimination (the ability of the model to separate individuals who develop events from those who do not)[71]. Discrimination is most often reported using a C-statistic, as we did in our study. In the case of binary data, the C-statistic is the probability that a randomly selected case has a higher value of a risk score than a randomly selected non-case[71]. The C-statistic is calculated as the area under the receiver-operating curve which plots the sensitivity (the proportion of future cases scoring above a given threshold in a prediction model) against 1 minus specificity (the proportion of future non-cases scoring below a given threshold in a prediction model) for consecutive cut-offs for the predicted risk[71,72]. In survival analysis without censoring, sensitivity and specificity can be estimated by empirical true positive and true negative fractions, as all subjects can be classified as cases or controls[67,73]. However, with incomplete follow-up

(censoring), the interpretation of the C-statistic is less obvious, because the status of subjects lost to follow-up before a specified time is unknown[67]. Furthermore, in the setting of competing risks, two definitions of the specificity can be considered depending on the way to deal with subjects who undergo the competing event[66,67]. If the competing risk is death of any cause (as in our study), controls can be defined as either 'alive and event free' or 'alive and event free or dead', leading to two different interpretations. 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 (random concordance), and values above 0.5 indicate positive discriminative ability, with a value of 1 reflecting perfect discrimination[74]. It is undecided what constitutes an "acceptable" C-statistic, but clinically implemented risk scores typically have a C-statistic around 0.65-0.75[36,41,75]. In our study, we examined the discriminatory ability of the CHA_2DS_2-VASc score using C-statistics and defined controls as patients who were alive and event free at the specified time points. According to previous assessments of a good C-statistic, we interpreted the obtained C-statistics in our study as modest.

A good risk prediction model should also exhibit good calibration (whether predicted risks agree with observed risks across the whole range of a risk score). In the context of stroke risk stratification, there has been limited emphasis on the calibration properties of risk scores[41]. This is justly so because of the way that stroke risk scores are used in, for example, AF: their purpose is to identify low risk patients, not to accurately predict risk across the full patient population. Calibration (in addition to discrimination) of prediction rules is often worthwhile to assess, particularly when one is interested in the performance of a risk score across the full range of the score. However, in our study predicted risks equal observed risks by definition, as there is no source population providing predicted risk estimates since our study was the first to address this particular setting. Additionally, calibration is essential for the aspect of external validation which is not relevant in our study[76]. The CHA_2DS_2-VASc score has been demonstrated to be a useful tool for identifying "low-risk" patients in various studies examining risks in AF patients[39,40]. Identification of truly low-risk patients requires a high negative predictive value (NPV) of a risk score[74], i.e., the ratio of event-free patients and the number of patients classified as low-risk. In our study, we found moderately high 1-year NPVs (approximately 90%) for identifying patients at low risk of events as defined by a score of 1, confirming that the CHA_2DS_2-VASc score is a useful tool for identifying low-risk patients in the HF population without AF.

Study-specific limitations

As our definition of comorbidity relied on information from the Danish National Patient Registry, we cannot eliminate that the true score is actually higher than what we assessed, since some patients may have unregistered comorbidity. This would

underestimate the risk score level and potentially overestimate the event risk associated with a specific risk score level. Additionally, changes in clinical practice over time can influence the application of prognostic models, and improvements in diagnostic tests, biomarker measurement, or treatments may change the prognosis of patients over time[35]. As the inclusion and follow-up period extended over 12 years in our study, temporal changes with improvements in treatment for HF/AF might be an issue. This may limit the generalizability of these historical data to align with risks observed under contemporary treatment standards. Therefore, it was important to do a split sample analysis according to early and late study period. In this analysis, we found similar absolute risks as in the main analysis indicating a robustness of our findings to changes in standard HF diagnostic and treatment modality during 2000-2012. Thus, the performance of the CHA_2DS_2-VASc score was not influenced by changes in clinical practice during the study period.

Clinical considerations

In the HF population, it is unknown whether each component of the CHA_2DS_2-VASc score contributes equally to an increased stroke risk. The CHA_2DS_2-VASc score was not originally developed for patients with HF, and some of the components of the score may not be associated with an increased stroke risk in the HF population. Therefore, we would not expect the score to perform perfectly in this population[33]. However, we found that the CHA_2DS_2-VASc score modestly predicted the risk of ischemic stroke and similarly to findings in studies of the AF population for which the score was originally designed[75,77]. This is not surprising, as many of the components of the CHA_2DS_2-VASc score are well-known risk factors of stroke in the general population[78] and, thus, most likely also stroke risk factors in the HF population.

Currently, the components of the CHA_2DS_2-VASc score are dichotomized with the exception of age. This approach may be simplistic, as some of the components may provide better risk stratification if subdivided. However, for a risk score to be clinically applicable it must not be too complicated or time-consuming to use. In the AF setting, few studies have looked at the opportunities to subdivide the components of the CHA_2DS_2-VASc score[79,80], but future studies are necessary. Similarly, studies examining this in the HF setting are warranted.

A new risk score specifically derived from data of patients with HF will possibly better predict ischemic stroke risk. However, in a recent study[15], a novel prognostic scoring model to predict stroke or death in patients with systolic HF and sinus rhythm including eight clinical characteristics (age, gender, hemoglobin, blood urea nitrogen, ejection fraction, diastolic blood pressure, diabetes status, and prior stroke or TIA) performed similarly (C-statistic: 0.63) to the CHA_2DS_2-VASc score in our study. Additionally, as seen in other cardiovascular diseases, it is more

likely that a well-performing, previously established risk score accepted by clinicians will have broader impact in clinical practice. Thus, based on our findings, the CHA_2DS_2-VASc score could turn out as a useful tool for stroke risk stratification of patients with HF and without AF and aid the clinician in identification of low- and high-risk subgroups.

4.3. PAPER 2: SEX AND ISCHEMIC STROKE RISK ACCORDING TO AGE

An important but somewhat controversial risk factor for stroke in the AF setting is that of female sex[55,81]. This risk factor has been widely discussed during the last years due to conflicting results[82,83]. In the AF population, the stroke risk attributable to female sex interacts with age, as female sex is not an independent predictor of stroke in AF patients aged <65 years and as the (low) absolute rates in this age group are similar between males and females[55,81,84]. It is of interest to elucidate the relevance of this simple and very inclusive risk factor in a HF setting of patients without AF. In particular, it is unknown whether the association between sex and stroke risk in HF is also influenced by the presence of well-known cardiovascular risk factors of stroke, such as age[28,36,75]. Previous studies have described the association between sex and the risk of stroke in HF; however, many studies did not exclude patients with AF[23,85,86]. One study of patients with HF and without AF found that being female did not add any excess risk of TE compared with being male, when simply comparing these groups without any adjustment for age or other variables[69]. Similarly, another study of patients with HF and without AF found an association between female sex and lower risk of the combined end point stroke or death[15]. However, inconsistent results have generally been reported[87–89], which may in part be explained by differences in the severity and etiology of HF. The etiology of HF is different in females compared with males because HF in males are more often caused by ischemic heart disease, which may have a great influence on the subsequent risk of stroke[90,91].

Increasing age has been associated with an increased risk of ischemic stroke both in the general population and in specific patient groups[92,93]. In the context of the CHA_2DS_2-VASc score in patients with AF, age is divided into three separate components; age ≥75 years, age 65-74 years, and age <65 years, where age ≥75 years and age 65-74 years are strong risk factors of ischemic stroke[20]. In the HF population without AF, the association between age and ischemic stroke risk has not been comprehensively investigated. One study of patients with HF and without AF identified age >60 years as a predictor of stroke or mortality[15]. Another study looked at several different risk factors for all strokes (ischemic or hemorrhagic) including age ≥75 years[28]. In this latter study, age ≥75 years was not associated with an increased risk of all strokes; however, a very wide confidence interval existed due to a very low event number in this patient group. In another study of patients with HF and without AF, age 65-74 years was a strong predictor of TE[69].

In *substudy 2*[94], female sex was associated with a lower risk of ischemic stroke compared with male sex at 1-year follow-up, as shown in **Table 1**. This seems to be a reversed association compared with findings from the AF population. The observed lower risks of ischemic stroke in females were not present in the older age groups, where the competing risk of death was substantial among males in

particular; males may die before they are diagnosed with stroke. However, the competing risk of death would only introduce selection bias if the males who die were also those who would have been more likely to experience a stroke than the surviving males, which is likely to be a reasonable assumption. Males and females may also die due to undiagnosed stroke, which could lead to misclassification of the outcome. When considering a more broadly defined thromboembolic end point, a decreased risk among females persisted across nearly all age groups after 5 years of follow-up.

Table 1. Results of ischemic stroke in substudy 2 after 1 year of follow-up.

Exposure\Outcome	**Ischemic stroke**				
	Patient number *	Event number *	Absolute risk (%) *	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)†
Male sex (reference)	44,196	1,542	3.7	1.00	1.00
Female sex (overall)	39,946	1,284	3.3	0.90 (0.84-0.97)	0.91 (0.83-1.00)
Age 50-59 years (females vs. males)	2,859	48	2.3	0.70 (0.51-0.96)	0.85 (0.59-1.23)
Age 60-69 years (females vs. males)	6,040	154	3.3	0.73 (0.61-0.88)	0.86 (0.69-1.07)
Age 70-79 years (females vs. males)	11,421	416	4.1	0.86 (0.76-0.97)	0.93 (0.80-1.08)
Age 80-89 years (females vs. males)	14,690	525	3.7	0.97 (0.85-1.10)	0.93 (0.80-1.09)
Age 90+ years (females vs. males)	4,939	141	2.7	1.25 (0.89-1.76)	1.38 (0.89-2.15)

** In the age-divided analysis, patient number, event number, and absolute risk are only shown for the female exposure group.*
†Adjusted for hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), vascular disease (binary), and age (continuous).

Study-specific limitations

Our finding of a lower risk of ischemic stroke in females with HF compared with males may have prognostic value for clinicians in daily practice: even if the same comorbidities are present, males are at a higher risk of ischemic stroke. The difference in risk may partly be explained by the etiology of HF in males and females, as males more often have HF due to ischemic cardiac disease and females more often have preserved ejection fraction[95]. Unfortunately, we did not have information about the etiology of HF. Similarly, the etiology of HF may be closely related to the ejection fraction which we did not have access to due to lack of echocardiographic findings in the registries. Nonetheless, our results indicate a sex difference in ischemic stroke risk even when taking into account the components of

the CHA_2DS_2-VASc score. This finding may change when additional information such as detailed biochemical data is taken into account; indeed, it is possible that a suitably large collection of physiological parameters or lifestyle differences would explain the sex differences. However, our prognostic study does not aim for nor permit causal inferences; therefore, other studies are needed to elucidate the underlying mechanism for the difference in ischemic stroke risk between male and female HF patients.

Female sex as a risk factor in the CHA_2DS_2-VASc score

In *substudy 1*, we applied the CHA_2DS_2-VASc score to the HF population, as the clinician would do in clinical practice. Consequently, patients with a score of 1 are all males, because female sex gives one additional point besides HF. As male sex may be associated with an increased risk of stroke in the HF population compared with female sex[28,69,94], this may explain why a score of 1 (including only males) was related to a higher or equivalent absolute risk of ischemic stroke and TE than a score of 2 (including both females and males).

Readily available risk factors, such as sex, are important in order to have successful implementation and use of risk stratification in a clinical environment. *Substudy 2* indicates that female sex is not a predictor of ischemic stroke and TE in the HF population and for the purpose of stroke risk stratification using e.g., a risk score, male sex would perhaps serve valuable as a risk component.

4.4. PAPER 3: VASCULAR DISEASE AND ISCHEMIC STROKE RISK

Vascular disease is an established risk factor for stroke and TE[96,97] and included in the CHA_2DS_2-VASc score[36]. Vascular disease is a broad term, including two common and severe diseases, that is, PAD and MI. HF is known to be complicated by comorbidities such as PAD and prior MI[98,99]. In a study of patients with HF and without AF, no difference in the risk of all strokes (ischemic or hemorrhagic) was found between the presence and absence of vascular disease during the study period[28]. Oppositely, another study found vascular disease to be a predictor of TE in patients with HF and without AF[69]. These conflicting results may be due to the observation that PAD and prior MI do not confer the same risk of TE which has been observed in a previous study of a non-HF population[100]. Accordingly, evaluation of the association between vascular disease and ischemic stroke risk in the HF population requires investigating PAD and prior MI separately, as previously done in other settings[100,101].

In *substudy 3*, PAD was associated with a higher 1-year rate of ischemic stroke and all-cause death when compared with HF patients with no vascular disease, whereas prior MI was not associated with a higher rate, as shown in **Table 2**. When comparing patients with PAD to patients with prior MI, PAD was associated with a higher rate of both outcomes. In our study, patients with PAD had more often experienced a previous stroke/TIA compared with both patients with prior MI or no vascular disease, and the prevalence of diabetes, hypertension, and renal disease was higher in patients with PAD. Thus, patients with PAD in general had more comorbidity predisposing for stroke. However, with risk stratification in focus our results indicate that patients with HF and PAD represent a subgroup of HF patients with increased risk of ischemic stroke, also when taking into account other common cardiovascular comorbidities. Therefore, in clinical practice, this subgroup of HF patients should receive specific attention regarding thromboprophylaxis. Oppositely, patients with prior MI were not a high-risk subgroup in our study which may be because these patients are already well treated with thromboprophylactic therapies, such as platelet inhibitors, statins, and changes in lifestyle (an issue which will be discussed later).

Unfortunately, strong differential competing mortality across exposure levels can lead to counterintuitive findings on a risk scale, which is a real concern for vascular disease as an exposure. As emphasized in the discussion of the methodological concerns when assessing stroke risk in a high-mortality population, this is an example of a situation where statements about event rates cannot be directly translated to statements about absolute risks. Therefore, in *substudy 3* we reported associations in terms of (Cox model) hazard rate ratios after 1 year of follow-up and repeated this analysis on a risk (ratio) scale in the supplemental material. In our study, associations were attenuated when viewed on a risk scale. This provides

important information from a clinical perspective as the absolute potential of prevention strategies among a high-risk subgroup, such as PAD patients, might be smaller than suggested by the associations seen in the rate assessments.

Study-specific limitations

The rate and risk calculations in our study may be overestimated, as the definition of PAD was based on diagnosis codes from the Danish National Patient Registry, and thus, we may have only included patients with more severe PAD requiring hospitalization or treatment (as PAD is known to be asymptomatic in almost 50% of cases)[102]. We cannot reject that these aspects may partially explain our findings. It would have been beneficial to have information, for example, about the ankle-brachial index and use this measurement in the definition of PAD, but due to the nature of our data this was not possible.

Table 2. Results of ischemic stroke in substudy 3 after 1 year of follow-up.

Exposure\Outcome	**Ischemic stroke**				
	Patient number	Event number	Absolute risk (%)	Crude hazard ratios (95% CI)	Adjusted hazard ratios (95% CI)†
No vascular disease (reference)	27,242	705	2.7	1.00	1.00
PAD	2,274	101	4.7	1.82 (1.47-2.24)	1.34 (1.08-1.65)
Prior MI	8,556	250	3.0	1.09 (0.94-1.26)	1.00 (0.86-1.15)

†Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous).

The need for future studies

Our work in this study focuses on the basic issue to establish whether patients with HF and vascular disease, especially PAD, are indeed a subgroup at high ischemic stroke risk. We did not examine vascular disease as a potential cause of ischemic stroke, and accordingly, causal relations and confounding by possible stroke risk factors are not an issue of concern. Therefore, statements about the causal relationship in this subgroup of patients with HF are not justifiable with our data.

As vascular disease is a well-recognized ischemic stroke risk factor in the general population, it is not surprising that PAD is also a risk factor in the HF population. Strokes in patients with vascular disease are often atherosclerotic by nature and, therefore, the next step will be to elucidate whether strokes in the HF population with vascular disease are also atherosclerotic, as this information is important when determining how to manage the increased risk. Additionally, as studies examining

vascular disease and stroke risk in the HF population have demonstrated conflicting results, future studies are warranted.

4.5. PAPER 4: DIABETES MELLITUS AND ISCHEMIC STROKE RISK

Diabetes mellitus is common in patients with HF[103], and patients with diabetes have been demonstrated to have altered hemostasis, platelet activity, and vascular endothelial function contributing to a prothrombotic state[104]. In previous studies of patients with HF, diabetes has been associated with a higher risk of stroke and TE[15,87,88]. A recent study identified insulin-treated diabetes as a predictor of stroke in patients with HF and without AF[50]. In addition, other studies of patients with HF and without AF found an association between diabetes and increased risk of stroke and TE[69,105]. Previous non-HF studies have demonstrated that a longer duration of diabetes influences the risk of ischemic stroke in the form of a dose-response relationship[79,106,107]. In addition, duration of diabetes has been associated with an increased risk of other cardiovascular diseases and cardio-vascular mortality[108,109]. Whether duration of diabetes influences the stroke risk in patients with HF has not previously been investigated.

In *substudy 4*[110], we examined diabetes as a risk factor in the context of stroke risk stratification in the HF population. Patients with diabetes had an increased risk of ischemic stroke compared to HF patients without diabetes, as shown in **Table 3**. Furthermore, a secondary analysis suggested that a longer duration of diabetes is associated with higher cumulative incidences of ischemic stroke, TE, and all-cause death. However, these associations were not as clear as expected and as seen in previous non-HF studies, especially not for the outcome of ischemic stroke[79,106,107]. Although these previous studies were not performed in HF populations, we would expect to find a similar association in patients with HF.

Table 3. Results of ischemic stroke in substudy 4 after 1 year of follow-up.

Exposure\Outcome	**Ischemic stroke**				
	Patient number	Event number	Absolute risk (%)	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)†
No diabetes (reference)	32,249	839	2.8	1.00	1.00
Diabetes	7,108	277	4.1	1.49 (1.30-1.70)	1.27 (1.07-1.23)

†Adjusted for sex (binary), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous).

Study-specific limitations

We included only diabetes patients diagnosed in a hospital setting or treated pharmacologically; thus, patients treated only non-pharmacologically with no history of a hospital admission were not included in our study. Therefore, our study may not include patients with diabetes who are treated solely in general practice and are well controlled on diet and lifestyle. Moreover, we were not able to distinguish between type 1 and type 2 diabetes, two etiologically distinct diseases which could influence our results, but previous studies have found an increased risk of stroke in both subtypes[111,112]. Despite these limitations, diabetes is most likely associated with an increased risk of ischemic stroke and TE in the HF population without AF, as suggested in our and previous studies[28,87].

The association between time since diabetes diagnosis and risk of ischemic stroke and TE was examined only in a secondary exploratory investigation in our study due to the limitations of register-based studies. The register-based proxy for the duration of diabetes used in our study has important limitations; it can be affected by delayed diagnosis, changes over time in diagnostic criteria, and changes over time in medical treatment. These limitations make it difficult to estimate the precise duration of diabetes, and thus, we might not find the correct relationship between the duration of diabetes and the outcomes. However, our study provides a good approximation of this relationship and to our knowledge is the first study examining this in the HF setting.

Clinical considerations

Diabetes is included as a component in the CHA_2DS_2-VASc score[36] and will possibly be useful for stroke risk stratification in HF patients. However, patients with diabetes are a very heterogeneous group with varying degrees of diabetes duration, glycemic control, and diabetic complications; thus, it may be beneficial to subdivide these patients according to severity of diabetes to optimize risk stratification. Whether duration of diabetes will further enhance the identification of high-risk HF patients needs to be assessed in addition to *substudy 4*. Additionally, future studies are still necessary to comprehensively examine whether longer duration of diabetes may further refine stroke risk stratification in the HF population, as we did not find a clear association in our study, perhaps due to the limitations of our study.

4.6. OTHER PUTATIVE ISCHEMIC STROKE RISK FACTORS

Besides the risk factors evaluated in the substudies of this thesis, other possible stroke risk factors in the HF setting exist. As previously mentioned, the focus of this PhD project was to identify risk factors of ischemic stroke useful for stroke risk stratification in the HF population and not to examine or interpret causal relationships. Therefore, the following sections will present and discuss the limited existing literature on other possible risk factors of stroke in the HF population without AF, not causal associations. Components of the CHA_2DS_2-VASc score, not discussed in the four substudies, have already been evaluated in previous studies in relation to a HF setting. These components will be discussed in the following sections. Additionally, few other clinically available and HF-related risk factors will be deliberated.

Prior thromboembolism

Generally, ischemic stroke has a high recurrence rate both at short- and long-term follow-up[113,114]. In the AF population, prior stroke is associated with an increased risk of a new stroke event[20,115] and included as a risk factor in the CHA_2DS_2-VASc score[36]. Among patients with HF, several comorbidities are often present including prior stroke or TE. A few studies have reported that a prior stroke, TIA, or TE is a strong predictor of a recurrent stroke in patients with HF and without AF[28,50]. In a Danish study of patients with HF and without AF, previous TE appeared to be a very strong predictor of future TE; however, the end point of ischemic stroke alone was not evaluated[69]. In an exploratory analysis of the WARCEF trial (the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial), prior stroke was a risk factor for ischemic stroke in patients with HF and without AF[116]. Additionally, prior stroke/TIA was included as a strong predictor of stroke or mortality in a recent published scoring algorithm for HF patients[15]. As prior stroke is an accepted and well-known predictor of recurrent stroke in the general population, it is not surprising that this variable is also a strong predictor of recurrent stroke in the HF population. Thus, a history of prior stroke should be taken into account when assessing the stroke risk in a HF patient in clinical practice. Future studies examining the etiology of prior stroke in relation to recurrent stroke in the HF population without AF is warranted.

Hypertension

Hypertension is an established risk factor for stroke and TE in several cardiovascular diseases[117,118], and possibly also in the HF population. Additionally, hypertension is included in the CHA_2DS_2-VASc score[36]. Hypertension and HF are common disorders seen in everyday clinical practice, and both

diseases are increasing in incidence and prevalence. The risk of ischemic stroke and TE in patients with both hypertension and HF have been evaluated in a few studies[21,28,69,119]. Among patients with incident HF and without AF, higher baseline systolic and diastolic pressure levels were associated with a higher rate of stroke[119]. In other studies, hypertension has been identified as a predictor of stroke and TE among patients with HF and without AF[21,28,69,105]. Additionally, a history of hypertension has been associated with an increased risk of hospitalization due to stroke in patients with HF and normal sinus rhythm[120]. Thus, the previous studies in the literature suggest that hypertension is associated with an increased risk of TE in HF patients and if included in a risk score would possibly improve the identification of high-risk subgroups in the HF population.

Miscellaneous putative risk factors beyond the CHA_2DS_2-VASc score

In the HF population, several other possible stroke risk factors exist, such as symptom severity, lifestyle factors, echocardiographic findings, laboratory biomarkers, etc[50,121]. Some of these risk factors have previously been identified as predictors of stroke in patients with HF and without AF[50]. However, future studies are necessary to confirm these findings.

Today, HF is often subdivided into HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF)[2]. An interesting question is whether the etiology and prevalence of stroke differ in patients with HFrEF and HFpEF, and thus, whether ejection fraction provides useful prognostic information regarding stroke risk. This issue is under debate due to inconsistent results[88,122–124]. No difference in embolic risk (risk of stroke, TIA, or systemic embolism) was found in a recent study of non-anticoagulated patients with HFrEF and HFpEF[122]. Similarly, in a post-hoc analysis of a study of patients with AF with HFrEF or HFpEF, no difference in ischemic stroke risk was found between the groups[123]. Oppositely, in other studies ejection fraction appeared to be independently associated with TE risk[15,125], and a study including women only indicated that the TE risk potentially differs in HFrEF and HFpEF[88]. Furthermore, an 18% increase in the risk of stroke for every 5% decline in ejection fraction was observed in another study[124]. However, both of these latter studies included patients with AF. The etiology of stroke in HFrEF and HFpEF without AF is still an unclear topic, but most likely, the etiology is closely associated with the underlying cause of HF[31]. With the available data in our study, we did not have information about ejection fraction and could not evaluate this information in relation to stroke risk. Thus, whether ejection fraction should be included in the assessment of a HF patient's risk of ischemic stroke and TE remains to be determined.

HF can also be subdivided according to the functional level. The New York Heart Association (NYHA) functional classification is often used to grade patients with HF according to their symptom severity (NYHA class I-IV; where class IV is severe symptoms)[126]. One study of patients with HF and without AF identified higher NYHA class as a predictor of ischemic stroke, as they found a higher HR of ischemic stroke among patients with NYHA class III/IV compared with patients with NYHA class II[50]. We were not able to evaluate the functional classification with our data; thus, future studies need to comprehensively evaluate this possible risk factor. It would be practical to use this predictor, as HF patients are already assessed using the NYHA class to estimate their functional level. However, the functional classification may change over time and with treatments, and therefore, may be a challenging variable to include in risk stratification of HF patients.

Renal disease is a frequent comorbidity in patients with HF[127,128]. Renal disease has been associated with an increased stroke risk in patients with AF [129,130] and recent investigations have examined whether it adds predictive value to the CHA_2DS_2-VASc score in the AF setting[131]. Whether this risk factor is associated with an increased risk of stroke and TE in HF patients without AF still needs to be elucidated, but this was beyond the scope of this PhD project. Before further evaluation has been performed, it is not possible to comment on whether renal disease will provide clinically useful stroke risk stratification in the HF population.

4.7. POTENTIAL OF STROKE RISK STRATIFICATION IN HEART FAILURE

Stroke risk stratification can complement clinical reasoning, inform patients about their stroke risk, and guide healthcare professionals in their decision making regarding further management[34,35]. In the HF population, there exists a great potential for routine clinical stroke risk stratification to help clinicians in identifying high-risk subgroups. As seen in the review of the literature in the previous sections, the components of the CHA_2DS_2-VASc score may be a good starting point when trying to identify subgroups in the HF population with a high stroke risk. Nearly all the components of the CHA_2DS_2-VASc score are risk factors of ischemic stroke and TE in the HF population, with the possible exception of female sex. Specifically in our studies, we identified male sex, PAD, and diabetes as risk factors of ischemic stroke. Several other clinically available risk factors may exist beyond those included in the CHA_2DS_2-VASc score, and the impact of these additional risk factors on stroke risk would need further investigation, as the existing literature on these risk factors is sparse. Identification of high-risk subgroups is an important first step towards providing a basis for evidence-based clinical risk stratification for preventing stroke and TE among HF patients without AF.

Compared to the CHA_2DS_2-VASc score, a risk score derived from data of patients with HF will possibly better identify high-risk subgroups, e.g., including male sex as a risk factor instead of female sex. However, as previously mentioned, it is more likely that a well-performing, formerly established risk score accepted by clinicians will have broader impact in clinical practice. Thus, based on our findings, the CHA_2DS_2-VASc score may have a role as a useful tool for stroke risk stratification of patients with HF and without AF. However, the clinical usefulness of a stroke risk score, such as the CHA_2DS_2-VASc score, in the HF population will need to be determined in a future well-designed randomized study, before it can be implemented in clinical practice. Additionally, future studies would need to examine how to handle patients who are categorized in a high-risk subgroup.

4.8. METHODOLOGICAL CONSIDERATIONS

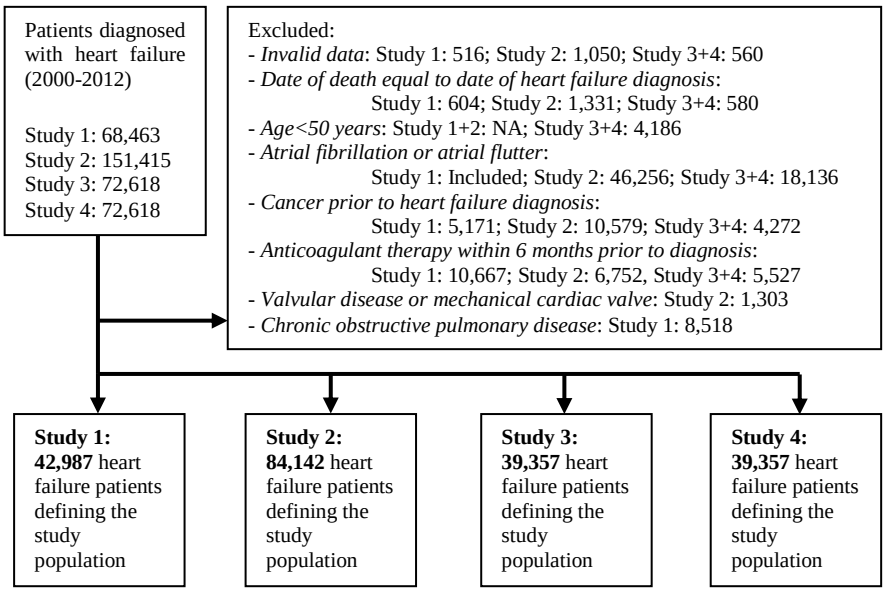
The four substudies described in the previous sections were designed as prospective population-based cohort studies using historical data. All study populations of the four substudies were drawn from the same Danish HF population. **Figure 2** shows a combined flowchart of all four substudies with the number of patients excluded in each substudy and the final study populations. The major strengths of these register-based nationwide studies were the large sample size, population-based coverage, and virtually complete follow-up of all patients, which reduce the risk of selection bias.

The study population in the four substudies consisted of patients with an incident diagnosis of HF. It is known that the stroke risk is higher in the first six months after diagnosis of HF[28] and, therefore, our results may demonstrate higher risks than found in other studies of HF patients. Furthermore, we investigated a real-life population using nationwide registries where we did not exclude the severely ill patients (as typically done in clinical trials); thus, our study population includes HF patients with several comorbidities predisposing for stroke events and again our event rates may be higher than those seen in clinical trials.

We only included patients aged >50 years, as HF in persons aged <50 years might represent a different group of patients, for example patients with congenital heart disease. Accordingly, our findings might not apply to younger HF patients. Additionally, our study population was ethnically non-diverse, since we investigated a Danish HF population which has a relatively stable and homogeneous demography[53], and therefore, our study results might not be generalizable to more diverse HF populations.

Patients with any diagnosis of cancer (ICD-10: C00-C97) within 5 years before HF diagnosis were excluded from the study population, since cancer patients represent a subgroup with high stroke risk and specialized thromboprophylactic treatment regimens[132]. You could argue that not all cancer types should prompt exclusion (e.g., patients who had a total prostatectomy done or patients with curative skin cancer); however, this distinction would be debatable. For the purpose of our study, we chose to exclude all patients with any cancer diagnosis within 5 years before HF diagnosis.

Figure 2. Combined flowchart of the four substudies.



Limitations of Danish nationwide registries for studies in heart failure

The use of the Danish nationwide registries in research entails some limitations. The following factors affect the value of register-based data in research: 1) completeness of registration of individuals, 2) the accuracy and degree of completeness of the registered data, 3) data accessibility and availability, and 4) possibilities of linkage with other data sources (record linkage)[54].

The diagnoses in the registries may not be complete or accurate. The diagnosis of HF in the Danish National Patient Registry has previously been validated with a sensitivity of 29%, a specificity of 99%, and a positive predictive value (PPV) of 81-84%[133,134]; thus, we did not capture all patients with HF and also cannot be certain that all patients identified as having HF had definite HF which could lead to imprecision in the risk estimates. However, as the specificity of the HF diagnosis was 99%, a more strict definition of HF will most likely not be necessary. The low sensitivity of 29% may reflect the inclusion of patients mainly with more severe HF. In this case, risk estimates obtained in this population may not apply to patients with less severe HF.

When using ischemic stroke as a primary outcome in a Danish register-based study, the outcome will be estimated using codes (ICD-10: I63, I64) in the Danish

National Patient Registry. As the end point depends on a diagnosis in the registry, it cannot be ruled out that some of the strokes might have been hemorrhagic strokes and thus, misclassified as ischemic strokes. In 2007, a validation study of the diagnosis of ischemic stroke in the Danish National Patient Registry found a PPV of approximately 97%[135]. Here, the number of subjects suffering from any stroke showed a tendency towards an overestimation in this registry, but the majority of the diagnoses of unspecified strokes were estimated to be of ischemic origin, indicating that the number of ischemic strokes seems to be underestimated. Thus, it may be reasonable to include unspecified stroke in the definition of ischemic stroke, as we did in our studies. In a review of the validity of diagnostic stroke codes in administrative databases from different countries[136], the diagnosis of ischemic stroke had a PPV of ≥82%. Thus, when using the registries the number of stroke events must be interpreted with caution, as it may be overestimated. Oppositely, some patients have fatal strokes and are therefore never admitted to a hospital, which underestimates the number of stroke events. One option to take into account the possible missing stroke events is to include deaths due to a TE in the outcome definitions, for example by using data from the Danish Register of Causes of Death[137–139]. However, in Denmark less than 10% of deceased have an autopsy performed, which impedes the usefulness of these data[138].

In studies of patients with HF and without AF, it is possible to exclude patients with a diagnosis of AF at baseline in the registries. A small validation study of the AF diagnosis in the Danish National Patient Registry found a positive predictive value of 99%[140]. However, not all patients with diagnosed AF are coded in the National Patient Register, as some patients are managed solely in general practice. Thus, some patients may be misclassified as non-AF patients in our study. Although not as important in the setting of our studies, it cannot be ruled out that some patients might have undiagnosed AF, since heart disease is associated with an increased risk of developing AF[141]. Among patients with HF who have experienced a stroke, about one-half have been reported to have AF[31]. To take into account the possibility that some patients would not be diagnosed with AF until weeks after the diagnosis of HF, we repeated the absolute and relative risk calculations after extending the definition of concomitant AF in *substudy 1* and *4* and found very similar results as in the main analyses. Patients may also develop AF during follow-up. This is not really a concern when examining the possibility of risk stratification, as in clinical practice we do not know whether or not a patient will develop AF in the future. Nonetheless, in *substudy 1, 3,* and *4* we did a sensitivity analysis censoring patients with HF who were diagnosed with AF during follow-up and found similar results as in the main analysis of each substudy. However, inclusion of patients with AF in the assumed HF without AF population may overestimate the absolute risk of stroke in such patients, as AF is a well-known risk factor of stroke[142]. The diagnoses of PAD, prior MI and diabetes mellitus were also found to be reasonably valid in the Danish National Patient Registry[140,143,144].

Data availability and accessibility may also be a problem when using register-based data, as the data collection has already been performed. For example, the Danish nationwide registries do not contain information about echocardiographic findings, and thus, it is not possible to distinguish between HF with preserved or reduced ejection fraction or to estimate the functional level (or NYHA class). Lifestyle factors, such as smoking habit, alcohol intake, physical activity, and BMI, are also inaccessible information, which could be an important limitation when investigating different risk factors and ischemic stroke risk. However, if the focus of a study is on the prognostic value of a risk factor in relation to ischemic stroke in the context of the CHA_2DS_2-VASc score (as in our studies), and not its causal role, confounding by other known stroke risk factors is not an issue of concern. We investigated whether different exposures were associated with ischemic stroke in patients with HF. Therefore, we adjusted for components of the CHA_2DS_2-VASc score, COPD (as some COPD patients may be misclassified as HF patients, possibly due to undistinguishable symptoms, which could potentially distort the investigated associations), and renal disease (as renal disease has been associated with an increased stroke risk in other patient groups[129,130] and, possibly, is also a risk factor of stroke in the HF population). This was not an attempt to adjust for confounding and hereby explore the potential causal relationship between the exposure and ischemic stroke, but to elucidate the potential predictive ability of the exposure for risk stratification in patients with HF, after adjustment for other possible risk factors. Careful considerations of how to deal with potential differences between exposed and non-exposed during follow-up are necessary to avoid distortions of the association in focus.

Baseline medications in Danish register-based studies are based on claimed prescriptions in the Danish National Prescription Registry. Therefore, it is unknown whether each patient will actually take the medication, and compliance is an important factor. With our register-based data, information about individual over-the-counter medications is not available. However, the potential for identifying, for example, aspirin use from prescription registries in Denmark is high, and only a very low proportion is sold over-the-counter[145]. Differences in antithrombotic treatment between exposed and non-exposed may distort the 'natural' associations if not taken into account; therefore we adjusted for antiplatelet therapy in *substudy 3*, as antiplatelet therapy may especially warp the association between vascular disease and stroke risk.

CHAPTER 5. REFLECTIONS ON THE FUTURE MANAGEMENT OF HIGH-RISK HEART FAILURE PATIENTS

After having identified high-risk subgroups within the HF population without AF, the next obvious question is how to handle these high-risk patients. It is tempting to direct the attention towards antithrombotic therapy; however, regarding stroke prevention in the HF population the relevance of antithrombotic therapy is controversial[17,19,29,146]. Today, cardiovascular international guidelines only recommend anticoagulant therapy in HF patients with concomitant AF, unless contraindicated[2,12,147]. Some guidelines also recommend anticoagulation in HF patients who have previously experienced a TE[12,147] or in the setting of a left ventricular thrombus[147,148]. A summary of recommendations for anticoagulant therapy in patients with HF is shown in **Table 4**. In HF patients without AF, antiplatelet therapy is only recommended in patients known to have coronary artery disease or prior MI[12]. Whether high-risk HF patients without AF or prior TE stand to gain from antiplatelet or anticoagulant therapy with either a vitamin K antagonist or one of the non-vitamin K antagonist oral anticoagulants (NOACs) is still unsettled.

Thromboprophylaxis in subgroups of patients with heart failure

Recently, the benefit of thromboprophylactic therapy in subgroups of patients with HF and without AF has been discussed[87,149]. We have identified subgroups in the HF population with an increased risk of ischemic stroke. However, we did not examine whether the identified high-risk subgroups would benefit from thromboprophylaxis or which thromboprophylaxis is most relevant in each subgroup of patients with HF and without AF. Therefore, the identified high-risk subgroups may provide new avenues for future randomized trials studying the effect of, for example, antithrombotic therapy in the HF population. However, the etiology of ischemic stroke may vary in HF patients with different co-morbidities[31], and thus, the effect of antithrombotic therapy, lipid-lowering drugs, or other thromboprophylactic strategies may differ across these subgroups of HF patients – an important aspect to take into consideration.

Patients with HF often have concomitant artery disease and, thus, are at high risk of atherothrombotic events. As described in the literature, these patients should receive appropriate antiplatelet therapy, as around 50% of cases of sudden cardiac death in HF are related to coronary atherothrombosis[16]. However, this patient group

possibly still has an increased risk of ischemic stroke and TE due to cardioembolism. As suggested by our results, a large proportion of patients with PAD were treated with an antiplatelet agent, but still had a moderately high 1-year absolute ischemic stroke risk, suggesting that this patient group may benefit from more thromboprophylaxis[149]. We did not see a similar increased rate of ischemic stroke among patients with prior MI, where an even greater proportion was treated with an antiplatelet agent. Our findings in the subpopulation of patients on antiplatelet therapy were consistent with the hypothesis of more intensified treatment and prophylaxis among MI patients, since patients on antiplatelet therapy with prior MI or no vascular disease had essentially the same rate of ischemic stroke. However, it was not the aim of the study to test this hypothesis; hence, future studies need to examine this. We did not examine which thromboprophylaxis is most relevant in patients with HF and vascular disease; therefore, statements about drug effects and preventive strategies in this subgroup of patients with HF are not justifiable with our data and the next step will be to elucidate the causal relations and the relevance of different treatment options in future studies.

The ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases from 2013 recommend antiplatelet therapy as secondary prevention in patients with diabetes at high risk of cardiovascular events[150]. In our study, we found a high absolute risk of TE, even though a large proportion of the study population was on antiplatelet therapy, indicating that more prophylaxis may be necessary. Previous studies of HF patients without AF and with concomitant diabetes only found a stroke risk high enough to possibly justify anticoagulation if other comorbidities were present simultaneously[28,87]. In our study population of HF patients with diabetes, other comorbidities were commonly present. This may indicate that in HF patients without AF but with concomitant diabetes in combination with other comorbidities, oral anticoagulation could be justifiable[87]. However, this speculation would need confirmation in prospective randomized trials.

As previously mentioned, patients with HF and without AF who have formerly experienced a TE or have a left ventricular thrombus are recommended anti-coagulant therapy in many guidelines[12,147,148,151]. For other subgroups in the HF population without AF, such as patients with hypertension or advanced age, the potential benefit from antithrombotic therapy is unknown. Regarding age, one explorative subgroup analysis has been performed in a post hoc analysis of patients younger and older than 60 years of age[152]. Younger patients benefited from warfarin over aspirin on the primary outcome (time to ischemic stroke, intracerebral hemorrhage, or death), whereas in older patients the different therapies did not differ with respect to the outcome. However, for the end point of ischemic stroke alone, both patients below and above 60 years of age demonstrated lower event rates when assigned to receive warfarin compared with aspirin. Additionally, the risk of stroke has been demonstrated to be highest during the first six months after the HF diagnosis and then attenuates over time[22,28], thus, short-term

anticoagulant therapy may be a solution[153]. Still, future trials are necessary before recommendations about antithrombotic therapy in subgroups of HF patients can be implemented in international guidelines. Furthermore, as AF is a common comorbidity among patients with HF and a strong risk factor for stroke, some events may be due to undiagnosed AF. Therefore, an important approach in the HF population without AF is to be aware of silent AF, e.g., by introducing AF screening programs in this population[153].

Table 4. Recommendations for anticoagulant therapy in heart failure from selected guidelines.

Guideline	Recommendations	Level of evidence	HF patients without AF	Level of evidence
ACC/AHA [12]	Anticoagulation is recommended for patients with chronic HF and AF (permanent/persistent/ paroxysmal) and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or TIA, or age ≥75 years). Chronic anticoagulation is reasonable for patients with chronic HF who have AF (permanent/persistent/ paroxysmal) but do not have any additional risk factor for cardioembolic stroke.	A B	Anticoagulation is not recommended in patients with chronic HF with reduced EF without AF, a prior TE, or a cardioembolic source.	B
ESC [2]	Anticoagulation is recommended for all patients with HF and AF (permanent/persistent/ paroxysmal) and a CHA_2DS_2-VASc score ≥1, without contraindications, and irrespective of whether a rate- or rhythm-management strategy is used.	A	Other than in patients with HF with AF (both HF with reduced and preserved EF), there is no evidence that an oral anticoagulant reduces mortality-morbidity compared with placebo or aspirin.	NA
HFSA [147]	Anticoagulation is recommended for all patients with HF and chronic or documented AF (permanent/persistent/ paroxysmal), unless contraindicated. Anticoagulation is recommended for all patients with HF and a history of systemic or pulmonary emboli, including stroke or TIA, unless contraindicated.	A C	HF patients with a recent large anterior MI with symptomatic or asymptomatic ischemic cardiomyopathy is recommended anticoagulation for a 3-month period post-MI.	B

Abbreviations: ACC = American College of Cardiology; AF = Atrial fibrillation; AHA = American Heart Association; EF = Ejection fraction; ESC = European Society of Cardiology; HF = Heart failure; HFSA = Heart Failure Society of America; MI = Myocardial infarction; TE = Thromboembolic event; TIA = Transient ischemic attack.

Considerations for routine use of antithrombotic drugs in heart failure

Looking at the possibilities of antithrombotic therapy in a more critical aspect; would it be well worth to even consider starting anticoagulant therapy in a population with a very high mortality rate? This is a difficult question to answer. Some deaths are likely to be attributable to undiagnosed stroke. A previous study suggested that anticoagulation may reduce mortality in patients with impaired left ventricular function[154]. Here, the reduction in all-cause mortality was suggested to be mainly driven by a reduction in cardiac mortality[154]. However, in another recent study, anticoagulation did not reduce mortality in patients with HF and in sinus rhythm[155]. Likewise, in other trials of patients with HF and without AF the rates of death were similar with warfarin and aspirin, a finding that is consistent with the lack of an effect of anticoagulants on mortality in patients with HF[156–158]. The lack of an effect of warfarin on mortality may suggest that most deaths in patients with HF who had severe impairment of left ventricular function are unrelated to TE and, instead, are most likely due to pump failure or ventricular arrhythmias[149]. Additionally, the risk of stroke in the HF population is modest, unless comorbidity is present, and therefore, the absolute stroke risk reduction with anticoagulation may also be modest. Thus, together with the probable lack of mortality benefit the absolute gain of anticoagulant therapy may only be justifiable in subgroups of HF patients who have a high stroke risk, such as in those with one or several comorbidities predisposing for stroke. However, it would be interesting to investigate the proportion of patients with HF who die from an ischemic stroke or TE or due to consequences of these events.

Another important issue to take into account is the risks and adverse effects of antithrombotic therapy[159]. Besides a number of factors influencing quality of life in patients using anticoagulant therapy, bleeding is a major adverse effect of anticoagulation. Although anticoagulant therapy was found to reduce the risk of ischemic stroke in previous trials of HF populations, it also caused increased risk of major bleeding, possibly since many risk factors are shared by both of these adverse outcomes[155,160]. In a recent randomized trial, however, the rate of the most feared type of bleeding, intracranial bleeding, did not differ between patients treated with warfarin and patients treated with aspirin, but the rate of major gastrointestinal bleedings was almost doubled in the warfarin group compared with the aspirin group[155]. Among anticoagulated patients with AF, use of the HAS-BLED score (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly, based on 9 possible points) is recommended to assess the bleeding risk[20,159]. If a patient has a HAS-BLED score ≥ 3, then the risks and benefits of anticoagulant therapy should be individually considered, and therapy will require regular monitoring to ensure effectiveness[161]. The HAS-BLED score is not meant to establish contra-indications for anticoagulation, but is rather used to estimate the bleeding risk in anticoagulated patients. Whether the HAS-BLED score can predict bleeding risk

among anticoagulated patients with HF and without AF has recently been investigated[162]. The authors found that the HAS-BLED score predicts bleeding risk in anticoagulated patients with HFrEF in sinus rhythm. These findings in combination with our findings in *substudy 1* suggest that the CHA_2DS_2-VASc score together with the HAS-BLED score could possibly be used to identify HF patients with a low or high stroke risk and a possibly favorable risk/benefit profile for anticoagulant therapy. However, this would need confirmation in future randomized trials.

If anticoagulation is not the optimal choice of antithrombotic therapy, antiplatelet therapy may be considered. Currently no data exist to support routine use of aspirin or other antiplatelet therapies in all patients with HF[2,12,147,151,158]. Antiplatelet therapy should in most cases be used in patients with atherosclerotic vascular disease[27,147]. However, in some studies of patients with HF, aspirin use has been associated with adverse outcomes, such as hospitalization for worsening HF[158,160], bleedings[158,160], serious gastrointestinal events[158], and pharmacological attenuation of the cardiovascular protective effect of angiotensin-converting enzyme inhibitor[163,164], an important agent in HF therapy. Additionally, aspirin resistance may occur more often in patients with HF[165]. Nonetheless, aspirin use has also been associated with a lower mortality in patients with left ventricular dysfunction and HF[163,166]. It is not the scope of this section to go into the discussion of possible adverse and beneficial effects of antiplatelet therapy in HF patients, but just to emphasize that antiplatelet therapy is also associated with clinical problems and the benefit of this thromboprophylactic therapy in patients with HF is controversial.

Non-vitamin K antagonist oral anticoagulants in heart failure

To overcome some of the limitations of standard anticoagulant therapy with warfarin such as food and drug interactions, frequent laboratory monitoring, and dose adjustments, the NOACs have been developed[167,168]. Yet, the role of the NOACs in patients with HF and without AF is unclear. An ongoing trial (COMMANDER HF)[169] explores the efficacy and safety of one of the NOACs, rivaroxaban, compared with placebo (standard care) after an exacerbation of HF in non-AF patients with HFrEF and documented coronary artery disease. This trial is expected to conclude in April 2017. However, additional trials examining the net clinical benefit of the NOACs in the HF population without AF is warranted, especially in specific high-risk subgroups within the HF population.

Even though these newer anticoagulants overcome some of the limitations of warfarin, one important limitation of the NOACs may particularly influence the potential use in HF patients. Several NOACs are predominantly eliminated renally, and therefore, their use is limited in patients with renal insufficiency[170,171].

Since renal and liver dysfunctions are common in patients with HF, the pharmacokinetic properties of the NOACs may impact the possibilities of these agents in a large proportion of patients with HF. A recent study has demonstrated that dose adjustment may be necessary when using NOACs in patients with AF and HF and concomitant renal impairment[172]. Future clinical trials, besides the COMMANDER HF trial, are warranted to elucidate the possibilities and safety of the NOACs in HF patients without AF.

CHAPTER 6. PERSPECTIVES AND CONCLUDING REMARKS

The research contained in this PhD thesis has contributed to the identification of the individual and collective importance of a number of risk factors for ischemic stroke and TE in patients with HF and without AF. The identification of high-risk subgroups is an important first step towards providing a basis for evidence-based clinical risk stratification for preventing stroke and TE among HF patients without AF.

We used the components of the CHA_2DS_2-VASc score as a starting point and identified male sex, PAD, and diabetes as risk factors of ischemic stroke. Previously, age, hypertension, and prior stroke have also been identified as stroke risk factors in the HF population without AF. We focused on the risk factors included in the CHA_2DS_2-VASc score, which are available for the clinician in daily clinical practice. These risk factors may provide the basis for a simple and recognizable approach to stroke risk stratification in the HF population, since the CHA_2DS_2-VASc score has been almost globally endorsed for use in AF patients. However, not all the individual components of the CHA_2DS_2-VASc score have been identified as established risk factors for ischemic stroke in the HF population without AF. Previous studies have even showed that some of these components are associated with a decreased ischemic stroke risk. Therefore, future studies are still necessary to confirm the results of our studies. Also, several other clinically available risk factors may exist beyond those included in the CHA_2DS_2-VASc score, and the impact of these additional risk factors would also be an area of interest for future research; for example, whether the stroke risk differs in patients with HFrEF and HFpEF, and whether the stroke risk increases with reduction in ejection fraction, which we were not able to investigate with our data. Similarly, as we excluded patients under 50 years of age, because the prevalence and contribution of the various stroke risk factors in this small subgroup are likely to be different from the typical elderly HF patient, our findings might not be generalizable to younger HF patients. Thus, future studies will need to examine this patient group separately.

We found that the CHA_2DS_2-VASc score was able to modestly predict patients with a high and low risk of ischemic stroke and TE. Whether a modified CHA_2DS_2-VASc score, including or substituting with other risk factors, will perform better than the original score still needs to be explored in future studies. Additionally, the clinical usefulness of a stroke risk score, e.g., the opportunity to identify subgroups of HF patients suitable for antithrombotic treatment using the CHA_2DS_2-VASc score, remains to be determined in a randomized controlled study.

Currently, the choice of antithrombotic medication in the HF population without AF should be made on a patient-by-patient basis and depends on a careful risk/benefit discussion between the patient and the clinician, especially among high-risk patients. Anticoagulant therapy prevents strokes, most likely embolic strokes, in patients with HF and without AF who have severe systolic dysfunction; but the general stroke rate is too low to justify the routine clinical use of anticoagulation in all patients with HF in the light of the increased risk of bleeding. Preventative strategies may be particularly relevant among high-risk subgroups, but whether full anticoagulant therapy would be beneficial in reducing the risk without increasing the risk of bleeding, that is, to yield a net clinical benefit in these patients, needs to be tested in an appropriately designed randomized controlled trial including high-risk patients potentially defined by a high CHA_2DS_2-VASc score.

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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

Original Investigation

Assessment of the CHA_2DS_2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation

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IMPORTANCE The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-75 years, sex category [female]) is used clinically for stroke risk stratification in atrial fibrillation (AF). Its usefulness in a population of patients with heart failure (HF) is unclear.

OBJECTIVE To investigate whether CHA_2DS_2-VASc predicts ischemic stroke, thromboembolism, and death in a cohort of patients with HF with and without AF.

DESIGN, SETTING, AND POPULATION Nationwide prospective cohort study using Danish registries, including 42 987 patients (21.9% with concomitant AF) not receiving anticoagulation who were diagnosed as having incident HF during 2000-2012. End of follow-up was December 31, 2012.

EXPOSURES Levels of the CHA_2DS_2-VASc score (based on 10 possible points, with higher scores indicating higher risk), stratified by concomitant AF at baseline. Analyses took into account the competing risk of death.

MAIN OUTCOMES AND MEASURES Ischemic stroke, thromboembolism, and death within 1 year after HF diagnosis.

RESULTS In patients without AF, the risks of ischemic stroke, thromboembolism, and death were 3.1% (n = 977), 9.9% (n = 3187), and 21.8% (n = 6956), respectively; risks were greater with increasing CHA_2DS_2-VASc scores as follows, for scores of 1 through 6, respectively: (1) ischemic stroke with concomitant AF: 4.5%, 3.7%, 3.2%, 4.3%, 5.6%, and 8.4%; without concomitant AF: 1.5%, 1.5%, 2.0%, 3.0%, 3.7%, and 7% and (2) all-cause death with concomitant AF: 19.8%, 19.5%, 26.1%, 35.1%, 37.7%, and 45.5%; without concomitant AF: 7.6%, 8.3%, 17.8%, 25.6%, 27.9%, and 35.0%. At high CHA_2DS_2-VASc scores (≥4), the absolute risk of thromboembolism was high regardless of presence of AF (for a score of 4, 9.7% vs 8.2% for patients without and with concomitant AF, respectively; overall $P<.001$ for interaction). C statistics and negative predictive values indicate that the CHA_2DS_2-VASc score performed modestly in this HF population with and without AF (for ischemic stroke, 1-year C statistics, 0.67 [95% CI, 0.65-0.68] and 0.64 [95% CI, 0.61-0.67], respectively; 1-year negative predictive values, 92% [95% CI, 91%-93%] and 91% [95% CI, 88%-95%], respectively).

CONCLUSIONS AND RELEVANCE Among patients with incident HF with or without AF, the CHA_2DS_2-VASc score was associated with risk of ischemic stroke, thromboembolism, and death. The absolute risk of thromboembolic complications was higher among patients without AF compared with patients with concomitant AF at high CHA_2DS_2-VASc scores. However, predictive accuracy was modest, and the clinical utility of the CHA_2DS_2-VASc score in patients with HF remains to be determined.

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Heart failure (HF) is associated with an increased risk of ischemic stroke and mortality, whether in sinus rhythm or atrial fibrillation (AF).[1-5] Risk stratification using readily available clinical variables may help identify subgroups at low and high risk of ischemic stroke and thromboembolic events (TE) in an HF population.

Simple clinical risk scores have been useful in other settings such as in patients with AF, for example, the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74 years, sex category [female]), which is recommended in current guidelines (based on 10 possible points, with higher scores indicating higher risk).[6,7] In recent years, use of the CHA_2DS_2-VASc score in predicting ischemic stroke, TE, and death has extended beyond the original disease state for which it was proposed.[8,9] In addition, it is recognized that the cluster of multiple stroke risk factors included within the CHA_2DS_2-VASc score increases the risk of ischemic stroke, TE, and death, whether or not AF is present. Thus, there is a need to study the extent to which concomitant AF modifies the pattern of the association between CHA_2DS_2-VASc score and the risk of ischemic stroke, TE, and death in patients with HF.

AF *atrial fibrillation*

COPD *chronic obstructive pulmonary disease*

HF *heart failure*

ICD-10 International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

NPV *negative predictive value*

TE *thromboembolism*

Evaluating an ischemic stroke and TE risk score in a population with a high mortality rate such as the HF population (5-year mortality of 45%-60%)[10,11] is not trivial because a competing-risks setting taking careful consideration of the interplay between mortality and ischemic stroke/TE risk is needed to provide meaningful risk assessments.[12,13]

We hypothesized that the CHA_2DS_2-VASc score could predict ischemic stroke, TE, and death in patients with HF without AF in a manner comparable with that evident in AF populations. We hypothesized that at high CHA_2DS_2-VASc scores, the risk would be comparable between patients with and without AF.

Methods

Registry Data Sources

We used 3 nationwide registries in this study: (1) the Danish National Patient Register,[14] which has registered all hospital admissions along with diagnoses since 1977 and has coded all diagnoses according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) since 1994; (2) the Danish National Prescription Registry,[15] which contains data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System; and (3) the Danish Civil Registration System, which holds information on date of birth, migration, vital status, date of death, and sex of all persons living in Denmark.[16] Data were linked via a unique personal identification number used in all Danish national registries. All 3 registries were used up to December 31, 2012 (end of follow-up). These registries have previously been well validated,[14,15,17] and the diagnoses of HF, AF, and ischemic stroke have been found to be valid.[17-19]

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency.

Study Population

The study population was identified as patients aged 50 years or older discharged with a primary diagnosis of incident HF (*ICD-10* codes I50, I42.0, I11.0, I13.0, and I13.2) in the period January 1, 2000, to December 31, 2012. Patients with AF were identified by a hospital diagnosis of AF or atrial flutter (*ICD-10* code I48) between 1994 and baseline. We excluded patients treated with a vitamin K antagonist (ATC codes B01AA03 and B01AA04) within 6 months prior to the HF diagnosis. Moreover, patients with a diagnosis of cancer (*ICD-10* codes C00-C97) within 5 years before HF diagnosis or with a prior diagnosis of chronic obstructive pulmonary disease (COPD [*ICD-10* code J44]) were excluded.

Comorbidities at baseline were identified using the Danish National Patient Register and the Danish National Prescription Registry. Ascertainment of baseline medication status was based on medication purchase in a 45-day window before or after the date of HF diagnosis. *ICD-10* codes and ATC codes were used to define comorbidities and medical therapies (eTable 1 in the Supplement).

Risk Stratification Using CHA_2DS_2-VASc Score

Based on the CHA_2DS_2-VASc score, patients were given 1 point for congestive HF, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease, and female sex and 2 points for age 75 years or older and previous TE.[20] Accordingly, a score of 1 in our analyses corresponds to patients with HF only and no additional stroke risk factors.

Outcomes

The primary end point was defined as a hospital diagnosis (according to the Danish National Patient Register) of ischemic stroke (*ICD-10* codes I63 and I64.9) or TE (ischemic stroke [*ICD-10* codes I63 and I64.9], transient ischemic attack [*ICD-10* code G45], systemic embolism [*ICD-10* code I74], pulmonary embolism [*ICD-10* code I26], or acute myocardial infarction [*ICD-10* codes I21 and I23]). All-cause death (according to the Danish Civil Registration System) was included as a secondary end point.

Statistical Analysis

Baseline characteristics at the time of HF diagnosis were described using means and standard deviations for continuous measures and percentages for categorical measures (**Table 1**).

Time-to-event analysis was used to describe the association between the CHA_2DS_2-VASc score and the risk of ischemic stroke, TE, and death, separately within the strata of patients with HF with and without a prior diagnosis of AF. Time

Table 1. Baseline Characteristics of the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation[a]

Clinical Characteristics	No. (%) of Patients	
	Without Atrial Fibrillation (n=33 592)	With Atrial Fibrillation (n=9395)
Female	14 817 (44.1)	4420 (47.1)
Age at baseline, mean (SD), y	74 (11.6)	78 (11.1)
Age group, y		
50-64	8284 (24.7)	1390 (14.8)
65-74	8334 (24.8)	1850 (19.7)
≥75	16 974 (50.5)	6155 (65.5)
Baseline comorbidity		
Hypertension	14 444 (43.0)	4082 (43.5)
Previous thromboembolism[b]	9559 (28.5)	2504 (26.7)
Vascular disease	8746 (26.0)	1884 (20.1)
Previous myocardial infarction	6650 (19.8)	1263 (13.4)
Diabetes	5769 (17.2)	1403 (14.9)
Peripheral arterial disease	2918 (8.7)	794 (8.5)
Previous ischemic stroke	2675 (8.0)	1085 (11.6)
Renal disease	1686 (5.0)	491 (5.2)
Hyperthyroidism	630 (1.9)	360 (3.8)
Liver disease	121 (0.4)	38 (0.4)
Baseline medications		
Loop diuretics	21 949 (65.3)	7131 (75.9)
Angiotensin-converting enzyme inhibitors	17 724 (52.8)	4625 (49.2)
Aspirin	16 457 (49.0)	4453 (47.4)
β-Blockers	15 365 (45.7)	5155 (54.9)
Nonloop diuretics	13 197 (39.3)	3763 (40.1)
Statins	10 394 (31.0)	1907 (20.3)
Aldosterone antagonists	7701 (22.9)	2408 (25.6)
Calcium channel antagonists	5674 (16.9)	1822 (19.4)
NSAIDs	4761 (14.2)	1223 (13.0)
Antidiabetics	4551 (13.6)	1016 (10.8)
Digoxin	3667 (10.9)	4862 (51.8)
Thienopyridines	3610 (10.8)	521 (5.6)
Angiotensin receptor blockers	3490 (10.4)	889 (9.5)
Vasodilators	640 (1.9)	221 (2.4)
Pacemaker/ICD	1169 (3.5)	628 (6.7)
Percutaneous coronary intervention	3107 (9.3)	394 (4.2)
Coronary artery bypass graft surgery	1691 (5.0)	447 (4.8)
Rehospitalization for heart failure during full follow-up		
1 event	13 172 (39.2)	3445 (36.7)
2-4 events	13 873 (41.3)	4140 (44.1)
≥5 events	6547 (19.5)	1810 (19.3)

Abbreviations: ICD, implantable cardioverter-defibrillator; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] All study patients had heart failure at baseline.

[b] Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

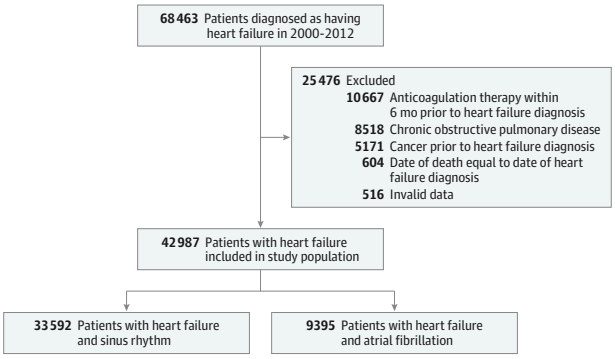
at risk was measured from the date of HF diagnosis until an event of ischemic stroke or TE, date of death, emigration, or end of study (December 31, 2012), whichever came first. Patients were censored if they began anticoagulant therapy during the follow-up period.

To enable comparison with other studies, we first calculated crude incidence rates of end points, stratified according to presence of concomitant AF. However, for the purpose of risk stratification, particularly in the context of competing risks, absolute risks (cumulative incidences/probabilities) are more relevant.[12,13] We calculated absolute risks for all end points using the Aalen-Johansen estimator[21] to take into account competing risks of death. Relative risks according to CHA_2DS_2-VASc score (relative to a CHA_2DS_2-VASc score of 1) were also calculated using the pseudovalue method to take into account competing risks of death.[22,23] The pseudovalue method reduces to simple regression with a log-link function on the event status indicator in the absence of censoring, whereas censored observations (for which the event status is not observed) are replaced with pseudo-observations based on Aalen-Johansen cumulative incidence estimates using the jackknife method. These methods have not been validated but are described in previous literature.[24,25] Wald *P* values for interactions on a risk ratio scale were used to quantify whether the overall association between CHA_2DS_2-VASc score and outcome risk differed between patients with and without AF.

To quantify the discriminatory properties of the CHA_2DS_2-VASc score, we used C statistics for each end point. This well-known measure of discrimination can be interpreted as the probability that a randomly selected patient who experiences the event of interest before a given time has a higher risk score than a control patient who does not experience an event before a given time. Because of competing risks of death, there are several valid definitions of control patients (alive and event free; alive and event free or dead) leading to different interpretations.[24,25] We used as controls patients who were alive and event free at 1- and 5-year follow-up and used the inverse-probability-of-censoring weighted estimator (assuming censoring and event times to be independent given CHA_2DS_2-VASc score).[24,25] Bootstrap confidence intervals for the C statistics were calculated using 1000 bootstrap samples. Furthermore, with the same definition of controls, we estimated for each end point the negative predictive value (NPV) of the CHA_2DS_2-VASc score with 1 as the cutoff; ie, the proportion of patients with CHA_2DS_2-VASc score = 1 who were alive and without the end point of interest at 1- and 5-year follow-up.

Sensitivity analysis was performed by repeating the absolute and relative risk calculations when extending the definition of concomitant AF at baseline to presence of a prior diagnosis of AF at baseline or within 30 days after HF diagnosis. This sensitivity analysis was performed because some patients might have a diagnosis of AF shortly after the HF diagnosis. Additionally, approximately 14% had a diagnosis of AF during 5 years of follow-up; thus, we performed another sensitivity analysis by repeating the absolute and relative risk calculations in the non-AF group after censoring patients who were diagnosed as having AF during follow-up. Moreover, a split sample analysis according to early (2000-2005) and late (2006-2012) study period was performed. Finally, we performed a sensitivity analysis in which we included patients with COPD. All sensitivity analyses were compared with the main analysis.

Figure 1. Selection of Study Population With Heart Failure With and Without Atrial Fibrillation



Because few prior studies have found that individual risk factors of the CHA_2DS_2-VASc score are associated with lower risk, not higher risk, of stroke in the HF population,[4,26,27] we performed a supplemental analysis of the association between each individual component of the CHA_2DS_2-VASc score and the risk of ischemic stroke.

The analyses were performed using Stata version 13 (Stata Corp) and R version 3.0.2 (R Foundation for Statistical Computing) with the package timeROC.[25] A 2-sided $P<.05$ was considered statistically significant.

Results

The study population comprised 42 987 patients with HF aged 50 years or older, among whom 21.9% had a diagnosis of AF at baseline (**Figure 1**). The median follow-up period with respect to ischemic stroke was 1.84 years (interquartile range, 0.22-4.59 years). The distribution of CHA_2DS_2-VASc scores in the study population according to presence of an AF diagnosis are shown in **Table 2**.

Incidence rates during the first year are shown in Table 2; overall, they exhibited the same fundamental characteristics as the absolute risks, which are presented in detail below. Incidence rates were generally attenuated after 5 years of follow-up (eTable 2 in the Supplement), indicating that most events occurred relatively shortly after the HF diagnosis. Numbers of events and person-years are shown in Table 2 and eTable 2 for 1 and 5 years of follow-up, respectively.

For patients with HF with and without a diagnosis of AF, **Figure 2** shows the absolute risks according to CHA_2DS_2-VASc during the first year after HF diagnosis, alongside the corresponding relative risks, comparing patients with a score higher than 1 with those with a score of 1 (no additional stroke risk factors). In both strata, the 1-year absolute risk generally increased with increasing CHA_2DS_2-VASc score but exhibited a less clear association for ischemic stroke among patients with HF and AF. For ischemic stroke and death, absolute risks were consistently higher among patients with HF and AF compared with those without AF (for ischemic stroke, with concomitant AF, 4.5%, 3.7%, 3.2%, 4.3%, 5.6%, and 8.4% and without concomitant AF, 1.5%, 1.5%, 2.0%, 3.0%, 3.7%, and 7% for scores 1-6, respectively; overall $P = .001$ for interaction; for all-cause death, with concomitant AF, 19.8%, 19.5%, 26.1%, 35.1%, 37.7%, and 45.5% and without concomitant AF, 7.6%, 8.3%, 17.8%, 25.6%, 27.9%, and 35.0%, for scores 1-6, respectively; overall $P<.001$ for interaction), but this pattern was not observed for the end point of TE at low CHA_2DS_2-VASc scores (for a score of 1, 9.0% vs 5.3%; for a score of 2, 8.3% vs 6.6%; for a score of 3, 7.9% vs 7.7%; overall $P<.001$ for interaction). The absolute risk of TE was higher among patients without AF compared with patients with concomitant AF at high CHA_2DS_2-VASc scores (for a score of 4, 9.7% vs 8.2%; for a score of 5, 11.9% vs 11.2%; for a score of 6, 18.0% vs 14.9%; overall $P<.001$ for interaction) (see eTable 3 in the Supplement for more results on the test for interaction). The absolute risk increased in a comparable manner at high CHA_2DS_2-VASc scores (≥4), exhibiting a clear dose-response relationship. Similar patterns were observed after 5 years of follow-up (eFigure 1 in the Supplement).

The discriminatory properties of the CHA_2DS_2-VASc score depended on the choice of end point and the duration of follow-up (**Table 3**). In patients without AF, the CHA_2DS_2-VASc score showed moderate predictive ability for the end point of ischemic stroke (C statistics at 1- and 5-year follow-up, 0.67 [95% CI, 0.65-0.68] and 0.69 [95% CI, 0.67-0.69], respectively). In patients with AF, the predictive ability for the end point of ischemic stroke was also modest (C statistics at 1- and 5-year follow-up, 0.64 [95% CI, 0.61-0.67] and 0.71 [95% CI, 0.68-0.73], respectively). When using NPV to identify patients at low risk of ischemic stroke, TE, and death, the CHA_2DS_2-VASc score yielded NPVs around 90% at 1-year follow-up for patients with HF without AF (NPVs, 92% [95% CI, 91%-93%] for ischemic stroke, 88% [95% CI, 87%-89%] for TE, and 93% [95% CI, 92%-94%] for death). At 5-year follow-up, NPVs were strongly attenuated.

Table 2. Crude Incidence Rates at 1 Year of Follow-up in the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation[a]

		No. of Additional Risk Factors on CHA_2DS_2-VASc Score					
End Points	Overall	1 (HF Only)	2	3	4	5	≥6
Patients Without Atrial Fibrillation							
Patients, No. (%)	33 592	2366 (7.0)	4503 (13.4)	7462 (22.2)	9183 (27.3)	5958 (17.7)	4120 (12.3)
Ischemic stroke							
Events, No.	977	29	62	141	258	212	275
Person-years, No.	9 448 812	711 473	1 393 807	2 180 746	2 529 593	1 599 137	707 004
Incidence rate, % (95% CI)	1.0 (1.0-1.1)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.6 (0.5-0.8)	1.0 (0.9-1.2)	1.3 (1.2-1.5)	2.6 (2.4-3.0)
Thromboembolism[b]							
Events, No.	3187	110	276	548	853	683	717
Person-years, No.	9 040 950	696 366	1 348 456	2 104 494	2 421 856	1 518 482	652 067
Incidence rate, % (95% CI)	3.5 (3.4-3.6)	1.6 (1.3-1.9)	2.0 (1.8-2.3)	2.6 (2.4-2.8)	3.5 (3.3-3.8)	4.5 (4.2-4.8)	7.5 (7.0-8.1)
Death							
Events, No.	6956	149	332	1256	2239	1596	1384
Person-years, No.	9 596 399	715 795	1 404 213	2 201 781	2 566 123	1 632 315	731 311
Incidence rate, % (95% CI)	7.2 (7.1-7.4)	2.1 (1.8-2.4)	2.4 (2.1-2.6)	5.7 (5.4-6.0)	8.7 (8.4-9.1)	9.8 (9.3-10.3)	12.9 (12.2-13.6)
Patients With Atrial Fibrillation							
Patients, No. (%)	9395	606 (6.5)	931 (9.9)	1752 (18.7)	2571 (27.4)	137 (20.6)	1598 (17.0)
Ischemic stroke							
Events, No.	318	8	11	32	82	80	105
Person-years, No.	1 592 497	55 019	110 265	294 757	477 528	365 633	180 083
Incidence rate, % (95% CI)	2.0 (1.8-2.2)	1.5 (0.7-2.9)	1.0 (0.6-1.8)	1.1 (0.8-1.5)	1.7 (1.4-2.1)	2.2 (1.8-2.7)	3.6 (3.0-4.4)
Thromboembolism[b]							
Events, No.	651	18	31	85	158	169	190
Person-years, No.	1 551 095	54 425	107 277	287 648	468 813	357 479	172 156
Incidence rate, % (95% CI)	4.2 (3.9-4.5)	3.3 (2.1-5.2)	2.9 (2.0-4.1)	3.0 (2.4-3.7)	3.4 (2.9-3.9)	4.7 (4.1-5.5)	6.9 (6.0-8.0)
Death							
Events, No.	2153	11	47	282	677	561	575
Person-years, No.	1 630 977	55 347	111 192	297 304	489 042	373 574	186 490
Incidence rate, % (95% CI)	13.2 (12.7-13.8)	2.0 (1.1-3.6)	4.2 (3.2-5.6)	9.5 (8.4-10.7)	13.8 (12.8-14.9)	15.0 (13.8-16.3)	18.9 (17.4-20.5)

[a] CHA_2DS_2-VASc score is calculated as congestive heart failure (1 point), hypertension (1 point), age 75 years or older (2 points), diabetes (1 point), stroke/transient ischemic attack/thromboembolism (2 points), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque; 1 point), age 65 to 75 years (1 point), female sex (1 point). All study patients had heart failure at baseline.

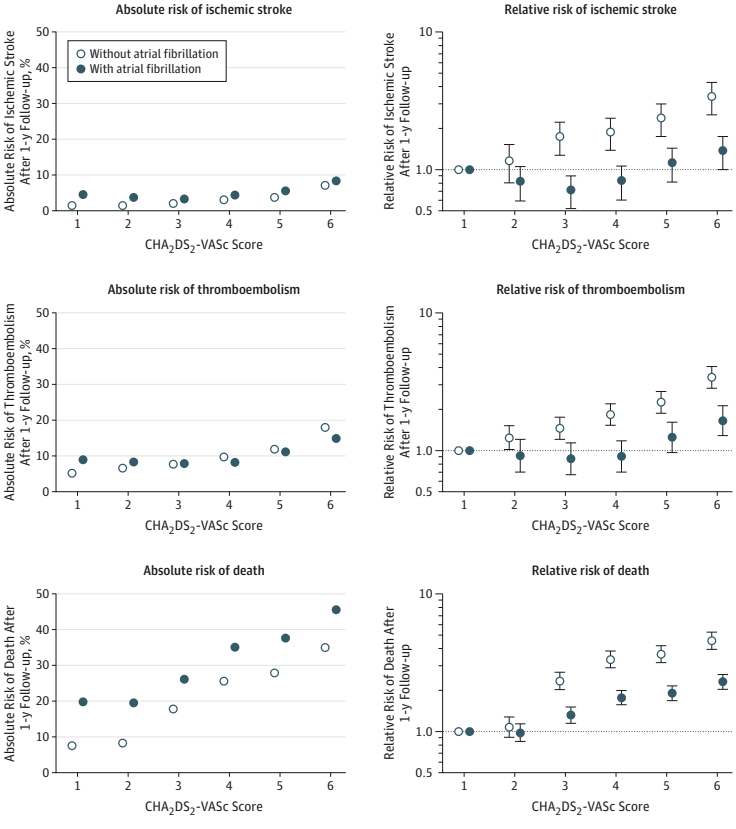
[b] Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

In the sensitivity analysis, repeating the absolute and relative risk calculations after extending the definition of concomitant AF, we found very similar results as in the main analysis (eFigure 2 in the Supplement). When censoring patients with HF who were diagnosed with AF during follow-up, similar results were found and the conclusions remained the same as in the main analysis (eFigure 3 in the Supplement). In the split sample analysis, we found similar results for all end points in both the early and late study period as in the main analysis for patients without AF (eFigure 4 and eFigure 5 in the Supplement). However, for patients with AF, we found higher relative risks of all end points in the early study period compared with the main analysis but similar results for the absolute risks. The C statistics were similar in both the early and late study period and comparable with the main analysis as follows: (1) in the early study period, for patients without AF, 0.66 (95% CI, 0.64-0.67) for ischemic stroke, 0.64 (95% CI, 0.63-0.64) for TE, and 0.63 (95% CI, 0.62-0.63) for death and for patients with AF, 0.62 (95% CI, 0.58-0.65), 0.61 (95% CI, 0.58-0.63), and 0.62 (95% CI, 0.60-0.64), respectively; (2) in the late study period, for patients without AF, 0.68 (95% CI, 0.66-70) for ischemic stroke, 0.63 (95% CI, 0.61-0.64) for TE, and 0.66 (95% CI, 0.65-0.67) for death and for patients with AF, 0.67 (95% CI, 0.63-0.72), 0.64 (95% CI, 0.61-0.68), and 0.64 (95% CI, 0.63-0.68), respectively.

In the sensitivity analysis, when we included patients with COPD, the results were qualitatively similar for patients without AF, but the absolute risks for patients with AF were lower and the relative risks were higher compared with the main analysis. Thus, the conclusions remained the same (eFigure 6 in the Supplement).

Supplemental analysis of the association between each individual component of the CHA_2DS_2-VASc score and the risk of ischemic stroke is shown in eTable 4 in the Supplement. In patients both with and without AF, female sex was not associated with an increased risk of ischemic stroke.

Figure 2. Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



Error bars indicate 95% CIs. Numbers of patients contributing data in each group for CHA_2DS_2-VASc scores from 1 to 6, respectively, were as follows: without atrial fibrillation, 2366, 4503, 7462, 9183, 5958, and 2733; with atrial fibrillation, 606, 931, 1752, 2571, 1937, and 980.

Discussion

In this cohort study, our principal findings were that (1) patients with HF had a high risk of ischemic stroke, TE, and death whether or not AF was present; (2) the CHA_2DS_2-VASc score was able to modestly predict these end points and had a moderately high NPV at 1-year follow-up; and (3) at high CHA_2DS_2-VASc scores (≥4), patients with HF without AF had high absolute risk of ischemic stroke, TE, and death, and the absolute risk increased in a comparable manner in patients with HF with and without AF, exhibiting a clear dose-response relationship. Indeed, the absolute risk of thromboembolic complications was higher among patients without AF compared with patients with concomitant AF at high CHA_2DS_2-VASc scores (≥4). To our knowledge, this is the first study to evaluate the predictive ability of the CHA_2DS_2-VASc score in estimating the risk of ischemic stroke, TE, and death in a population of patients with incident HF with and without AF.

Patients with HF and without AF are at increased risk of ischemic stroke and TE, and in recent randomized trials, these end points (which were secondary trial end points) were reduced by warfarin therapy.[28-30] In the Danish Diet, Cancer and Health cohort, we previously demonstrated the high risk of stroke and mortality among patients with HF without AF, which was lower if warfarin therapy was prescribed.[4]

Patients with HF have an increased risk of ischemic stroke, TE, and death regardless of whether AF is present.[28] In our study, one of our principal findings was that the absolute risk of ischemic stroke among patients without AF was about 1.5% per year or higher with CHA_2DS_2-VASc scores of 2 or higher, with associated 5-year absolute ischemic stroke risks in excess of 4% or more. Risks were even higher among the patients with HF with AF in our study. Similar absolute risks were found when stratifying analyses according to early and late study period, indicating a robustness of our findings to changes in standard HF diagnostic and treatment modes between 2000 and 2012. In the general AF population, a stroke risk of greater

Table 3. Assessment of the CHA_2DS_2-VASc Score at 1- and 5-Year Follow-up in the Heart Failure Study Population According to Prior Diagnosis of Atrial Fibrillation[a]

	Without Atrial Fibrillation		With Atrial Fibrillation	
	C Statistic (95% CI)	NPV, % (95% CI)[b]	C Statistic (95% CI)	NPV, % (95% CI)[b]
Ischemic stroke				
At 1 y	0.67 (0.65-0.68)	92 (91-93)	0.64 (0.61-0.67)	91 (88-95)
At 5 y	0.69 (0.67-0.69)	78 (77-80)	0.71 (0.68-0.73)	69 (60-77)
Thromboembolism[c]				
At 1 y	0.63 (0.62-0.64)	88 (87-89)	0.62 (0.60-0.64)	88 (84-92)
At 5 y	0.67 (0.67-0.68)	73 (71-74)	0.69 (0.67-0.71)	61 (51-69)
Death				
At 1 y	0.64 (0.63-0.64)	93 (92-94)	0.63 (0.62-0.65)	94 (91-97)
At 5 y	0.68 (0.67-0.68)	81 (79-82)	0.70 (0.69-0.72)	76 (67-84)

Abbreviation: NPV, negative predictive value.

[a] CHA_2DS_2-VASc score is calculated as congestive heart failure (1 point), hypertension (1 point), age 75 years or older (2 points), diabetes (1 point), stroke/transient ischemic attack/thromboembolism (2 points), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque; 1 point), age 65 to 75 years (1 point), female sex (1 point). All study patients had heart failure at baseline.

[b] Using a cutoff value of 1.

[c] Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

than 1% per year is often used as a cut point to identify patients in whom the benefits of long-term oral anticoagulation may outweigh the risks of bleeding.[31] In the present HF population, patients without AF with a CHA_2DS_2-VASc score of 2 or higher had a stroke risk greater than 1% per year. Although it is not clear whether this cut point would apply directly to the HF population without AF, our results may suggest that subgroups of patients with HF without AF and with 2 or more components of the CHA_2DS_2-VASc score besides HF are at high enough risk of ischemic stroke to benefit from anticoagulation therapy; especially with availability of the non-vitamin K antagonist oral anticoagulants.

Our other principal finding is that in patients with HF with elevated CHA_2DS_2-VASc scores (≥4), the absolute risk of ischemic stroke, TE, and death was very high. At these high CHA_2DS_2-VASc scores, the absolute risk increased in a comparable manner in patients with HF with and without AF, exhibiting a clear dose-response relationship, so that the absolute risk of TE was even greater among patients without AF compared with those with concomitant AF. The poor prognosis of AF for ischemic stroke and death in patients with HF was evident in our study, but the observation that additional risk factors in patients with HF are particularly significant among those without AF is an important result. Indeed, preventative strategies to reduce ischemic stroke and TE risk in this large patient population require further investigation.

The C statistics demonstrated that the performance of the CHA_2DS_2-VASc score was dependent on the type of end point and the length of follow-up. In patients with HF without AF, the CHA_2DS_2-VASc score performed moderately in discriminating patients experiencing an ischemic stroke from stroke-free survivors. The C statistics for predicting "events" in this study are also comparable with other commonly used risk scores based on clinical risk factors (for example, the $CHADS_2$ score in AF). Although these initial results demonstrate a potential use of the score, the direct clinical utility of stroke risk stratification in patients with HF is an open question. In this high-risk population, all-cause mortality remains the key concern, as indicated by the very high mortality rates and the corresponding relatively poorer performance of the risk score for predicting events after 5 years of follow-up. On the other hand, CHA_2DS_2-VASc yielded a moderately high 1-year NPV for identifying patients at "low risk" of stroke or death (approximately 90%). This is consistent with the CHA_2DS_2-VASc score as a useful tool for identifying "low-risk" patients, as evident in various studies examining risks in AF patients.[32,33] In our study, we found a less clear association between ischemic stroke risk and increasing CHA_2DS_2-VASc score among patients with HF and AF, exhibiting a possible J-shaped association or possibly no meaningful association, which could be due to the low event numbers with some of the scores. Furthermore, not all the individual components of the CHA_2DS_2-VASc score have been identified as established risk factors of ischemic stroke in the HF population without AF. Previous studies have even showed that some of these components are associated with a decreased ischemic stroke risk,[4,26,27] which our supplemental analysis also demonstrates. In spite of these previous findings, the CHA_2DS_2-VASc score was able to modestly predict the risk of ischemic stroke in our study. Future studies examining the individual drivers of risk derived from the CHA_2DS_2-VASc score are still needed.

The major strengths of this study are the validated outcomes and large sample size uniquely possible with this type of cohort study. Selection into the study was not an issue because we investigated a nationwide population of patients with incident HF with and without AF, with limited loss to follow-up. We also accounted for competing risk of death, an important issue when investigating the performance of risk scores in populations with a high mortality.[13,24]

The study has some limitations. We were unable to distinguish between HF with preserved vs reduced ejection fraction or to estimate the functional classification/symptoms severity because we did not have access to echocardiograms. In a previous systematic review, whether a clinical diagnosis of

HF is a significant risk factor remained inconclusive, although when the diagnosis is certain (recent decompensation requiring hospitalization, as in Danish registries), it does seem to be a significant risk factor irrespective of left ventricular systolic function.[5] However, functional classification among patients with HF would also vary over time and with treatments. In addition, we investigated the risk in patients with incident HF, and our results may not relate to the general population of patients with HF. However, we also reported risks after 5 years of follow-up, and we believe these results are comparable with the general HF population. Because of the high mortality rate in the HF population (and therefore, the short follow-up in this study), we focused on the 1-year risks. The HF diagnosis has previously been validated with a sensitivity of 29%, a specificity of 99%, and a positive predictive value of 81%,[18] and based on the validation study we did not capture all patients with HF and also cannot be certain that all patients identified as having HF had definite HF, which could lead to imprecision in the risk estimates. However, we included only patients with a primary discharge diagnosis of HF to optimize the probability of including only correctly identified patients with HF.

We investigated a real-life population using nationwide registries in which we did not exclude severely ill patients (as typically done in clinical trials); thus, our study population includes patients with HF with several comorbidities predisposing for stroke events, and our event rates may be higher than that seen in clinical trials. Indeed, Nielsen and Chao[13] discussed the issue with different event rates observed from different populations.

We cannot rule out that some patients without AF might have had undiagnosed AF because heart disease is associated with an increased risk of developing AF and AF is silent in up to a quarter of patients. In our sensitivity analyses, extending the AF definition and censoring if development of AF occurred during follow-up, we found similar results as in the main analysis. Additionally, our study population was ethnically and socially nondiverse. Thus, our study results might not be generalizable to more diverse HF populations. Furthermore, we excluded patients with HF younger than 50 years; accordingly, our findings may not apply to younger patients with HF.

We did not have information about smoking habits; however, we excluded patients with a diagnosis of COPD, which are primarily patients with an intensive smoking habit or history, and therefore, our results might not be valid for patients with COPD. However, in our sensitivity analysis, when we included patients with COPD, the conclusions remained the same.

Because of the nature of our nationwide registry study, follow-up depended on the National Civil Registration System, in which some deaths are likely to be attributable to an undiagnosed stroke. Finally, the diagnosis of ischemic stroke was defined by the Danish Hospital Discharge Register, and not all stroke end points have been defined by cerebral imaging; thus, the data did not allow classification of ischemic stroke types. However, the ischemic stroke diagnosis has previously been validated.[17]

Conclusions

Among patients with incident HF with or without AF, the CHA_2DS_2-VASc score was associated with risk of ischemic stroke, thromboembolism, and death. The absolute risk of thromboembolic complications was higher among patients without AF compared with patients with concomitant AF at high CHA_2DS_2-VASc scores. However, predictive accuracy was modest, and the clinical utility of the CHA_2DS_2-VASc score in patients with HF remains to be determined.

ARTICLE INFORMATION

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Study concept and design: Melgaard, Gorst-Rasmussen, Larsen, Lip.
Acquisition, analysis, or interpretation of data: Melgaard, Lane, Rasmussen, Larsen, Lip.
Drafting of the manuscript: Melgaard, Gorst-Rasmussen, Lane, Larsen, Lip.
Critical revision of the manuscript for important intellectual content: Melgaard, Lane, Rasmussen, Larsen, Lip.
Statistical analysis: Melgaard, Gorst-Rasmussen.
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Supplementary Online Content

Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA_2DS_2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA*. doi:10.1001/jama.2015.10725

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. ICD-10 Codes and ATC-Codes Used in the Study

ICD 10-Codes and ATC-Codes used in the Study	
Main diagnosis	**ICD 10-codes**
Congestive heart failure	I50.0-I50.9, I11.0, I13.0, I13.2
Atrial fibrillation	I48.0-I48.9
Endpoints	
Stroke (ischemic)	I63.0-I63.9, I64.9
Ischemic stroke (Thromboembolic event)	I63.0-I63.9, I64.9
Transient ischemic attack (Thromboembolic event)	G45.0-G45.9*
Systemic embolism (Thromboembolic event)	I74.0-I74.9
Pulmonary embolism (Thromboembolic event)	I26.0-I26.9
Acute myocardial infarction (Thromboembolic event)	I21.0-I21.9, I23.0-I23.9
Comorbidities	**ICD 10-codes**
Prior stroke (ischemic or hemorrhagic)	I60.0-I60.9, I61.0-I61.9, I62.0-I62.9, I63.0-I63.9, I64.9
Acute myocardial infarction	I21.0-I21.9, I23.0-I23.9
Peripheral ischemic disease†	I70.2-I70.9, I71.0-I71.9, I73.9
Vascular disease	I21.0-I21.9, I23.0-I23.9, I70.0, I70.2-I70.9, I71.0-I71.9, I73.9
Diabetes mellitus	E10.0-E10.9, E11.0-E11.9
Hypertension	I10.0-I10.9, I11.0-I11.9, I12.0-I12.9, I13.0-I13.9, I15.0–I15.9
Renal disease	I12.0-I12.9, I13.0-I13.9, N00-N07, N11.0-N11.9, N14.0-N14.4, N17.0-N17.9, N18.0-N18.9, N19, Q61.0-Q61.9
Liver disease	B15.0-B15.9, B16.0-B16.9, B17.0-B17.9, B18.0-B18.9, B19.0-B19.9, K70.4, K72.0-K72.9, K76.6
Hyperthyroidisme	E05.0-E05.9, E06.0-E06.9
Chronic obstructive pulmonary disease (COPD)	J44.0-J44.9
Valvular disease (exclusion criteria)	I05.0-I05.9, I06.0-I06.9, I34.0-I34.9, I35.0-I35.9
Mechanical cardiac valve (exclusion criteria)	Z95.2, Z95.3, Z95.4
Cancer any type (exclusion criteria)	C00-C97
Concomitant medication	**ATC-codes**
Warfarin (exclusion criteria)	B01AA03
Phenprocoumon (exclusion criteria)	B01AA04
ACE-inhibitors	C09AA
Angiotensin receptor blockers	C09CA
Beta-blockers	C07
Non-loop diuretics	C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G,C09BA, C09DA, C09XA52
Aldosterone antagonists	C03DA
Loop diuretics	C03C
Statins	C10

Concomitant medication	**ATC-codes**
Non steroidal anti-inflammatory drugs (NSAIDs)	M01A
Aspirin	B01AC06
Thienopyridines	B01AC04, B01AC22, B01AC24
Antidiabetics	A10
Calcium chanel antagonists	C07F C08 C09BB C09DB
Digoxin	C01AA05
Vasodilators	C02DB C02DD C02DG C04 C05
Interventions	**Procedure codes (SKS code)**
Pacemakr/ICD	FPG FPE
Percutaneous coronary intervention(PCI)	FNG
Coronary artery bypass graft (CABG)	FNA FNC FND FNE

** Not inclusive G45.3 (Amaurosis fugax)*

† *Peripheral arterial disease, refers to the obstruction of large arteries not within the coronary, aortic arch vasculature, or brain*

eTable 2. Crude Incidence Rates at 5-Year Follow-up in the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation

Endpoint	CHA_2DS_2-VASc score - Additional risk factor						
	Overall	1 (HF only)	2	3	4	5	6+
Non-AF							
Patients in each score, No. (%)	33,592	2,366 (7.0)	4,503 (13.4)	7,462 (22.2)	9,183 (27.3)	5,958 (17.7)	4,120 (12.3)
Ischemic stroke							
Events, No.	2,080	64	151	395	548	455	467
Person-years	3.14e+07	2.723.598	5.204.536	7.478.778	8.172.942	4.930.078	2.058.004
Incidence rate (95% CI)	0.7 (0.6-0.7)	0.2 (0.2-0.3)	0.3 (0.2-0.3)	0.5 (0.5-0.6)	0.7 (0.6-0.7)	0.9 (0.8-1.0)	1.6 (1.5-1.8)
Thromboembolism†							
Events, No.	5,572	202	506	1,073	1,501	1,224	1,066
Person-years	2.93e+07	2.632.036	4.941.719	7.057.264	7.607.543	4.532.796	1.824.215
Incidence rate (95% CI)	1.9 (1.8-1.9)	0.7 (0.7-0.9)	1.0 (0.9-1.1)	1.5 (1.4-1.6)	2.0 (1.9-2.1)	2.7 (2.6-2.9)	4.1 (3.9-4.4)
Death							
Events, No.	13,836	354	818	2,633	4,444	3,144	2,443
Person-years	3.25e+07	2.765.491	5.305.327	7.686.298	8.450.027	5.161.519	2.206.065
Incidence rate (95% CI)	4.3 (4.3-4.3)	1.3 (1.2-1.4)	1.5 (1.4-1.7)	3.4 (3.3-3.6)	5.3 (5.1-5.4)	6.1 (5.9-6.3)	7.7 (7.4-8.0)

AF							
Patients in each score, No. (%)	9,395	606 (6.5)	931 (9.9)	1,752 (18.7)	2,571 (27.4)	1,937 (20.6)	1,598 (17.0)
Ischemic stroke							
Events, No.	590	14	19	69	159	158	171
Person-years	4.092.929	145.003	305.795	789.468	1.265.106	918.162	423.061
Incidence rate (95% CI)	1.4 (1.3-1.6)	1.0 (0.6-1.6)	0.6 (0.4-1.0)	0.9 (0.7-1.1)	1.3 (1.1-1.5)	1.7 (1.5-2.0)	2.6 (2.2-3.0)
Thromboembolism†							
Events, No.	1,124	31	49	152	294	296	302
Person-years	3.897.488	139.425	291.140	756.390	1.225.451	877.400	386.309
Incidence rate (95% CI)	2.9 (2.7-3.1)	2.2 (1.6-3.2)	1.7 (1.3-2.2)	2.0 (1.7-2.4)	2.4 (2.1-2.7)	3.4 (3.0-3.8)	5.0 (4.4-5.6)
Death							
Events, No.	3,766	26	90	561	1,190	963	936
Person-years	4.301.442	147.071	310.708	809.780	1.332.492	975.518	453.103
Incidence rate (95% CI)	8.8 (8.5-9.0)	1.8 (1.2-2.6)	2.9 (2.4-3.6)	6.9 (6.4-7.5)	8.9 (8.4-9.5)	9.9 (9.3-10.5)	12.9 (12.1-13.7)

All study patients had heart failure at baseline

Incidence rates are reported as % per year over 5 years of follow-up

Abbreviations: HF=heart failure; CHA_2DS_2-VASc score=congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/TIA/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–75 years, sex category (female); CI=confidence interval

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, acute myocardial infarction

eTable 3. Crude Relative Risks at 1-Year Follow-up in the Heart Failure Population, When Comparing Patients With and Without Atrial Fibrillation

Non-AF patients vs AF patients (reference: AF patients)			
ENDPOINT	Risk score	RR after 1 year (95% CI)	Test for interaction, overall
ISCHEMIC STROKE	**CHA_2DS_2-VASc score**		*P=0.001*
	1 (HF only)	Ref.	
	2 additional risk factor	2.21 (1.53-3.19)	
	3 additional risk factors	1.60 (1.20-2.15)	
	4 additional risk factors	1.42 (1.13-1.78)	
	5 additional risk factors	1.37 (1.08-1.75)	
	6+ additional risk factors	1.05 (0.85-1.30)	
THROMBO-EMBOLISM†	**CHA_2DS_2-VASc score**		*P=0.000*
	1 (HF only)	Ref.	
	2 additional risk factor	1.32 (1.09-1.60)	
	3 additional risk factors	1.07 (0.91-1.26)	
	4 additional risk factors	0.86 (0.75-1.00)	
	5 additional risk factors	0.90 (0.78-1.04)	
	6+ additional risk factors	0.75 (0.65-0.86)	
DEATH	**CHA_2DS_2-VASc score**		*P=0.000*
	1 (HF only)	Ref.	
	2 additional risk factor	2.32 (2.01-2.69)	
	3 additional risk factors	1.41 (1.28-1.54)	
	4 additional risk factors	1.28 (1.20-1.37)	
	5 additional risk factors	1.25 (1.16-1.35)	
	6+ additional risk factors	1.17 (1.09-1.27)	

All study patients had heart failure at baseline

Abbreviations: AF=atrial fibrillation; CHA_2DS_2-VASc score=congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/TIA/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–75 years, sex category (female)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, acute myocardial infarction

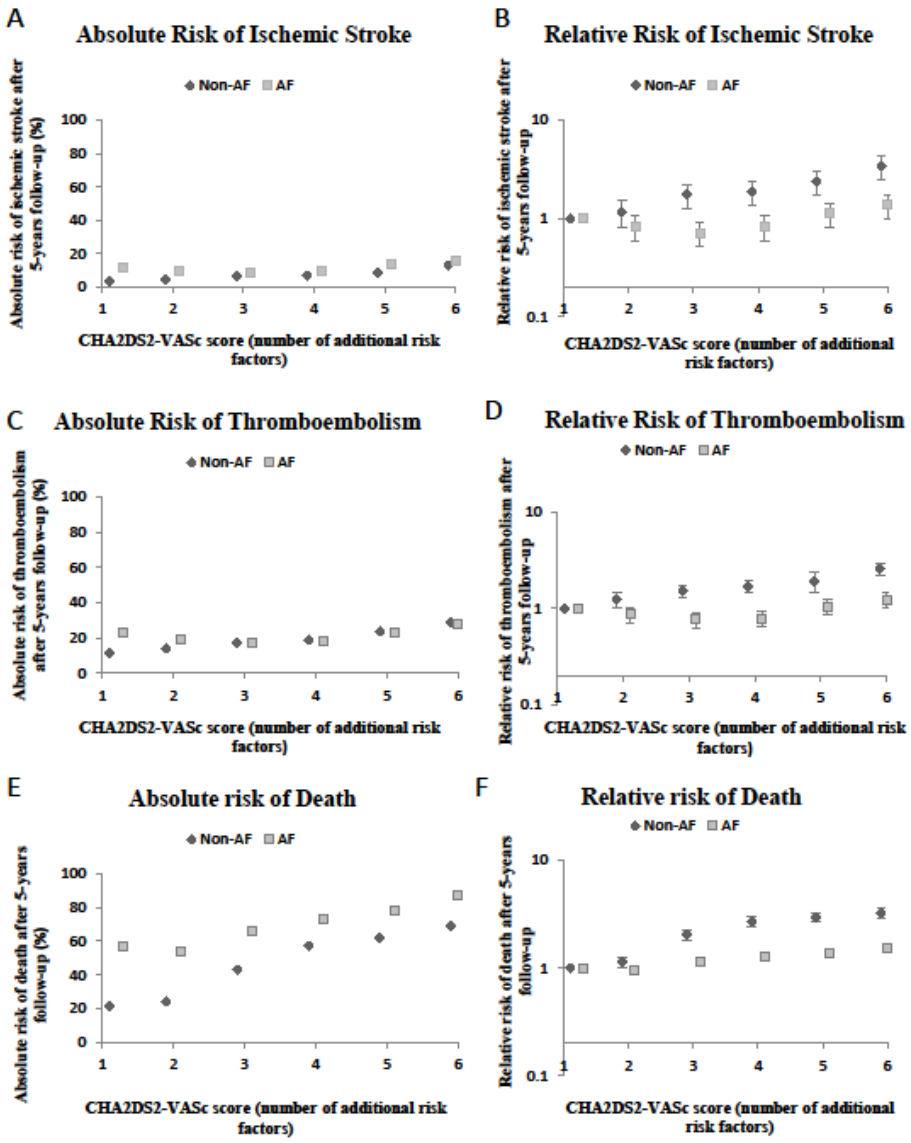
eTable 4. Association Between Each Individual Component of the CHA_2DS_2-VASc Score and Ischemic Stroke Risk

Individual components of the CHA_2DS_2-VASc score	Non-AF		AF	
	Crude RR (95% CI)		Crude RR (95% CI)	
Hypertension	1.30	(1.13-1.51)	1.24	(1.09-1.40)
Age ≥75 years	1.33	(1.17-1.51)	1.34	(1.20-1.49)
Diabetes	1.50	(1.29-1.73)	1.42	(1.25-1.62)
Stroke/TIA/thromboembolism	4.92	(4.34-5.58)	4.40	(3.94-4.90)
Vascular disease	1.32	(1.16-1.51)	1.24	(1.10-1.40)
Age 65-75 years	1.57	(1.34-1.85)	1.64	(1.41-1.90)
Female sex	0.84	(0.74-0.95)	0.96	(0.86-1.07)

All study patients had heart failure at baseline

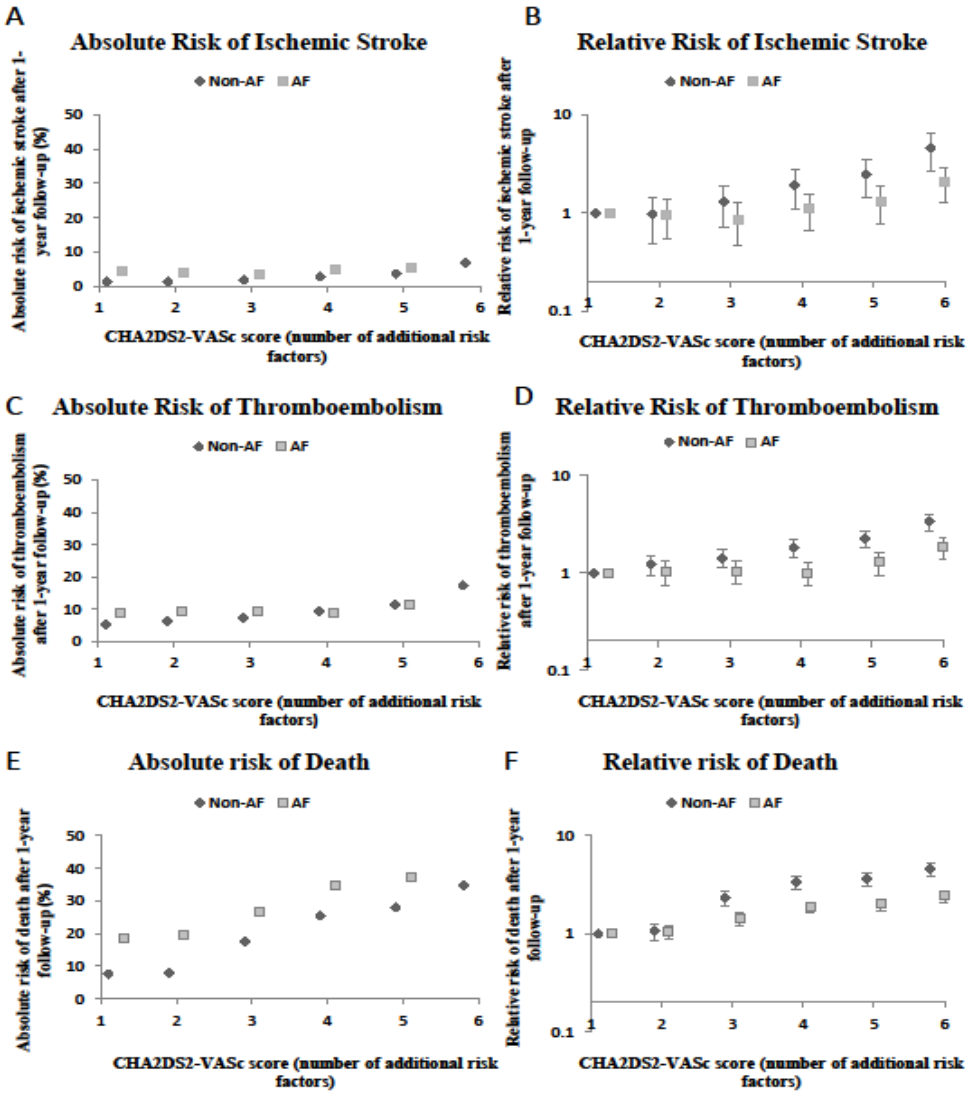
Abbreviations: AF: atrial fibrillation; CHA_2DS_2-VASc score=congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/TIA/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–75 years, sex category (female); CI: confidence interval; RR: relative risk; TIA: transient ischemic attack

eFigure 1. Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During 5-Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



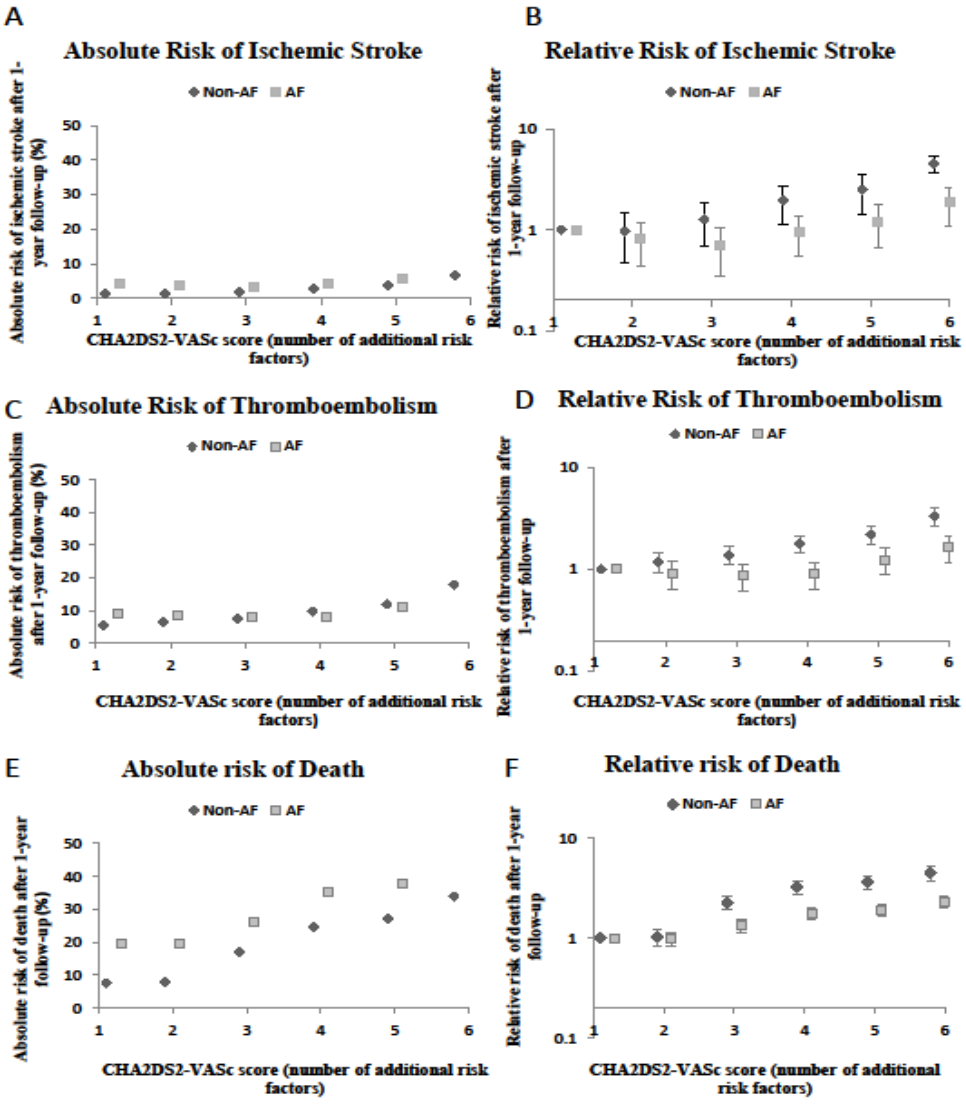
A) Absolute risk of ischemic stroke; B) Relative risk of ischemic stroke; C) Absolute risk of thromboembolism; D) Relative risk of thromboembolism; E) Absolute risk of death; F) Relative risk of death. Number of patients contributing data in each group for each CHA_2DS_2-VASc score (non-AF: 2,366, 4,503, 7,462, 9,183, 5,958, and 2,733; AF: 606, 931, 1,752, 2,571, 1,937, and 980, for score 1-6).

eFigure 2. Sensitivity Analysis (Extending the Definition of Concomitant AF at Baseline): Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



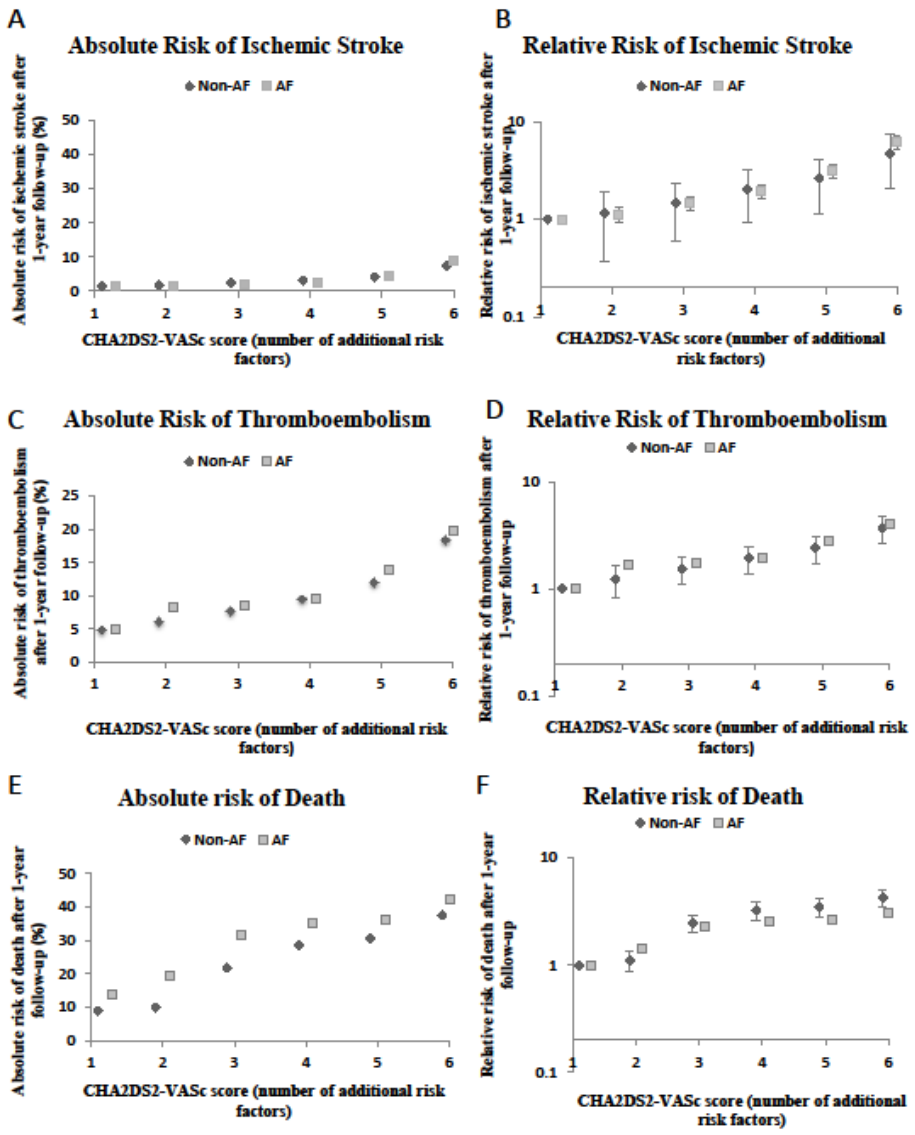
A) Absolute risk of ischemic stroke; B) Relative risk of ischemic stroke; C) Absolute risk of thromboembolism; D) Relative risk of thromboembolism; E) Absolute risk of death; F) Relative risk of death. Number of patients contributing data in each group for each CHA_2DS_2-VASc score (non-AF: 2,277, 4,377, 7,267, 8,941, 5,817, and 2,671; AF: 695, 1,057, 1,947, 2,813, 2,078, and 1,042, for score 1-6).

eFigure 3. Sensitivity Analysis (Censoring Patients Who Get a Diagnosis of AF During Follow-up): Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



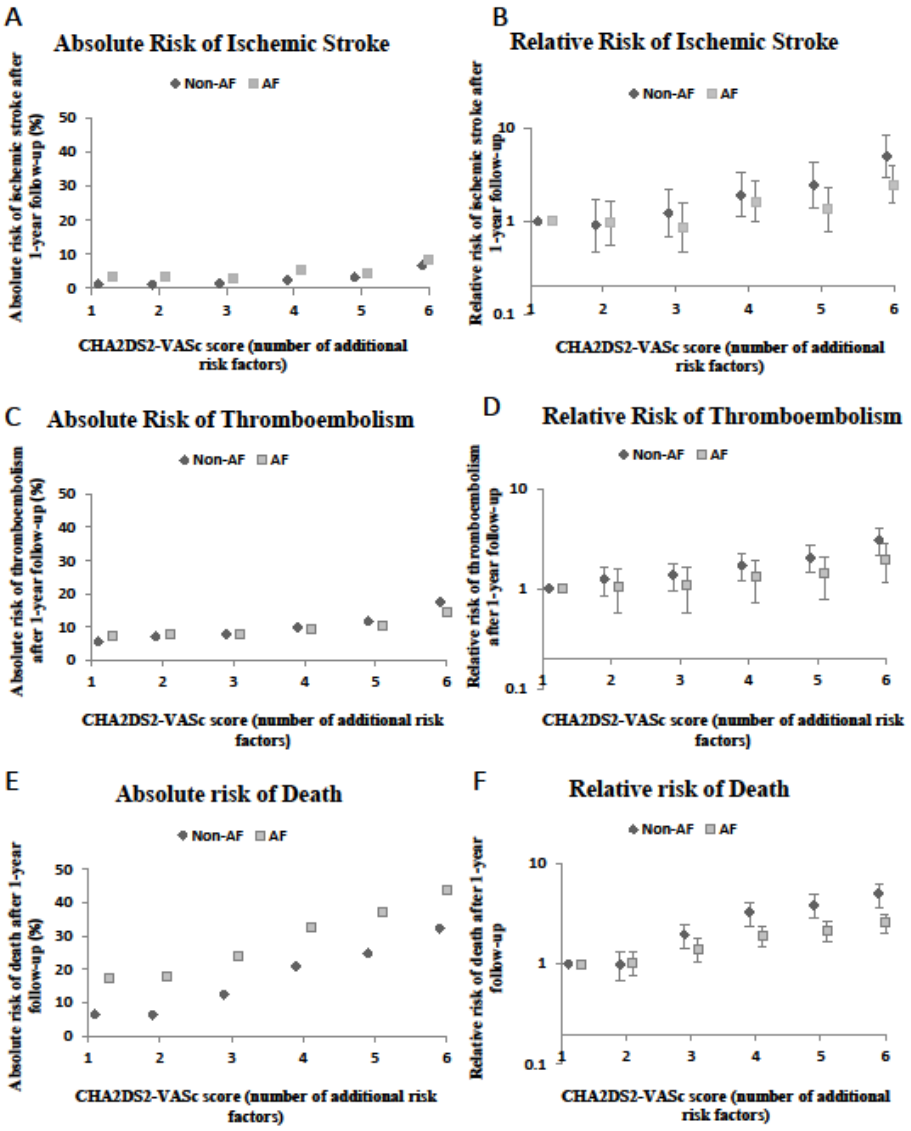
A) Absolute risk of ischemic stroke; B) Relative risk of ischemic stroke; C) Absolute risk of thromboembolism; D) Relative risk of thromboembolism; E) Absolute risk of death; F) Relative risk of death. Number of patients contributing data in each group for each CHA_2DS_2-VASc score (non-AF: 2,366, 4,503, 7,462, 9,183, 5,958, and 2,733; AF: 606, 931, 1,752, 2,571, 1,937, and 980, for score 1-6).

eFigure 4. Sensitivity Analysis (Split Sample Analysis – Early Study Period (2000-2005)): Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



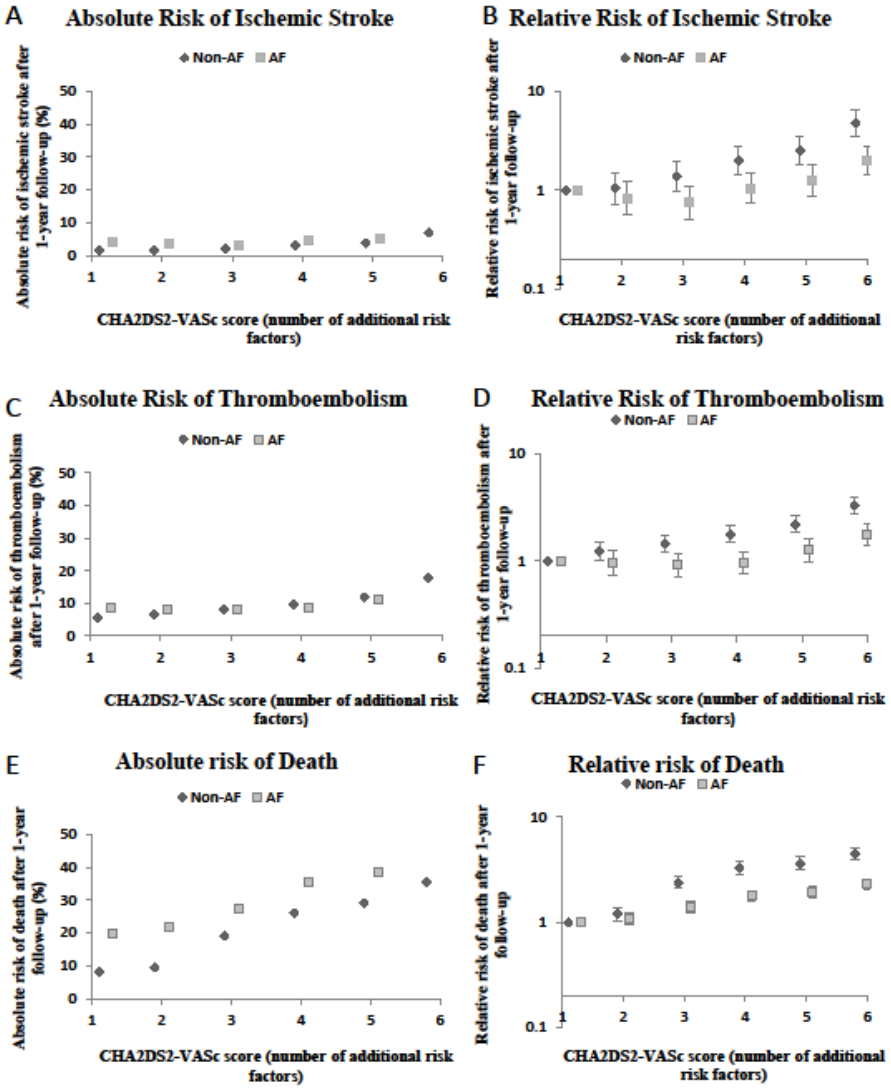
A) Absolute risk of ischemic stroke; B) Relative risk of ischemic stroke; C) Absolute risk of thromboembolism; D) Relative risk of thromboembolism; E) Absolute risk of death; F) Relative risk of death. Number of patients contributing data in each group for each CHA_2DS_2-VASc score (non-AF: 1,281, 2,398, 4,334, 5,526, 3,280, and 1,429; AF: 267, 419, 1,005, 1,539, 1,063, and 493, for score 1-6).

eFigure 5. Sensitivity Analysis (Split Sample Analysis – Late Study Period (2006-2012)): Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



A) Absolute risk of ischemic stroke; B) Relative risk of ischemic stroke; C) Absolute risk of thromboembolism; D) Relative risk of thromboembolism; E) Absolute risk of death; F) Relative risk of death. Number of patients contributing data in each group for each CHA_2DS_2-VASc score (non-AF: 1,096, 2,124, 3,175, 3,710, 2,726, and 1,322; AF: 349, 550, 878, 1,211, 1,046, and 596, for score 1-6).

eFigure 6. Sensitivity Analysis (Including Patients With COPD): Absolute Risks and Relative Risks by CHA_2DS_2-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



A) Absolute risk of ischemic stroke; B) Relative risk of ischemic stroke; C) Absolute risk of thromboembolism; D) Relative risk of thromboembolism; E) Absolute risk of death; F) Relative risk of death. Number of patients contributing data in each group for each CHA_2DS_2-VASc score (non-AF: 2,605, 5,269, 8,784, 10,670, 6,935, and 4,816; AF: 664, 1,095, 2,238, 3,204, 2,474, and 2,076, for score 1-6).

Appendix B. Paper 2

Female sex is associated with a lower risk of stroke in patients with heart failure

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Background Stroke in patients with heart failure is associated with poor outcomes. Risk stratification schemes may improve clinical decision making in this patient population. This study investigated whether female sex is a risk factor for stroke in patients with heart failure in sinus rhythm.

Methods This is a population-based cohort study of patients diagnosed with heart failure during 2000 to 2012, identified by record linkage between nationwide Danish registries. Our primary outcome was stroke, and secondary outcome was thromboembolic event. We used relative risks (RRs) after 1 and 5 years to compare males with females within each of the following age groups: 50 to 59 years, 60 to 69 years, 70 to 79 years, 80 to 89 years, and 90+ years. Analyses took into account the competing risks of death.

Results During the study period, 84,142 patients were diagnosed with heart failure, of which 39,946 (47.5%) were females. At 5-year follow-up, female sex was associated with a lower risk of stroke compared with males (adjusted overall hazard ratio 0.91, 95% CI 0.85-0.96). The observed lower risks of stroke in females were not present in the older age groups, where the competing risk of death was substantial among males in particular. When considering a more broadly defined thromboembolic end point, a decreased risk among females persisted across nearly all age groups after 5-year follow-up (adjusted overall hazard ratio 0.93, 95% CI 0.91-0.96).

Conclusions We found an association between female sex and decreased stroke risk in patients with heart failure, which persisted after adjustment for concomitant cardiovascular risk factors. The association was attenuated with increasing age, possibly because of competing risks of death. (Am Heart J 2015;169:396-403.e2.)

Heart failure (HF) is associated with an increased risk of stroke, also in patients without concomitant atrial fibrillation (AF).[1] Recent prospective randomized controlled trials of antithrombotic therapy in HF revealed that the benefit of warfarin in reducing stroke was counterbalanced by an increased risk of bleeding.[2-5] However, the extent to which subgroups within the HF population would benefit from anticoagulation was not investigated. Risk stratification using readily available clinical variables may help identifying subgroups at low and high risk of stroke in a population of patients with HF without concomitant AF. An important but somewhat controversial risk factor for stroke in the AF setting is that of female sex,[6,7] and it is of interest to elucidate the relevance of this simple risk factor in an HF setting. In particular, it is unknown whether the association between sex and stroke risk in HF is influenced by the presence of well-known cardiovascular risk factors of stroke.[1,8,9]

Examining risk factors for stroke in a population of patients with HF poses important methodological challenges. Specifically, the high all-cause mortality among patients with HF (5-year mortality of 45%-60%)[10,11] leads to a competing risks setting in which careful consideration of the interplay between mortality and stroke risk is needed to provide meaningful stroke risk assessments. In addition, careful accounting for the effects of age heterogeneity is needed when investigating sex as a risk factor because high age, in itself, is a key risk factor for stroke.[12]

We hypothesized that, in a population of patients with incident HF, female sex would be associated with a higher risk of stroke compared with male sex, also when taking into account sex differences in age and other known risk factors of stroke. To investigate this hypothesis, we used data from Danish nationwide registries to identify a population of patients with incident HF with no concomitant AF or anticoagulant therapy. Within this population, we compared the male and female 1- and 5-year stroke risk in a setting

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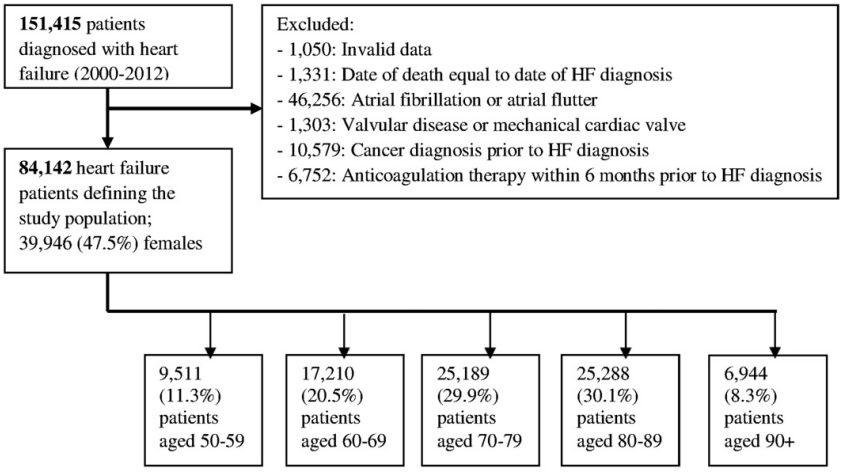
Figure 1



Flowchart of patients included in the final study population.

incorporating competing risks because of death, while also taking into account age and other established cardiovascular risk factors of stroke.

Methods

Registry data sources

We used 3 different nationwide registries in this study: (1) Danish National Patient Registry,[13] which has registered all hospital admissions along with diagnoses since 1977 and codes all diagnoses according to the *International Classification of Diseases, 10th Revision* (*ICD-10*), since 1994; (2) The National Prescription Registry,[14] which contains data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System; (3) The Danish Civil Registration System, which holds information on date of birth, migration, vital status, date of death, and sex of all persons living in Denmark.[15] Data were linked via unique personal identification number used in all Danish national registries. All 3 registries were up to December 31, 2012. These registries have previously been validated,[13,14,16] and the diagnoses of HF and stroke were found to have high validity.[16,17]

Study population

The study population was identified as patients aged >50 years, discharged with an incident diagnosis of HF in sinus rhythm in the period January 1, 2000, to December 31, 2012 (*ICD-10*: I50, I11.0, I13.0, I13.2). To restrict to patients without AF, we excluded those who had a prior diagnosis of AF (I48), valvular disease (I05, I06, I34, I35), or mechanical cardiac valve (Z95.2, Z95.3, Z95.4). We moreover excluded patients treated with anticoagulant medication (ATC: B01AA03, B01AA04) within 6 months before the HF diagnosis. Lastly, patients with a diagnosis of cancer (*ICD-10*: C00-C97) within 5 years before HF diagnosis were excluded (Figure 1).

Comorbidities were assessed at time of HF diagnosis identified using the Danish National Patient Registry and the Danish National Prescription Registry. Ascertainment of baseline medication status was based on medication purchase in a 30-day window before or after the date of HF diagnosis. *ICD-10* codes and ATC codes used to define comorbidities and medical therapy are provided in the online-only material (see online Appendix Supplementary Table I).

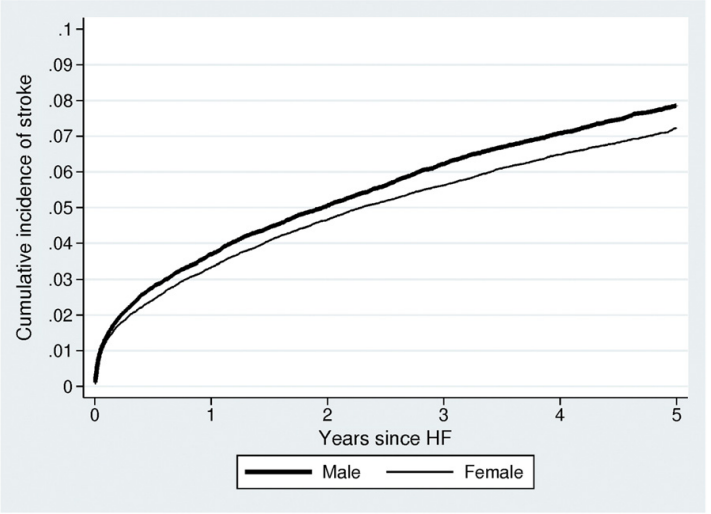
Outcomes

The primary end point was defined as a stroke diagnosis resulting in an *ICD-10* code of ischemic stroke (*ICD-10*: I63, I64.9). As a broader secondary end point, we defined a thromboembolic event to be a diagnosis of ischemic stroke (*ICD-10*: I63, I64.9), transient ischemic attack (*ICD-10*: G45), systemic embolism (*ICD-10*: I74), pulmonary embolism (*ICD-10*: I26.0, I26.9), or acute myocardial infarction (*ICD-10*: I21, I23). Because of the high mortality in the HF population, all-cause death was also included as an end point in a competing risks setting to enable correct risk assessment.

Statistical methods

Baseline characteristics were described separately for each sex stratum with means and SD for continuous measures and proportions for categorical measures.

Figure 2



Cumulative incidence of stroke for males and females.

Time-to-event analysis was used to estimate the association between female sex and the risk of stroke. Time at risk was measured from baseline date (date of HF diagnosis) and until the relevant event (stroke, all-cause death, or thromboembolic event), emigration, initiation of anticoagulant therapy, or end of study (December 31, 2012), whichever came first.

Crude cumulative incidence curves of stroke (Figure 2) and death (Figure 3) according to sex were constructed based on Aalen-Johansen estimator[18] for competing risks data. We proceeded to perform regression analyses to calculate 1-year and 5-year RR of an end point according to sex, stratifying analyses by age at time of diagnosis (50-59 years, 60-69 years , 70-79 years, 80-89 years, and 90+ years). To this end, we used generalized linear regression alongside the pseudovalue method to take into account the competing risks of death.[19,20] The pseudovalue regression technique reduces to simple regression (with a log-link function) on the event status indicator at 1 and 5 years in the absence of censoring. Concomitant baseline comorbidities such as hypertension, diabetes, prior thromboembolism, prior myocardial infarction, and peripheral artery disease are well-known risk factors of stroke in other heart diseases.[8,9] Accordingly, to assess the independent prognostic value of sex among established cardiovascular risk factors, we also fitted the regression models after adjustment for these risk factors.

Sensitivity analyses were performed by repeating the RR calculations when treating initiation of antiplatelet therapy as a censoring event. An additional end point, deep venous thrombosis, and a broad end point, composite of "stroke/thromboembolic event or death", were also analyzed in sensitivity analyses and compared with the main analysis.

The analyses were performed using Stata version 13 (Stata Corporation; College Station, TX). A 2-sided $P < .05$ was considered statistically significant. The study was conducted and reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Ethical considerations

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency (J. No. File No. 2012-41-0633).

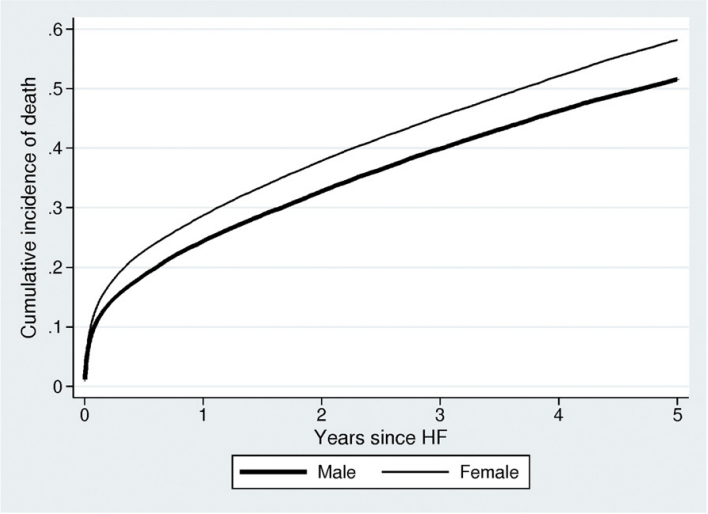
Sources of funding

No extramural funding was used to support this work. This study was conducted independently of any industry or other grant support. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

The study population comprised 84,142 patients with HF aged >50 years, of which 39,946 (47.5%) were females. The median follow-up time for stroke or death was 2.1 years (interquartile range 0.3-4.8).

Figure 3



Cumulative incidence of death for males and females.

Baseline characteristics of the study population are shown in Table I. The mean ages of the cohort were 78 (SD 10.9) and 73 (SD 10.7) years for females and males, respectively. Females were in general older, with 49.2% aged >80 years at study start, compared with 28.6% of the males. Males more often had a history of previous myocardial infarction and vascular disease plus a minor higher prevalence of peripheral ischemic disease and diabetes. In addition, more males than females were prescribed angiotensin-converting enzyme inhibitors, β-blockers, statins, and aspirin.

In the study population, the 1- and 5-year absolute risks of stroke were 3.5% and 7.6%, and the absolute risks of death were 26.4% and 54.8%, respectively (the absolute risks of composite end point "stroke or death" were 30.0% and 60.6%, respectively).

The RRs of stroke comparing females with males within each age group are shown in Table II. Within 5 years after HF diagnosis, female sex was associated with an overall 9% (RR 0.91, 95% CI 0.85-0.96) lower risk of stroke compared with males, after adjusting for concomitant risk factors. Formal statistical tests for interactions suggested an age-by-sex interaction after 5 years of follow-up (stroke $P = .03$, death $P = .02$, thromboembolic event $P = .07$). Turning to effect size estimates, a lower risk among females was observed in most age groups; except in the age group of 90+ years where the 5-year adjusted RR was 1.33 (95% CI 0.98-1.79) indicating a nonsignificant risk increase among females. Older age attenuated the RRs toward 1.00 indicating a modifying effect of age on the association between sex and stroke. Findings for the 1-year risks were qualitatively similar to those for the 5-year risks, although formal statistical tests for age-by-sex interaction were generally nonsignificant.

For the competing event of all-cause death, female sex was associated with a significantly decreased 5-year risk of death compared with males (adjusted RR 0.93, 95% CI 0.92-0.94). When stratifying on age groups, females had a lower RR of death after adjusting for cardiovascular risk factors compared with males both after 1- and 5-year follow-up in all age groups, except those aged 60 to 69 years at 1-year follow-up.

For the broader secondary end point of "any thromboembolic event", the 1- and 5-year absolute risks were 16.3% and 31.0%, respectively. Females still had an overall lower risk of events after 5 years of follow-up, which persisted after adjusting for concomitant risk factors (adjusted RR 0.93, 95% CI 0.91-0.96), but in contrast to the findings for the end point of stroke, the lower female risk was observed in the crude results for all age groups, including the older age groups.

Sensitivity analyses

Around 40% of patients were taking antiplatelet therapy at baseline. In the sensitivity analysis that excluded patients on antiplatelet therapy at baseline and censored patients starting on antiplatelet therapy during follow-up, we found similar results as in the main analyses

Table I. Baseline characteristics of study population, stratified according to sex

Clinical characteristics	Males	Females
n (%)	44,196 (52.5)	39,946 (47.5)
Average age at baseline, y (SD)	73 (10.9)	78 (10.7)
Age 50-59 y, % (n)	15.1 (6,652)	7.2 (2,859)
Age 60-69 y, % (n)	25.3 (11,170)	15.1 (6,040)
Age 70-79 y, % (n)	31.2 (13,768)	28,6 (11,421)
Age 80-89 y, % (n)	24.0 (10,598)	36.8 (14,690)
Age 90+ y, % (n)	4.6 (2,008)	12.4 (4,936)
Baseline comorbidity, % (n)		
Previous stroke (ischemic or hemorrhagic)	11.1 (4,913)	10.2 (4,064)
Previous thromboembolism*	40.1 (17,699)	31.6 (12,627)
Previous myocardial infarction	30.0 (13,277)	20.8 (8,316)
Peripheral ischemic disease	11.6 (5,130)	8.8 (3,527)
Vascular disease	37.5 (16,575)	27.1 (10,832)
Diabetes	15.6 (6,896)	12.8 (5,125)
Hypertension	30.3 (13,406)	32.9 (13,124)
Renal disease	6.8 (3,014)	4.9 (1,974)
Liver disease	0.6 (261)	0.4 (145)
Hyperthyroidism	0.9 (378)	3.7 (1,488)
COPD	17.4 (7,668)	19.3 (7,694)
Baseline medication, % (n)		
ACE inhibitors	44.9 (19,849)	32.8 (13,092)
Aldosterone antagonists	6.9 (3,036)	8.0 (3,199)
β-Blockers	38.8 (17,161)	29.7 (11,842)
Non–loop diuretics	29.7 (13,117)	31.0 (12,370)
Loop diuretics	55.0 (24,288)	57.1 (22,798)
Statins	29.0 (12,839)	18.7 (7,477)
NSAIDs	10.9 (4,824)	13.6 (5,412)
Aspirin	40.3 (17,828)	34.6 (13,816)
Thienopyridines	13.7 (6,067)	8.6 (3,430)

Abbreviations: *COPD*, Chronic obstructive pulmonary disease; *ACE*, angiotensin-converting enzyme; *NSAIDs*, nonsteroidal antiinflammatory drugs.
* Combined ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, and acute myocardial infarction.

(see online Appendix Supplementary Table II, online-only material). The sensitivity analysis of deep venous thrombosis as an outcome showed an adjusted overall lower risk in females compared with males (see online Appendix Supplementary Table III, online-only material). When investigating the composite end point of stroke/thromboembolic event or all-cause death, female sex was associated with a lower risk of the composite end point in most age groups; however, the association was weaker than in the main analysis (see online Appendix Supplementary Table IV, online-only material).

Discussion

In this large cohort study, we found an association between female sex and decreased stroke risk in patients with HF older than 50 years, which persisted after adjustment for concomitant risk factors. In the older age groups, where the competing risk of death was substantial among males in particular, the association between female sex and stroke risk was attenuated and even reversed. When considering a more broadly defined thromboembolic end point, our findings were consistent with those for stroke, indicating a decreased risk among females across nearly all age groups.

Previous studies have described the association between sex and the risk of stroke in HF; however, many studies did not exclude patients with HF with AF.[21–23] Inconsistent results have been reported,[24–26] which may in part be explained by the severity and type of HF because HF with preserved ejection fraction is more common in females than males.[27] The etiology of HF is also different in females compared with males because HF in males are more often caused by ischemic heart disease, which may have a great influence on the risk of stroke.[28,29]

In studies involving patients with AF, some but not all studies report female sex to be associated with an increased risk of stroke.[30–33] This association appears to be reversed in the present HF population. However, we emphasize that our prognostic findings do not permit etiologic conclusions; other studies are needed to elucidate biologic reasons for the differences in male and female patients with HF.

In the HF population, females were generally older than males, leading to a higher risk of death when age was not taken into account. However, upon stratification by age groups, females generally had a lower risk of death. Females had a lower risk of stroke compared with males, but this association was attenuated with increasing age. Considering the 1-year RRs, this phenomenon could be attributed to the competing risks of death; males die before they are diagnosed with a stroke. An alternative explanation could be that HF with an ischemic etiology may develop at a later age among women.

We took into account competing risks in our analyses, an issue that has received limited attention in prior literature on cardiovascular risk stratification. For HF populations such as the present, where around 60% of participants died during the first 5 years of follow-up, not accounting for competing risk of death could lead to overestimation of risk and inappropriate risk stratification.[34,35]

Clinical importance

Our finding of a lower risk of stroke in females with HF compared with males may have prognostic value for clinicians in daily practice; even if the same comorbidities are present, males are at a higher risk of stroke. This may warrant focus on modifiable risk factors in male patients with HF compared with female patients with HF to reduce the risk of stroke, especially if the etiology of HF is due to ischemic heart disease.

Strengths and limitations

This study investigated a contemporary population of patients with incident HF in sinus rhythm followed up in nationwide registers, which has limited loss to follow-up, and therefore, the study is unlikely to be subject to serious selection bias. The major strengths of this study

Table II. Relative risks of stroke, all-cause death, and thromboembolic event after 1 year and 5 years of follow-up according to sex and age group (reference males, RR 1.00)

Primary end point	1 year after HF diagnosis				5 years after HF diagnosis			
Stroke	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	0.90	0.84-0.97	0.91	0.83-1.00	0.92	0.87-0.97	0.91	0.85-0.96
Age (y), 50-59	0.70	0.51-0.96	0.85	0.59-1.23	0.95	0.77-1.17	1.00	0.80-1.25
Age (y), 60-69	0.73	0.61-0.88	0.86	0.69-1.07	0.72	0.64-0.82	0.81	0.70-0.92
Age (y), 70-79	0.86	0.76-0.97	0.93	0.80-1.08	0.89	0.81-0.97	0.89	0.81-0.98
Age (y), 80-89	0.97	0.85-1.10	0.93	0.80-1.09	1.02	0.93-1.12	0.96	0.87-1.07
Age (y), 90+	1.25	0.89-1.76	1.38	0.89-2.15	1.23	0.94-1.61	1.33	0.98-1.79
Death	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	1.18	1.15-1.21	0.90	0.88-0.93	1.13	1.11-1.14	0.93	0.92-0.94
Age (y), 50-59	0.95	0.81-1.10	0.97	0.83-1.14	0.85	0.76-0.95	0.85	0.76-0.94
Age (y), 60-69	1.07	0.99-1.16	1.09	1.01-1.18	0.95	0.91-1.00	0.95	0.90-1.00
Age (y), 70-79	0.97	0.93-1.02	0.98	0.93-1.02	0.94	0.92-0.97	0.94	0.91-0.97
Age (y), 80-89	0.90	0.87-0.93	0.90	0.87-0.93	0.92	0.90-0.94	0.92	0.90-0.93
Age (y), 90+	0.82	0.78-0.86	0.83	0.79-0.87	0.95	0.93-0.98	0.95	0.93-0.97
Secondary end point	1 year after HF diagnosis				5 years after HF diagnosis			
Thromboembolic event†	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	0.86	0.83-0.89	1.00	0.96– 1.04	0.91	0.88-0.94	0.93	0.91-0.96
Age (y), 50-59	0.74	0.64-0.86	1.01	0.88-1.16	0.69	0.59-0.82	0.86	0.74-0.99
Age (y), 60-69	0.78	0.71-0.85	1.00	0.91-1.08	0.75	0.68-0.81	0.87	0.81-0.94
Age (y), 70-79	0.88	0.83-0.94	1.03	0.97-1.10	0.89	0.84-0.93	0.96	0.92-1.01
Age (y), 80-89	0.86	0.80-0.91	0.97	0.91-1.03	0.88	0.85-0.92	0.94	0.90-0.98
Age (y), 90+	0.91	0.80-1.04	1.07	0.92-1.24	0.93	0.86-1.00	1.01	0.93-1.10

Wald test for age-by-sex interaction in the adjusted analyses according to end point: stroke 1 year, $P = .43$; stroke 5 years, $P = .03$; death 1 year, $P = .00$; death 5 years, $P = .02$; thromboembolism 1 year, $P = .60$; thromboembolism 5 years, $P = .07$.

* Adjusted for hypertension (binary), diabetes (binary), prior thromboembolism (binary), vascular disease (binary), and age (continuous).

† Combined ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, and acute myocardial infarction.

are the high validity of the major outcomes and the large sample size uniquely possible with this type of cohort study.

The study also has several limitations. Because of the nature of our nationwide registry study, follow-up depended on the National Civil Registration System, where some deaths are likely to be attributable to an undiagnosed stroke. The diagnosis of stroke was defined by the Danish Hospital Discharge Register, and not all stroke end points have been defined by cerebral imaging. Furthermore, we cannot rule out that some patients might have had undiagnosed AF.

In our study, we were unable to distinguish between HF with preserved and reduced ejection fraction or estimate the functional classification, which we recognize as a major limitation. On the other hand, stroke and thromboembolism rates are broadly similar in hospitalized patients with HF, whether with preserved or reduced ejection fraction.[22,36–38]

Around 18% of the study population had a prior diagnosis of chronic obstructive pulmonary disease; therefore, some patients might have been misclassified as patients with HF because of symptoms that were actually related to their diagnosis of chronic obstructive pulmonary disease. However, the diagnosis of HF in the Danish National Patient Registry has been validated as very specific.[17]

Lastly, the present study only provides information on the prognostic value of sex, with respect to stroke risk, when taking into account standard cardiovascular comorbidities. Other studies are needed to elucidate biologic reasons for differences in prognosis between males and females.

In conclusion, we found an association between female sex and decreased stroke risk in patients with HF, which persisted after adjustment for concomitant cardiovascular risk factors. The association was attenuated with increasing age, possibly because of competing risks of death.

Disclosure of conflict of interests

All authors had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the design, analysis, interpretation of data, drafting the article, or revising it critically for important intellectual content, and approved the final version to be published. All authors have signed the authorship form.

Professor 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.

Associate professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim. Associate professor Larsen and professor Rasmussen have been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. Other authors – none declared.

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Appendix

Supplementary Table I. *ICD-10* codes and ATC codes used in the cohort study

ICD-10 codes and ATC codes used in the study

Main diagnosis	*ICD-10* codes
Congestive HF	I50.0-I50.9, I11.0, I13.0, I13.2
End points	
Stroke (ischemic)	I63.0-I63.9, I64.9
Ischemic stroke (thromboembolic event)	I63.0-I63.9, I64.9
Transient ischemic attack (thromboembolic event)	G45.0-G45.9*
Systemic embolism (thromboembolic event)	I74.0-I74.9
Pulmonary embolism (thromboembolic event)	I26.0-I26.9
Acute myocardial infarction (thromboembolic event)	I21.0-I21.9, I23.0-I23.9
Deep venous thrombosis	I80.1-I80.9, I81.9, I63.6, I67.6, I82.2, I82.3, I82.8, I82.9
Comorbidities	
Prior stroke (ischemic or hemorrhagic)	I60.0-I60.9, I61.0-I61.9, I62.0-I62.9, I63.0-I63.9, I64.9
Acute myocardial infarction	I21.0-I21.9, I23.0-I23.9
Peripheral ischemic disease†	I70.2-I70.9, I71.0-I71.9, I73.9
Vascular disease	I21.0-I21.9, I23.0-I23.9, I70.0, I70.2-I70.9, I71.0-I71.9, I73.9
Diabetes mellitus	E10.0-E10.9, E11.0-E11.9
Hypertension	I10.0-I10.9, I11.0-I11.9, I12.0-I12.9, I13.0-I13.9, I15.0–I15.9
Renal disease	I12.0-I12.9, I13.0-I13.9, N00-N07, N11.0-N11.9, N14.0-N14.4, N17.0-N17.9, N18.0-N18.9, N19, Q61.0-Q61.9
Liver disease	B15.0-B15.9, B16.0-B16.9, B17.0-B17.9, B18.0-B18.9, B19.0-B19.9, K70.4, K72.0-K72.9, K76.6
Hyperthyroidisme	E05.0-E05.9, E06.0-E06.9
Chronic obstructive pulmonary disease (COPD)	J44.0-J44.9
AF and flutter (exclusion criteria)	I48
Valvular disease (exclusion criteria)	I05.0-I05.9, I06.0-I06.9, I34.0-I34.9, I35.0-I35.9
Mechanical cardiac valve (exclusion criteria)	Z95.2, Z95.3, Z95.4
Cancer any type (exclusion criteria)	C00-C97
Concomitant medication	ATC codes
Warfarin (exclusion criteria)	B01AA03
Phenprocoumon (exclusion criteria)	B01AA04
ACE-inhibitors	C09AA
Angiotension receptor blockers	C09CA
Beta-blockers	C07
Non-loop diuretics	C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G,C09BA, C09DA, C09XA52
Aldosterone antagonists	C03DA
Concomitant medication	
Loop diuretics	C03C
Statins	C10
Non steroidal anti-inflammatory drugs (NSAIDs)	M01A
Aspirin	B01AC06
Thienopyridines	B01AC04, B01AC22, B01AC24

* Not inclusive G45.3 (Amaurosis fugax).
† Peripheral arterial disease refers to the obstruction of large arteries not within the coronary, aortic arch vasculature, or brain.

Supplementary Table II. Sensitivity analysis after excluding patients on antiplatelet therapy at baseline and censoring during follow-up: RRs of stroke, all-cause death, and thromboembolic event after 1 year and 5 years of follow-up according to sex and age group (reference: males, RR 1.00)

Primary end point	1 year after HF diagnosis				5 years after HF diagnosis			
Stroke	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	0.79	0.71-0.89	0.92	0.80-1.06	0.90	0.82-1.00	0.96	0.87-1.06
Age (y), 50-59	0.40	0.21-0.75	0.63	0.35-1.14	0.43	0.21-0.87	0.56	0.34-0.94
Age (y), 60-69	0.70	0.53-0.93	0.95	0.69-1.31	0.77	0.60-0.98	0.94	0.74-1.19
Age (y), 70-79	0.78	0.64-0.94	1.03	0.82-1.28	0.89	0.75-1.04	0.96	0.82-1.12
Age (y), 80-89	0.92	0.75-1.13	0.91	0.72-1.16	1.11	0.94-1.32	1.11	0.93-1.31
Age (y), 90+	0.97	0.57-1.64	0.98	0.51-1.86	1.11	0.68-1.82	1.28	0.78-2.08
Death	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	1.05	1.02-1.09	0.89	0.87-0.92	1.04	1.01-1.06	0.92	0.90-0.94
Age (y), 50-59	0.73	0.58-0.92	0.77	0.62-0.96	0.45	0.33-0.62	0.48	0.36-0.65
Age (y), 60-69	0.86	0.77-0.96	0.90	0.82-1.00	0.76	0.70-0.83	0.77	0.71-0.84
Age (y), 70-79	0.91	0.86-0.97	0.95	0.89-1.00	0.90	0.86-0.94	0.90	0.87-0.94
Age (y), 80-89	0.88	0.84-0.92	0.90	0.86-0.94	0.94	0.91-0.97	0.95	0.92-0.98
Age (y), 90+	0.82	0.77-0.87	0.84	0.79-0.90	0.99	0.95-1.04	1.00	0.96-1.04
Secondary end point	1 year after HF diagnosis				5 years after HF diagnosis			
Thromboembolic event†	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	0.82	0.77-0.88	0.98	0.91-1.04	0.89	0.83-0.94	0.91	0.86-0.96
Age (y), 50-59	0.57	0.40-0.83	0.86	0.64-1.15	0.30	0.09-0.96	0.50	0.28-0.87
Age (y), 60-69	0.67	0.56-0.80	0.95	0.81-1.12	0.58	0.46-0.72	0.74	0.62-0.88
Age (y), 70-79	0.81	0.73-0.91	1.00	0.90-1.11	0.89	0.80-0.99	0.96	0.88-1.06
Age (y), 80-89	0.88	0.79-0.99	1.00	0.90-1.12	0.92	0.84-1.01	0.98	0.90-1.07
Age (y), 90+	0.95	0.75-1.21	1.08	0.85-1.38	0.92	0.78-1.09	1.00	0.85-1.17

* Adjusted for hypertension (binary), diabetes (binary), prior thromboembolism (binary), prior myocardial infarction (binary), peripheral artery disease (binary), and age (continuous).
† Combined ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, and acute myocardial infarction.

Supplementary Table III. Relative risks of deep venous thrombosis after 1 year and 5 years of follow-up according to sex and age group (reference: males, RR 1.00)

End point	1 year after HF diagnosis				5 years after HF diagnosis			
Deep venous thrombosis	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	1.18	0.98-1.41	0.85	0.61-1.18	1.16	1.03-1.30	0.95	0.79-1.14
Age (y), 50-59	1.78	1.00-3.18	1.26	0.31-5.11	1.12	0.77-1.63	0.78	0.43-1.40
Age (y), 60-69	1.03	0.66-1.59	0.94	0.42-2.09	1.18	0.91-1.53	0.96	0.66-1.38
Age (y), 70-79	1.15	0.84-1.58	0.79	0.40-1.59	1.20	0.98-1.48	0.98	0.71-1.35
Age (y), 80-89	1.01	0.72-1.40	0.76	0.42-1.37	1.24	0.99-1.56	1.04	0.75-1.44
Age (y), 90+	2.60	0.95-7.10	1.90	0.25-14.18	3.12	1.20-8.12	2.29	0.59-8.94

* Adjusted for hypertension (binary), diabetes (binary), prior thromboembolism (binary), prior deep venous thrombosis (binary), prior myocardial infarction (binary), peripheral artery disease (binary), and age (continuous).

Supplementary Table IV. Relative risks of stroke/thromboembolism or all-cause death after 1 year and 5 years of follow-up according to sex and age group (reference: males, RR 1.00)

End point	1 year after HF diagnosis				5 years after HF diagnosis			
Composite end point	Crude RR	95% CI	Adjusted RR*	95% CI	Crude RR	95% CI	Adjusted RR*	95% CI
Overall	1.05	1.05-1.07	0.94	0.93-0.96	1.06	1.04-1.07	0.94	0.93-0.95
Age (y), 50-59	0.86	0.78-0.94	0.93	0.85-1.02	0.84	0.78-0.89	0.86	0.80-0.91
Age (y), 60-69	0.93	0.88-0.98	0.99	0.94-1.04	0.91	0.88-0.95	0.93	0.90-0.96
Age (y), 70-79	0.95	0.91-0.98	1.00	0.96-1.03	0.94	0.92-0.96	0.95	0.94-0.97
Age (y), 80-89	0.90	0.87-0.92	0.93	0.90-0.95	0.94	0.92-0.95	0.94	0.93-0.95
Age (y), 90+	0.84	0.80-0.87	0.87	0.84-0.91	0.96	0.94-0.98	0.97	0.95-0.98

* Adjusted for hypertension (binary), diabetes (binary), prior thromboembolism (binary), prior myocardial infarction (binary), peripheral artery disease (binary), and age (continuous).

Appendix C. Paper 3

Vascular Disease and Risk Stratification for Ischemic Stroke and All-Cause Death in Heart Failure Patients without Diagnosed Atrial Fibrillation: A Nationwide Cohort Study

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Abstract

Background: Stroke and mortality risk among heart failure patients previously diagnosed with different manifestations of vascular disease is poorly described. We conducted an observational study to evaluate the stroke and mortality risk among heart failure patients without diagnosed atrial fibrillation and with peripheral artery disease (PAD) or prior myocardial infarction (MI).

Methods: Population-based cohort study of patients diagnosed with incident heart failure during 2000-2012 and without atrial fibrillation, identified by record linkage between nationwide registries in Denmark. Hazard rate ratios of ischemic stroke and all-cause death after 1 year of follow-up were used to compare patients with either: a PAD diagnosis; a prior MI diagnosis; or no vascular disease.

Results: 39,357 heart failure patients were included. When compared to heart failure patients with no vascular disease, PAD was associated with a higher 1-year rate of ischemic stroke (adjusted hazard rate ratio [HR]: 1.34, 95% confidence interval [CI]: 1.08-1.65) and all-cause death (adjusted HR: 1.47, 95% CI: 1.35-1.59), whereas prior MI was not (adjusted HR: 1.00, 95% CI: 0.86-1.15 and 0.94, 95% CI: 0.89-1.00, for ischemic stroke and all-cause death, respectively). When comparing patients with PAD to patients with prior MI, PAD was associated with a higher rate of both outcomes.

Conclusions: Among incident heart failure patients without diagnosed atrial fibrillation, a previous diagnosis of PAD was associated with a significantly higher rate of the ischemic stroke and all-cause death compared to patients with no vascular disease or prior MI. Prevention strategies may be particularly relevant among HF patients with PAD.

Introduction

Heart failure (HF) is associated with an increased risk of ischemic stroke and mortality[1], for which vascular disease is also an established risk factor[2,3]. In the general population, vascular disease is associated with an increased risk of cardiovascular events[4,5]. However, currently there is a lack of research on risk of ischemic stroke and mortality among incident HF patients in sinus rhythm previously diagnosed with different manifestations of vascular disease. Estimating the risk of ischemic stroke and all-cause death among HF patients in sinus rhythm with vascular disease is an important step towards finding subgroups of HF patients who might benefit from thromboprophylaxis, as suggested in a recent study[6] which found a high risk of ischemic stroke and thromboembolism among HF patients without AF.

Vascular disease is a broad term, including two common and severe diseases, that is, peripheral artery disease (PAD) and myocardial infarction (MI). HF is known to be complicated by comorbidities such as PAD and prior MI[7,8], and assessment of these two comorbidities in relation to ischemic stroke, mortality, and prevention is important in a HF setting. However, PAD and prior MI may not confer the same risk of ischemic stroke[9]. Accordingly, evaluation of the association between vascular disease and ischemic stroke risk in the HF population requires investigating PAD and prior MI separately, as previously done in other settings[9,10]. The task of identifying subgroups of patients with HF who are at a high risk of stroke is clinically highly relevant because many such strokes may be preventable, for example, by pharmacological thromboprophylaxis.

The objective of the present observational cohort study was to assess the prognostic value of a prior diagnosis of PAD or MI in relation to the risk of ischemic stroke and all-cause death in HF patients, using Danish nationwide administrative registry data. We hypothesized that in a population of incident HF patients without AF (and not taking a vitamin K antagonist (VKA) to avoid issues with effect modification by anticoagulation therapy), a prior diagnosis of either PAD or MI would be associated with a higher risk of ischemic stroke and all-cause death, when compared to no vascular disease, also when taking into account concomitant cardiovascular risk factors of ischemic stroke. Second, we hypothesized that PAD and prior MI would not contribute equally to this risk, since a difference in risk of ischemic stroke and all-cause death has been observed in other cardiovascular settings[9].

Methods

Registry Data Sources

We used three different nationwide registries in this study: i) The Danish National Patient Registry[11] which has registered all hospital admissions along with diagnoses since 1977 and codes all diagnoses according to the 10th revision of the International Classification of Diseases (ICD-10) since 1994; ii) The National Prescription Registry[12] which contains data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System; iii) The Danish Civil Registration System which holds information on date of birth, migration, vital status, date of death, and sex of all persons living in Denmark[13]. Data were linked via unique personal identification number used in all Danish national registries. All three registries were up to December 31st 2012. These registries have previously been validated[11,12,14], and the diagnosis of HF, ischemic stroke, PAD and MI was found to be valid[14–16].

Study Population

The study population was identified as in- or outpatients aged>50 years, diagnosed with a primary discharge diagnosis of incident (first-time diagnosis) HF in the period January 1st 2000 - December 31st 2012 (ICD-10: I50, I42.0, I11.0, I13.0, I13.2). "Vascular disease" was defined as a diagnosis of either PAD (ICD-10: I70.2-I70.9, I73.9) or MI (ICD-10: I21.0-I21.9, I23.0-I23.9) between 1994 and time of HF diagnosis. Patients with prior diagnoses of both PAD and MI were not included in the analyses: this is a small and seriously ill patient group, against which direct comparisons would have both limited statistical power and clinical use. To restrict to patients without AF, we excluded those who had a prior diagnosis of AF or atrial flutter (I48) between 1994 and time of HF diagnosis. We moreover excluded patients treated with a vitamin K antagonist (ATC: B01AA03, B01AA04) within six months prior to the HF diagnosis to avoid considering effect modification by anticoagulation therapy. Lastly, patients with a diagnosis of cancer (ICD-10: C00-C97) within 5 years before HF diagnosis were excluded, since cancer patients represent a subgroup with high stroke risk[17] and specialized thromboprophylactic treatment regimens.

Additional comorbidities were assessed at time of HF diagnosis identified using the Danish National Patient Registry and the Danish National Prescription Registry which have registered diagnoses (using ICD-10) and prescriptions since 1994. Ascertainment of baseline medication status was based on medication purchase in a 45-day window before or after the date of HF diagnosis. ICD-codes and ATC-codes used to define comorbidities and medical therapy are provided in the Supplementary material [please see **S1 Table** in the supporting materials].

Outcomes

The primary endpoint was defined as an ischemic stroke diagnosis (ICD-10: I63, I64). Because of the high mortality in the HF population and the fact that in registries some deaths may be due to undiagnosed stroke, especially since postmortems and cerebral scanning are not mandated, all-cause death was also included as a primary endpoint.

Statistical Methods

Baseline characteristics were described separately for patients with no vascular disease, PAD, and prior MI; using means and standard deviation for continuous variables, and proportions for categorical variables.

Time-to-event analysis was used to describe the association with the three-level vascular disease exposure (no vascular disease; prior PAD; prior MI) and risk of ischemic stroke or all-cause death. Time at risk was measured from baseline date (date of HF diagnosis) and until an event of ischemic stroke, all-cause death, emigration, or end of study (December 31st 2012), whichever came first. Additionally, patients were censored if they initiated anticoagulant therapy during the follow-up period.

We have previously advocated risks (probabilities) rather than rates for assessing associations in a HF population, since risks lead to statements which are more clinically and prognostically relevant when faced with a high competing mortality risk[18]. However, strong differential competing mortality across exposure levels can lead to counterintuitive findings on a risk scale. This is a real concern for vascular disease as an exposure. Accordingly, we reported associations in terms of (Cox model) hazard rate ratios after 1 year of

follow-up. Following the suggestions of Andersen et al.[19] to consider both risk and rate assessments, we repeated this analysis on a risk (ratio) scale; see the Supplementary material for methodological details.

Specifically, for the primary analysis, Cox regression was used to calculate 1-year hazard rate ratios of the endpoints according to the presence of PAD or prior MI (5-year hazard ratios are reported in the Supplementary material). Concomitant baseline comorbidities such as hypertension, diabetes, renal disease, and prior ischemic stroke are well-known risk factors of ischemic stroke in other heart diseases[20,21]. Thus, in order to assess the independent prognostic value of PAD and prior MI, we also fitted Cox models after adjusting for these risk factors; alongside with chronic obstructive pulmonary disease (COPD), age and sex. Antiplatelet therapy may modify the association between vascular disease and ischemic stroke risk; therefore, we calculated 1-year hazard rate ratios of the endpoints according to the presence of PAD or prior MI, and stratified by antiplatelet therapy at baseline (5-year hazard ratios are reported in the Supplementary material).

We performed a sensitivity analysis in which we censored patients receiving a diagnosis of AF during follow-up. We also performed a sensitivity analysis in which patients with a history of stroke were excluded (since a prior stroke diagnosis is a strong risk factor for a subsequent stroke)[22].

The analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA). A two-sided p-value of <0.05 was considered statistically significant. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Ethical Considerations

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency (J. No. File No. 2012-41-0633).

Results

The study population comprised 39,357 HF patients aged>50 years, among which 69.2% had no vascular disease, 5.8% had PAD and 21.7% had prior MI (3.3% had both) [please see **Figure 1** at the end of the manuscript]. The median follow-up time for ischemic stroke or all-cause death was 2.5 years (interquartile range 0.6-5.3).

Baseline patient characteristics are summarized in **Table 1** at the end of the manuscript. The mean age among patients with no vascular disease was 74.3 years (standard deviation (SD): 11.7) compared to 74.9 years (SD: 9.9) and 73.1 years (SD: 10.9) years for patients with PAD and prior MI, respectively. Patients with PAD had more often experienced a previous stroke or transient ischemic attack compared to both patients with prior MI or no vascular disease, and the prevalence of diabetes, hypertension, renal disease, and COPD was higher in patients with PAD. More patients with prior MI were taking medical therapy with ACE-inhibitors, beta-blockers and statins. Furthermore, almost 75% of the patients with prior MI were on antiplatelet therapy, compared to around 50% of the patients with PAD.

The number of ischemic strokes and deaths in each patient group after 1 year of follow-up are shown in **Table 2** at the end of the manuscript. For patients with no vascular disease, PAD, or prior MI, the absolute risks of both endpoints are shown in **Table 2**. The 1-year absolute risks of ischemic stroke and all-cause death were highest in patients with PAD (4.7% and 30.8%, respectively). For the 5-year event numbers and absolute risks please see **e-Table 2** in the Supplementary material.

In the Cox regression analysis, when compared to HF patients with no vascular disease, PAD was associated with a higher 1-year rate of ischemic stroke (adjusted hazard rate ratio [HR]: 1.34, 95% confidence interval [CI]: 1.08-1.65) and all-cause death (adjusted HR: 1.47, 95% CI: 1.35-1.59), whereas prior MI was not (adjusted HR: 1.00, 95% CI: 0.86-1.15 and 0.94, 95% CI: 0.89-1.00, for ischemic stroke and all-cause death, respectively), as shown in **Table 3** at the end of the manuscript. When comparing patients with PAD to patients with prior MI, PAD was associated with a higher rate of both endpoints (adjusted HR: 1.36, 95% CI: 1.07-1.72 and 1.53, 95% CI: 1.40-1.68, for ischemic stroke and all-cause death, respectively). Similar results were obtained after 5-years follow-up [please see **e-Table 3** in the Supplementary material].

The stratified HRs of ischemic stroke and all-cause death after 1-year follow-up, according to antiplatelet therapy at baseline, are shown in **Table 4** at the end of the manuscript. Regardless of antiplatelet therapy status at baseline, PAD was associated with a higher 1-year rate of ischemic stroke and all-cause death when compared to HF patients with no vascular disease or prior MI. In patients on antiplatelet therapy, we found similar rates of ischemic stroke and all-cause death among patients with prior MI compared to those with no vascular disease. In patients not on antiplatelet therapy, prior MI was associated with an increased rate of all-cause death, when compared to no vascular disease. Similar results were obtained after 5-years

follow-up [please see **e-Table 4** in the Supplementary material].

The 1- and 5-year relative risks of ischemic stroke and all-cause death, comparing patients with PAD or prior MI to patients with no vascular disease are shown in **e-Table 7** and **e-Table 8** in the Supplementary material. We found similar crude associations as in the rate-based calculations, but the associations attenuated after adjustment for cardiovascular risk factors, especially for the endpoint of ischemic stroke.

Sensitivity analyses
In the sensitivity analysis in which patients were censored when they were diagnosed with AF during follow-up, findings were similar to the main analysis [please see **e-Table 5** in the Supplementary material]. When excluding patients with a history of stroke, PAD was associated with an even higher rate of ischemic stroke in the adjusted analyses compared to patients with no vascular disease and prior MI [please see **e-Table 6** in the Supplementary material].

Discussion

In this large nationwide cohort study of HF patients without AF, we found a significantly higher rate of ischemic stroke and all-cause death amongst HF patients with PAD compared to patients with no vascular disease or prior MI, even after extensive adjustment for concomitant cardiovascular risk factors. Similar results were obtained in the stratified analysis, regardless of antiplatelet therapy. However, for the risk (probability) based calculations, the picture was less consistent.

To our knowledge, this is the first study to comprehensively evaluate the association between PAD and prior MI and ischemic stroke and all-cause death in a HF population without diagnosed AF. The current evidence on the risk of ischemic stroke in subgroups of HF patients without diagnosed AF is very limited[23–25]. In our population, PAD was associated with a roughly 30% higher rate of ischemic stroke compared to patients without vascular disease. We did not see a similar increased rate of ischemic stroke among patients with prior MI, as expected. Indeed, we found PAD to be associated with a higher rate of ischemic stroke compared to prior MI.

Our findings for the rate of stroke and mortality are consistent with the possibility of less secondary prevention strategies in PAD patients compared to MI patients, as seen in other settings[26,27]. In our study, a larger proportion of patients with prior MI were taking medical therapy with ACE-inhibitors, beta-blockers, statins, and antiplatelet therapy compared to patients with PAD. This was despite patients with PAD having more comorbidities, such as prior stroke/transient ischemic attack, diabetes, and hypertension. The lower rate of ischemic stroke and all-cause death among prior MI patients compared to PAD patients may reflect a more ill patients group of those with PAD[28]. Alternatively, these findings may reflect a more intensified treatment and prophylaxis among patients with coronary artery disease[27]. For example, antiplatelet therapy is known to reduce the risk of ischemic stroke[29,30]. Our findings in the subpopulation of patients on antiplatelet therapy were consistent with the hypothesis of more intensified treatment and prophylaxis among MI patients, since patients on antiplatelet therapy with prior MI or no vascular disease had essentially the same rate of ischemic stroke.

Clinical implications
Reduced secondary prevention in PAD patients compared to patients with coronary artery disease has been observed in several studies[26,27]; not-withstanding guideline recommendations that the same secondary prevention should be used in patients with PAD and prior MI[31,32]. Our results provide some indication that, in clinical practice, HF patients with PAD may represent a higher-risk subgroup in terms of ischemic stroke and all-cause death risk compared to prior MI patients. It is possible that more focus on secondary prevention could improve prognosis for this patient group. Currently, an ongoing trial (COMMANDER HF) is exploring the efficacy and safety of Rivaroxaban (one of the non-vitamin K antagonist oral anticoagulants) compared with placebo (standard care) after an exacerbation of HF in non-AF patients with HF with reduced ejection fraction and documented coronary artery disease. However, whether full anticoagulation therapy would be beneficial in HF patients with PAD is an open question in need of further investigation before recommendations about changes in management of these patients can be given, since recent prospective randomized controlled trials of antithrombotic therapy in HF have not investigated such subgroup issues[33–36].

We provided both risk/probability (risk ratio) and rate (hazard ratio) assessments of associations[19]. While risk and rate assessments are traditionally thought of as being equivalent, they can be fundamentally different in the face of competing morality risk[37]. In the present study, associations were attenuated when viewed on a risk scale. This is important information from a clinical perspective, since it may indicate a smaller absolute potential (e.g. in terms of number of strokes prevented) of prevention strategies among PAD patients than otherwise suggested by the hazard ratios.

Strengths and Limitations

The major strengths of this study are the validated outcomes and large sample size uniquely possible with this type of cohort study. Selection into the study was not an issue, since we investigated a nationwide population cohort of incident HF patients without AF, with limited loss to follow-up.

The study also has several important limitations. We were unable to distinguish between HF with preserved and reduced ejection fraction or estimate the functional classification, since we did not have access to echocardiograms. However, no difference in embolic risk (risk of stroke, transient ischemic attack, systemic embolism) was found in a recent study of non-anticoagulated patients with HF with reduced or preserved ejection fraction[38]. Similarly, in a post-hoc analysis of a study of AF patients with HF with reduced or preserved ejection fraction, no difference in ischemic stroke risk was found between the groups[39]. The diagnosis of HF has previously been validated and had a positive predictive value of 81-100%[16,40]. Based on the validation study, we did not capture all patients with HF and also cannot be certain that all patients identified as having HF had definite HF, which could lead to imprecision in the risk estimates. However, we included only patients with a primary discharge diagnosis of HF to optimize the probability of including only correctly identified patients with HF. We excluded HF patients younger than 50 years of age, and accordingly, our findings may not apply to younger HF patients.

The exposure variable of vascular disease may also be subject to misclassification and incomplete ascertainment. Moreover, we did not have information about the ankle-brachial index, and were hence unable to use this measurement in the definition of PAD.

We lacked information on smoking habits, which is a key concomitant risk factor for ischemic stroke; it is possible that some of the association between PAD and ischemic stroke risk is explained by smoking, but since the focus of the study was on the prognostic value of vascular disease in relation to ischemic stroke, not its causal role, confounding is not an issue. Similarly, we did not have information about the etiology of HF, which could influence the association between vascular disease and stroke risk; however, we were only interested in the prognostic importance of vascular disease, not the causal association.

We included unspecified stroke (ICD-10: I64) in the definition of ischemic stroke, as most strokes are of ischemic origin. However, we cannot rule out that some of these strokes might have been hemorrhagic strokes and thus, misclassified as ischemic strokes. Also, we cannot rule out that some patients might have had undiagnosed AF, since heart disease is associated with an increased risk of developing AF, however, censoring for presence of AF during follow-up did not change the main conclusions.

Last, the study was carried as a nationwide study in the Danish population, which both ethnically and socioeconomically is fairly homogeneous. Future studies are needed to evaluate if our findings hold in more diverse populations.

Conclusion

Among incident HF patients without AF, prior PAD was associated with a significantly higher rate of ischemic stroke and all-cause death compared to both patients with no vascular disease and with prior MI, even after adjustment for concomitant cardiovascular risk factors.

Acknowledgment

All authors had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the design, analysis, interpretation of data, drafting the article, or revising it critically for important intellectual content and approved the final version to be published.

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Table 1: Baseline characteristics of study population, stratified according to vascular disease.

Clinical characteristics	No vascular disease	Peripheral artery disease	Prior myocardial infarction
N, % (n)	69.2 (27,242)	5.8 (2,274)	21.7 (8,556)
Sex (females), % (n)	48.4 (13,191)	45.3 (1,030)	33.0 (2,824)
Average age at baseline, years (SD)	74.3 (11.7)	74.9 (9.9)	73.1 (10.9)
Baseline comorbidity, % (n)			
Previous stroke/transient ischemic attack	11.2 (3,060)	22.3 (507)	14.1 (1,203)
Diabetes	12.0 (3,264)	23.1 (525)	16.1 (1,374)
Hypertension	28.5 (7,752)	44.5 (1,012)	35.0 (2,991)
Renal Disease	4.5 (1,215)	10.0 (228)	5.8 (495)
Liver Disease	0.5 (136)	0.4 (9)	0.3 (29)
Hyperthyroidism	2.7 (723)	3.7 (83)	2.1 (182)
COPD	13.3 (3,632)	19.7 (447)	11.2 (959)
Baseline medication, % (n)			
ACE-inhibitors	47.9 (13,040)	46.5 (1,058)	62.5 (5,345)
Angiotensin receptor blocker	10.0 (2,721)	12.8 (292)	11.0 (941)
Beta-blockers	37.2 (10,138)	36.8 (837)	64.3 (5,497)
Aldosterone antagonists	22.9 (6,225)	22.7 (516)	23.3 (1,990)
Non-loop diuretics	40.0 (10,902)	40.0 (910)	35.5 (3,034)
Loop diuretics	66.2 (18,041)	70.8 (1,609)	60.6 (5,185)
Statins	21.0 (5,732)	34.0 (772)	57.1 (4,888)
NSAIDs	14.6 (3,973)	14.4 (327)	12.3 (1,048)
Aspirin	40.5 (11,032)	49.7 (1,129)	68.4 (5,851)
Thienopyridines	3.8 (1,043)	6.4 (145)	31.6 (2,703)

(Abbreviations: COPD=chronic obstructive pulmonary disease; NSAIDs=non-steroidal anti-inflammatory drugs; SD=standard deviation; TIA=transient ischemic attack)

Table 2: Event numbers and absolute risks of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.

ENDPOINT	Event number	Absolute risk*, %
Ischemic stroke		
No vascular disease	705	2.7
PAD	101	4.7
Prior MI	250	3.0
All-cause death		
No vascular disease	5486	21.5
PAD	661	30.8
Prior MI	1509	18.5

(Abbreviations: HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease)

*Taking into account competing risks of death (Aalen-Johansen estimator).

Table 3: Hazard rate ratios of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.

ENDPOINT	PRIMARY EFFECT ESTIMATES	
Ischemic stroke	Crude HR (95% CI)	Adjusted HR* (95% CI)
PAD vs. no vascular disease	1.82 (1.47 – 2.24)	1.34 (1.08 – 1.65)
Prior MI vs. no vascular disease	1.09 (0.94 – 1.26)	1.00 (0.86 – 1.15)
PAD vs. prior MI	1.67 (1.32 – 2.10)	1.36 (1.07 – 1.72)
All-cause death	Crude HR (95% CI)	Adjusted HR* (95% CI)
PAD vs. no vascular disease	1.51 (1.40 – 1.64)	1.47 (1.35 – 1.59)
Prior MI vs. no vascular disease	0.85 (0.80 – 0.90)	0.94 (0.89 – 1.00)
PAD vs. prior MI	1.78 (1.63 – 1.95)	1.53 (1.40 – 1.68)

(Abbreviations: HF: heart failure; HR: hazard ratio; MI: myocardial infarction; PAD: peripheral artery disease; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

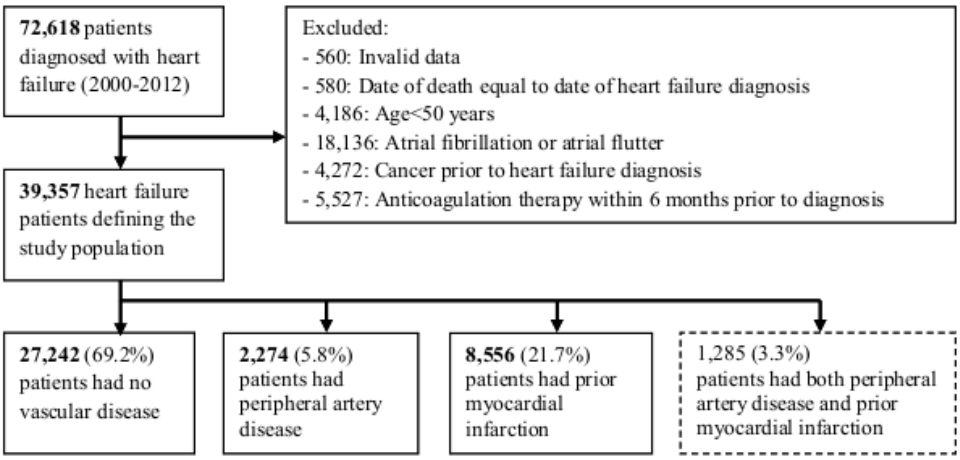
Table 4: Hazard rate ratios of ischemic stroke and all-cause death after 1-year follow-up, stratified by antiplatelet therapy at baseline.

ENDPOINT	STRATIFIED ADJUSTED ESTIMATES*	
Ischemic stroke	No antiplatelet therapy HR (95% CI)	Antiplatelet therapy HR (95% CI)
PAD vs. no vascular disease	1.49 (1.10 – 2.01)	1.23 (0.91 – 1.65)
Prior MI vs. no vascular disease	1.03 (0.79 – 1.34)	1.02 (0.85 – 1.22)
PAD vs. prior MI	1.45 (1.00 – 2.12)	1.23 (0.90 – 1.68)
All-cause death	No antiplatelet therapy HR (95% CI)	Antiplatelet therapy HR (95% CI)
PAD vs. no vascular disease	1.43 (1.29 – 1.60)	1.65 (1.45 – 1.86)
Prior MI vs. no vascular disease	1.27 (1.17 – 1.38)	0.99 (0.91 – 1.07)
PAD vs. prior MI	1.11 (0.98 – 1.26)	1.64 (1.44 – 1.87)

(Abbreviations: HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease; HR: hazard ratio; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

Figure 1: Flowchart of patients included in the final study population.



Supporting Information

e-Table 1. ICD-10 codes and ATC-codes used in the cohort study.

e-Table 2. Event numbers and absolute risks of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.

e-Table 3. Hazard rate ratios of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.

e-Table 4. Hazard rate ratios of ischemic stroke and all-cause death after 5-year follow-up, stratified by antiplatelet therapy at baseline.

e-Table 5. Sensitivity analysis censoring patients diagnosed with AF during follow-up: Hazard rate ratios of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.

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e-Table 7. Relative risks of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.

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Methodological details. Analysis on a risk-scale.

e-Table 1. ICD-10 codes and ATC-codes used in the cohort study.

ICD 10-Codes and ATC-Codes used in the Study	
Main diagnosis	**ICD 10-Codes**
Congestive heart failure	I50.0-I50.9, I11.0, I13.0, I13.2
Acute myocardial infarction	I21.0-I21.9, I23.0-I23.8
Peripheral arterial disease*	I70.2-I70.9, I73.9
Endpoint	
Stroke (ischemic)	I63.0-I63.9, I64
Comorbidities	**ICD 10-Codes**
Prior stroke (ischemic or hemorrhagic) / transient ischemic attack	I60.0-I60.9, I61.0-I61.9, I62.0-I62.9, I63.0-I63.9, I64.9, G45†
Vascular disease	I21.0-I21.9, I23.0-I23.9, I70.0, I70.2-I70.9, I73.9
Diabetes mellitus	E10.0-E10.9, E11.0-E11.9
Hypertension	I10.0-I10.9, I11.0-I11.9, I12.0-I12.9, I13.0-I13.9, I15.0–I15.9
Renal disease	I12.0-I12.9, I13.0-I13.9, N00-N07, N11.0-N11.9, N14.0-N14.4, N17.0-N17.9, N18.0-N18.9, N19, Q61.0-Q61.9
Liver disease	B15.0-B15.9, B16.0-B16.9, B17.0-B17.9, B18.0-B18.9, B19.0-B19.9, K70.4, K72.0-K72.9, K76.6
Hyperthyroidisme	E05.0-E05.9, E06.0-E06.9
Chronic obstructive pulmonary disease (COPD)	J44.0-J44.9
Atrial fibrillation and flutter (exclusion criteria)	I48
Cancer any type (exclusion criteria)	C00-C97
Concomitant medication	**ATC-Codes**
Warfarin (exclusion criteria)	B01AA03
Phenprocoumon (exclusion criteria)	B01AA04
ACE-inhibitors	C09AA
Angiotension receptor blockers	C09CA
Beta-blockers	C07
Non-loop diuretics	C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G,C09BA, C09DA, C09XA52
Aldosterone antagonists	C03DA
Loop diuretics	C03C
Statins	C10
Non steroidal anti-inflammatory drugs (NSAIDs)	M01A
Aspirin	B01AC06
Thienopyridines	B01AC04, B01AC22, B01AC24

**Peripheral arterial disease, refers to the obstruction of large arteries not within the coronary, aortic arch vasculature, or brain*
†Not inclusive G45.3 (Amaurosis fugax)

e-Table 2. Event numbers and absolute risks of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.

ENDPOINT	Event number	Absolute risk*, %
Ischemic stroke		
No vascular disease	1559	6.8
PAD	185	9.2
Prior MI	569	7.9
All-cause death		
No vascular disease	10805	48.5
PAD	1239	66.1
Prior MI	2977	42.9

(Abbreviations: MI: myocardial infarction; PAD: peripheral artery disease)

* Taking into account competing risks of death (Aalen-Johansen estimator).

e-Table 3. Hazard rate ratios of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.

ENDPOINT	PRIMARY EFFECT ESTIMATES	
Ischemic stroke	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
PAD vs. no vascular disease	1.68 (1.44 – 1.96)	1.32 (1.13 – 1.54)
Prior MI vs. no vascular disease	1.11 (1.01 – 1.22)	1.04 (0.94 – 1.15)
PAD vs. prior MI	1.56 (1.28 – 1.79)	1.23 (1.04 – 1.46)
All-cause death	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
PAD vs. no vascular disease	1.60 (1.51 – 1.70)	1.52 (1.43 – 1.61)
Prior MI vs. no vascular disease	0.84 (0.81 – 0.87)	0.91 (0.88 – 0.95)
PAD vs. prior MI	1.91 (1.79 – 2.04)	1.63 (1.53 – 1.75)

(Abbreviations: HF: heart failure; HR: hazard rate ratio; MI: myocardial infarction; PAD: peripheral artery disease; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

e-Table 4: Hazard rate ratios of ischemic stroke and all-cause death after 5-year follow-up, stratified by antiplatelet therapy at baseline.

ENDPOINT	STRATIFIED ADJUSTED ESTIMATES*			
Ischemic stroke	**No antiplatelet therapy HR (95% CI)**		**Antiplatelet therapy HR (95% CI)**	
PAD vs. no vascular disease	1.51	(1.21 – 1.87)	1.18	(0.95 – 1.47)
Prior MI vs. no vascular disease	1.16	(0.98 – 1.38)	1.05	(0.93 – 1.18)
PAD vs. prior MI	1.25	(0.96 – 1.62)	1.11	(0.88 – 1.39)
All-cause death	**No antiplatelet therapy HR (95% CI)**		**Antiplatelet therapy HR (95% CI)**	
PAD vs. no vascular disease	1.48	(1.36 – 1.60)	1.65	(1.51 – 1.79)
Prior MI vs. no vascular disease	1.14	(1.07 – 1.22)	0.95	(0.90 – 1.00)
PAD vs. prior MI	1.27	(1.15 – 1.41)	1.72	(1.57 – 1.88)

(Abbreviations: HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease; HR: hazard ratio; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

e-Table 5. Sensitivity analysis censoring patients diagnosed with AF during follow-up: Hazard rate ratios of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.

ENDPOINT	PRIMARY EFFECT ESTIMATES	
Ischemic stroke	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
PAD vs. no vascular disease	1.78 (1.44 – 2.21)	1.29 (1.04 – 1.61)
Prior MI vs. no vascular disease	1.12 (0.96 – 1.29)	1.02 (0.88 – 1.18)
PAD vs. prior MI	1.60 (1.26 – 2.03)	1.30 (1.02 – 1.66)
All-cause death	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
PAD vs. no vascular disease	1.51 (1.39 – 1.64)	1.46 (1.34 – 1.59)
Prior MI vs. no vascular disease	0.85 (0.80 – 0.90)	0.94 (0.86 – 1.00)
PAD vs. prior MI	1.77 (1.61 – 1.95)	1.53 (1.39 – 1.68)

(Abbreviations: HF: heart failure; HR: hazard rate ratio; MI: myocardial infarction; PAD: peripheral artery disease; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

e-Table 6. Sensitivity analysis excluding patients with a history of stroke: Hazard rate ratios of incident stroke after 1-year follow-up, according to vascular disease.

ENDPOINT	PRIMARY EFFECT ESTIMATES	
Ischemic stroke	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
PAD vs. no vascular disease	1.68 (1.42 – 2.00)	1.52 (1.28 – 1.81)
Prior MI vs. no vascular disease	1.09 (0.99 – 1.21)	1.09 (0.98 – 1.21)
PAD vs. prior MI	1.54 (1.28 – 1.86)	1.38 (1.14 – 1.67)

(Abbreviations: HF: heart failure; HR: hazard rate ratio; MI: myocardial infarction; PAD: peripheral artery disease; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

Methodological details. Analysis on a risk-scale.

In order to have the complete risk assessment of vascular disease in HF patients, both rates and relative risks are needed. Thus, regression analysis was used to compare the 1- and 5-years relative risks of the endpoints according to the presence of PAD or prior MI. To this end, we used generalized linear regression alongside the pseudovalue method in order to take into account the competing risks of death (Klein J, Andersen P. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics*. 2005;61:223–229; Klein J, Logan B, Harhoff M, Andersen P. Analyzing survival curves at a fixed point in time. *Stat Med*. 2007;26:4505–4519). The pseudo-value regression technique reduces to simple regression (with a log-link function) on the event status indicator at 1 year in the absence of censoring, whereas censored observations (for which the event status is not observed) are replaced with pseudo-observations based upon Aalen-Johansen cumulative incidence estimates using the jackknife method.

e-Table 7. Relative risks of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.

ENDPOINT	PRIMARY EFFECT ESTIMATES	
Ischemic stroke	**Crude RR (95% CI)**	**Adjusted RR* (95% CI)**
PAD vs. no vascular disease	1.69 (1.38 – 2.08)	1.10 (0.84 – 1.45)
Prior MI vs. no vascular disease	1.11 (0.96 – 1.28)	0.95 (0.78 – 1.15)
PAD vs. prior MI	1.53 (1.22 – 1.93)	1.18 (0.82 – 1.69)
All-cause death	**Crude RR (95% CI)**	**Adjusted RR* (95% CI)**
PAD vs. no vascular disease	1.43 (1.34 – 1.54)	1.32 (1.23 – 1.41)
Prior MI vs. no vascular disease	0.86 (0.82 – 0.91)	0.99 (0.94 – 1.04)
PAD vs. prior MI	1.67 (1.54 – 1.80)	1.20 (1.10 – 1.30)

(Abbreviations: HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease; RR: relative risk; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

e-Table 8. Relative risks of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.

ENDPOINT	PRIMARY EFFECT ESTIMATES	
Ischemic stroke	**Crude RR (95% CI)**	**Adjusted RR* (95% CI)**
PAD vs. no vascular disease	1.35 (1.16 – 1.56)	0.98 (0.82 – 1.17)
Prior MI vs. no vascular disease	1.16 (1.06 – 1.27)	1.09 (0.98 – 1.21)
PAD vs. prior MI	1.16 (0.99 – 1.36)	0.85 (0.70 – 1.05)
All-cause death	**Crude RR (95% CI)**	**Adjusted RR* (95% CI)**
PAD vs. no vascular disease	1.36 (1.31 – 1.42)	1.24 (1.20 – 1.29)
Prior MI vs. no vascular disease	0.88 (0.86 – 0.91)	0.95 (0.93 – 0.98)
PAD vs. prior MI	1.54 (1.47 – 1.61)	1.27 (1.22 – 1.32)

(Abbreviations: HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease; RR: relative risk; 95% CI: 95% confidence interval)

*Adjusted for sex (binary), hypertension (binary), diabetes (binary), prior stroke/transient ischemic attack (binary), COPD (binary), renal disease (binary), and age (continuous)

Appendix D. Paper 4

Diabetes mellitus and risk of ischemic stroke in patients with heart failure and no atrial fibrillation

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Abstract

Objective: The risk of ischemic stroke, systemic thromboembolism, and all-cause death among heart failure patients previously diagnosed with diabetes mellitus is poorly described. We evaluated the risk of these endpoints among heart failure patients without diagnosed atrial fibrillation according to the presence of diabetes mellitus.

Methods: Population-based nationwide cohort study of non-anticoagulated patients diagnosed with incident heart failure during 2000-2012, identified by record linkage between nationwide registries in Denmark. We calculated relative risks after 1 year to evaluate the association between diabetes and risk of events in 39,357 heart failure patients, among whom 18.1% had diabetes. Analysis took into account competing risks of death.

Results: Absolute risks of all endpoints were higher in patients with diabetes compared to patients without diabetes after 1-year follow-up (ischemic stroke: 4.1% vs. 2.8%; thromboembolism: 11.9% vs. 8.6%; all-cause death: 22.1% vs. 21.4%). Diabetes was significantly associated with an increased risk of ischemic stroke (adjusted relative risk [RR]: 1.27, 95% confidence interval [CI]: 1.07-1.51); thromboembolism (RR: 1.20, 95% CI: 1.11-1.30); and all-cause death (RR: 1.17, 95% CI: 1.11-1.23). Additionally, time since diabetes diagnosis was associated with higher adjusted cumulative incidences of ischemic stroke, thromboembolism, and all-cause death (p for trend, $p<0.001$).

Conclusions: Among heart failure patients *without* atrial fibrillation, diabetes was associated with a significantly increased risk of ischemic stroke, thromboembolism, and all-cause death compared to those without diabetes, even after adjustment for concomitant cardiovascular risk factors. Increased focus on secondary prevention in heart failure patients with diabetes may be warranted.

Introduction

Heart failure (HF) is associated with an increased risk of ischemic stroke and systemic thromboembolic events (TE), even without atrial fibrillation (AF)[1,2]. Comorbidities such as diabetes mellitus are common in patients with HF[3], and in previous studies of HF patients, diabetes has been associated with a higher risk of stroke and systemic TE[4–6]. In addition, previous non-HF studies have demonstrated that a longer duration of diabetes influence the risk of ischemic stroke[7,8]. A recent study identified insulin-treated diabetes as a predictor of stroke in HF patients without AF[9]. However, for the evaluation of possible risk factors for stroke risk stratification in patients with HF and without AF, quantifying the association between both presence and duration of diabetes and the risk of ischemic stroke, systemic TE, and all-cause death among HF patients is an important step. Additionally, this investigation will provide a basis for suggesting subgroups of HF patients who might benefit from thromboprophylaxis, as recommended in a recent study[10]. This is particularly relevant for HF patients without prior AF who are not traditionally considered candidates for thromboprophylaxis. However, assessing predictors of ischemic stroke and systemic TE risk in a high-mortality population such as HF patients (5-year mortality of 45-60%)[11,12] is not trivial because a competing risks setting in which careful consideration of the interplay between mortality and ischemic stroke/systemic TE risk is needed to provide meaningful risk assessment[13,14]. Thus, any analysis of ischemic stroke and systemic TE in such a high-risk population would need to take into account the competing risk of death, although this has not been considered in many previous studies of HF populations.

The aim of this study was to prospectively and thoroughly investigate the association between diabetes and the risk of ischemic stroke, systemic TE, and all-cause death in patients with incident HF *without diagnosed AF* (and not taking a vitamin K antagonist to

avoid issues with effect modification by anticoagulation therapy) to possibly identify a high-risk subgroup which could be used in stroke risk stratification in the HF population. We investigated the hypothesis that the presence of diabetes in non-anticoagulated incident HF patients without diagnosed AF would be associated with a higher risk of adverse events, and second, that this risk would increase with longer duration of diagnosed diabetes.

Methods

Registry Data Sources

We used three different nationwide registries in this study: i) Danish National Patient Registry[15] which has registered all hospital admissions along with diagnoses since 1977 and codes all diagnoses according to the 10th revision of the International Classification of Diseases (ICD-10) since 1994; ii) The National Prescription Registry[16] which contains data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System; iii) The Danish Civil Registration System which holds information on date of birth, migration, vital status, date of death, and sex of all persons living in Denmark[17]. Data were linked via a unique personal identification number used in all Danish national registries. All three registries were up to December 31st 2013. These registries have previously been well-validated[15,16,18], and the diagnoses of HF, diabetes, AF, and ischemic stroke have been found to be valid[18–22].

Study Population

The study population was identified as in- or outpatients aged>50 years, discharged with a primary diagnosis of incident HF (first-time diagnosis of HF) in the period January 1st 2000 - December 31st 2012 (ICD-10: I50, I42.0, I11.0, I13.0, I13.2). Diabetes mellitus was identified using ICD codes or a claimed prescription of a glucose-lowering drug (ICD-8: 24900, 24909, 25008, 25009; ICD-10: E10, E11.0; ATC: A10). Duration of diabetes was calculated from date of first diagnosis (ICD-8 or ICD-10 code), or from the date of first claimed prescription of a glucose-lowering drug, whichever came first, until the time of discharge with a diagnosis of HF. To restrict our analysis to patients without AF, we excluded those who had a prior diagnosis of AF or atrial flutter (ICD-10: I48) between 1994 and date of HF diagnosis. We also excluded patients treated with a vitamin K antagonist (ATC: B01AA03, B01AA04) within six months prior to the HF diagnosis (to avoid issues with effect modification by anticoagulation therapy). During our inclusion period, the use of non-vitamin K antagonist oral anticoagulants was almost non-existent in the HF population, and therefore, not relevant in this study. Patients with a diagnosis of cancer (ICD-10: C00-C97) within 5 years before HF diagnosis were also excluded, since cancer patients represents a subgroup with high stroke risk[23] and specialized thromboprophylactic treatment regimens.

Additional comorbidities at baseline were identified using the Danish National Patient Registry and the Danish National Prescription Registry which have registered diagnoses (using ICD-10 codes) and prescriptions (using ATC codes) since 1994. Ascertainment of baseline medication status was based on medication purchase in a 45-day window before or after the date of HF diagnosis. ICD-codes and ATC-codes used to define comorbidities and medical therapies are provided in the online-only Supplement [see **eTable 1** in the Supplementary material].

Outcomes

The primary endpoints were defined as an ischemic stroke diagnosis (ICD-10: I63, I64) or a diagnosis of a systemic TE (ischemic stroke (ICD-10: I63, I64), transient ischemic attack (ICD-10: G45), systemic arterial embolism (ICD-10: I74), or acute myocardial infarction (ICD-10: I21, I23)). Because of the high mortality in the HF population, all-cause death (according to The Danish Civil Registration System) was also included as a primary endpoint.

Statistical Methods

Baseline characteristics (at time of HF diagnosis) were described separately for patients with and without diabetes, using means and standard deviation for continuous measures and proportions for categorical measures.

Time-to-event analysis was used to describe the association between diabetes and the risk of ischemic stroke, systemic TE, and all-cause death. Time at risk was measured from baseline date (date of HF diagnosis) and until an event of ischemic stroke or systemic TE, date of death, emigration, or end of study (December 31st 2013), whichever came first. Additionally, patients were censored if they initiated anticoagulant therapy during the follow-up period.

Absolute risks of all endpoints were estimated based on Aalen-Johansen[24] estimator for competing risks data according to presence of diabetes. Regression analysis was used to compare the 1-year relative risk of the three endpoints according to presence of diabetes. To this end, we used generalized linear regression alongside the pseudo-value method in order to take into account the competing risk of death[25,26]. The pseudo-value regression technique reduces to simple regression (with a log-link function) on the event status indicator at 1 year in the absence of censoring. The associations between diabetes and risk of the three

endpoints were presented using both crude relative risks and relative risks adjusted for age, sex, and cardiovascular risk factors, such as hypertension, vascular disease, renal disease, chronic obstructive pulmonary disease, and prior stroke/transient ischemic attack. We repeated these analyses after 5 years of follow-up in the Supplementary material. Additionally, we provided the results of each component of the systemic thromboembolic end point in the Supplementary material.

In a secondary analysis with a more explorative focus, duration of diagnosed diabetes was analyzed as a categorical variable (duration of <5 years, 5-10 years, and >10 years). We used an inverse-probability-weighting approach[27] to calculate adjusted cumulative incidence curves for all endpoints (taking into account competing risks)[24] for each duration category. P-values for trend were obtained by entering the categorical duration of the diagnosed diabetes variable as a continuous ordinal covariate in a linear regression model for the pseudo-values at 1 year, adjusting for concomitant risk factors as before.

As a sensitivity analysis, since some patients might be taken glucose-lowering drug due to a pre-diabetic state, we repeated the main analysis when using only diagnosis codes (ICD-8/ICD-10 codes) to define patients with diabetes. Furthermore, we performed a similar sensitivity analysis, where we defined patients with diabetes only if they had a diagnosis code of diabetes and concomitantly had claimed a prescription for a glucose-lowering drug. We also performed a sensitivity analysis in which patients with a history of ischemic stroke were excluded (since a prior ischemic stroke diagnosis is a strong risk factor for a subsequent stroke)[28]. Additionally, as some patients might get a diagnosis of AF shortly after the HF diagnosis, a sensitivity analysis was performed by repeating the absolute and relative risk calculations when extending the definition of concomitant AF at baseline; presence of a prior diagnosis of AF at baseline or within 30 days after HF diagnosis. Furthermore, some patients are diagnosis with AF during follow-up; thus, we performed another sensitivity analysis by repeating the absolute and relative risk calculations after censoring patients who are diagnosed with AF during follow-up.

Analyses were performed using Stata version 13 (Stata Corporation, College Station, TX, USA) and R version 3.0.2 (The R Foundation for Statistical Computing). A two-sided p-value of <0.05 was considered statistically significant.

Ethical Considerations

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency (J. No. File No. 2012-41-0633).

Results

The study population comprised 39,357 HF patients aged >50 years, among which 18.1% had diabetes [**Figure 1**]. The median follow-up period with respect to ischemic stroke was 2.5 years (interquartile range: 0.6-5.3 years). The baseline characteristics of the study population are summarized in **Table 1**. A history of stroke/transient ischemic attack, systemic TE, myocardial infarction, vascular disease, hypertension, and renal disease was more frequent among patients with diabetes than in patients without diabetes. Additionally, patients with diabetes were more often on statins and antiplatelet therapy.

The absolute risks of all endpoints were higher in patients with diabetes compared to patients without diabetes after 1-year follow-up (ischemic stroke: 4.1% vs. 2.8%; systemic TE: 11.9% vs. 8.6%; all-cause death: 22.1% vs. 21.4%) [**Table 2**]. After 1-year follow-up, diabetes was independently associated with an increased risk of ischemic stroke (adjusted relative risk [RR]: 1.27, 95% confidence interval [CI]: 1.07-1.51); systemic TE (adjusted RR: 1.20, 95% CI: 1.11-1.30); and all-cause death (adjusted RR: 1.17, 95% CI: 1.11-1.23) [**Table 2**]. Similar conclusions were obtained after 5-years follow-up [see **eTable 8** in the Supplementary material]. When examining the individual components of the systemic thromboembolic end point, diabetes was associated with an increased risk of myocardial infarction, and for the end point of transient ischemic attack and systemic embolism separately, the event numbers were too low to make any conclusions [see **eTable 9** in the Supplementary material].

For the secondary exploratory investigation of the association between time since diabetes diagnosis and outcomes, **Figure 2B** and **Figure 2C** suggest a dose-response relationship between diabetes diagnosis and the cumulative incidences of systemic TE and all-cause death (p for trend; systemic TE: $p<0.001$; all-cause death: $p<0.001$). For the endpoint of ischemic stroke, a dose-response relationship between time since diabetes diagnosis and outcome risk was less clear [**Figure 2A**] (p for trend; ischemic stroke: $p<0.001$). Raw numerical values for the absolute risks of ischemic stroke, systemic TE, and all-cause death after 1-year follow-up, stratified according to duration of diabetes, are shown in **eTable 7** in the Supplementary material.

In the sensitivity analysis using only ICD-codes to define patients with diabetes, we found similar results as in the main analysis [see **eTable 2** in the Supplementary material]. Likewise, in the sensitivity

analysis using ICD-codes in combination with ATC-codes to define patients with diabetes, the results were similar to the main analysis [see **eTable 6** in the Supplementary material]. When excluding patients with prior ischemic stroke, the risk of ischemic stroke and systemic TE was lower in the whole study population. Diabetes was still associated with an increased risk of ischemic stroke, although borderline non-significant. However, for the endpoint of systemic TE and death the conclusions remained the same as in the main analysis [see **eTable 3** in the Supplementary material]. In the sensitivity analysis, repeating the absolute and relative risk calculations after extending the definition of concomitant AF, we found very similar results as in the main analyses [see **eTable 4** in the Supplement]. When censoring patients with HF who are diagnosed with AF during follow-up, similar results were found and the conclusions remained the same as in the main analysis [see **eTable 5** in the Supplement].

Discussion

In this large prospective study, we found a higher risk of ischemic stroke, systemic TE, and all-cause death among HF patients with diabetes compared to HF patients without diabetes after 1-year follow-up, and even after extensive adjustment for concomitant cardiovascular risk factors. Second, there was a dose-response relationship between time since diabetes diagnosis and the cumulative incidences of systemic TE and all-cause death. To our knowledge, this is the first study to thoroughly examine diabetes as a risk factor of ischemic stroke/systemic TE and the association between duration of diabetes and the end points in a HF population without AF.

Patients with diabetes have altered hemostasis, platelet activity, and vascular endothelial function contributing to a prothrombotic state[29]. In our study, patients with diabetes had more comorbidities, such as hypertension, vascular disease, prior stroke/systemic TE, and ischemic heart disease compared to HF patients without diabetes. All these comorbidities are well-known risk factors of ischemic stroke and recurrent stroke. The presence of comorbidities and the prothrombotic state might partly explain the link between diabetes and the higher risk of systemic TE. However, we emphasize that our study focused on exploring the prognostic value of diabetes in relation to systemic thromboembolic risks; we cannot draw conclusions on causality. Furthermore, as mentioned, diabetes was associated with an increased risk of ischemic stroke and systemic TE even after adjustment for other cardiovascular risk factors which highlight the significance of this risk factor in the HF population without AF.

A longer duration of diabetes has previously been demonstrated to be associated with the risk of ischemic stroke in the form of a dose-response relationship[7]. Additionally, duration of diabetes is associated with an increased risk of other cardiovascular diseases and cardiovascular mortality[30,31]. In our study, we found a dose-response relationship between the time since diabetes diagnosis and cumulative incidences of systemic TE and all-cause death. The relationship between time since diabetes diagnosis and risk of ischemic stroke, on the other hand, was more equivocal, which may be attributed to limitations of the register-based definition of diabetes duration (see limitations below).

Clinical Perspectives

The increasing prevalence of both HF and diabetes highlights the clinical relevance of our findings.

In this study, diabetes was associated with an increased risk of ischemic stroke and most likely this comorbidity will be useful for stroke risk stratification in HF patients without AF. However, patients with diabetes are a very heterogeneous group with varying degrees of diabetes duration, glycemic control, and diabetic complications; thus, it may be necessary to subdivide these patients according to severity of diabetes for optimal risk stratification. Whether duration of diabetes will enhance the identification of high-risk HF patients need to be further examined in future studies.

Currently, patients with HF and without AF are not routinely recommended antiplatelet or anticoagulant therapy[32]. HF patients with diabetes have an increased risk of various thromboembolic diseases and may represent a high-risk subgroup of HF patients without AF that could potentially benefit from intensive thromboprophylaxis. However, this speculation would need further examination in future studies.

Strengths and Limitations

The major strengths of this study are the validated outcomes and large sample size uniquely possible with this type of cohort study. Selection into the study was not an issue, since we investigated a nationwide population cohort of incident HF patients without AF, with limited loss to follow-up. We also accounted for the competing risk of death, an important issue when investigating risk predictors in populations with high mortality[14,33].

The study also has some important limitations. We were unable to distinguish between HF with preserved and reduced ejection fraction or estimate the functional classification, since we did not have access to echocardiograms. Whether the prevalence of stroke differs in patients with preserved and reduced ejection fraction is currently unknown due to inconsistent

results[5,34–36]. However, no difference in embolic risk (risk of stroke, transient ischemic stroke, or systemic embolism) was found in a recent study of non-anticoagulated HF patients with reduced and preserved ejection fraction[34]. Similarly, in a post-hoc analysis of a study of AF patients with HF with reduced or preserved ejection fraction, no difference in ischemic stroke risk was found between the groups[35]. On the other hand, the functional classification among patients with HF would also vary over time and with treatments.

The diagnosis of HF has previously been validated with a sensitivity of 29%, a specificity of 99%, and a positive predictive value of 81-100%[20,21]; thus, we did not capture all patients with HF and also cannot be certain that all patients identified as having HF had definite HF, which could lead to imprecision in the risk estimates. In addition, we cannot rule out that some patients without AF might have had undiagnosed AF, since heart disease is associated with an increased risk of developing AF and AF is 'silent' in up to a quarter of patients; however, in the sensitivity analysis, where patients were censored if they developed AF during follow-up, the conclusions remained the same as in the main analysis.

We only included patients aged >50 years, as HF in persons aged <50 years might represent a different group of patients, for example patients with congenital heart disease. Accordingly, our findings may not apply to younger HF patients. Additionally, our study population was ethnically non-diverse, since we investigated a Danish HF population. Thus, our study results might not be generalizable to more diverse HF populations.

Patients with diabetes but without a hospital-based diagnosis of diabetes and treated only non-pharmacologically were not included in this study, thus, our population is unlikely to include patient groups with a reversible state of diabetes. This may explain the lower prevalence of diabetes (18%) in our cohort compared to other HF cohorts (approximately 30%)[9,37]. Moreover, we were not able to distinguish between type 1 and type 2 diabetes which would be a very relevant separation.

We did not have access to information regarding smoking habits, body mass index, and lipid profile which we recognized as important factors when investigating diabetes and ischemic stroke risk. However, since the focus was on the prognostic value of a diabetes diagnosis, not its causal role, confounding by possible stroke risk factors is not an issue of concern in this study. We investigated whether the presence of diabetes was associated with ischemic stroke, systemic TE, and death in patients with HF, and therefore, we adjusted for well-known cardiovascular risk factors for stroke. This was not an attempt to adjust for confounding and hereby explore the potential causal relationship between the exposure and outcomes, but to elucidate the potential predictive ability of the exposure to risk stratification in patients with HF, after adjustment for other possible risk factors.

In the secondary, exploratory analysis we calculated the duration of diabetes as the time from first diagnosis with an ICD-8/ICD-10 code or from the first claimed prescription of a glucose-lowering drug, whichever came first, until the time of discharge with a diagnosis of HF. This register-based proxy for the duration of diabetes has important limitations; it can be affected by delayed diagnosis, changes over time in diagnostic criteria, and changes over time in medical treatment. Due to these limitations, we examined the association between duration of diabetes and risk of events as a secondary, explorative analysis. The above-mentioned limitations could explain the less clear dose-response relationship between time since diabetes diagnosis and the cumulative incidence of ischemic stroke.

Finally, the diagnosis of ischemic stroke was defined by the Danish Hospital Discharge Register, and not all stroke endpoints have been defined by cerebral imaging, and thus, the data did not allow classification of various ischemic stroke types. We included unspecified stroke (ICD-10: I64) in the definition of ischemic stroke, as most strokes are of ischemic origin. However, we cannot rule out that some of these strokes might have been hemorrhagic strokes and thus, misclassified as ischemic strokes. Nonetheless, the ischemic stroke diagnosis has previously been validated[18].

In conclusion, diabetes was associated with a significantly higher risk of ischemic stroke, systemic TE, and all-cause death in HF patients without AF, which persisted after adjustment for concomitant cardiovascular risk factors, and longer time since diabetes diagnosis was associated with higher risks.

Acknowledgment section
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data, drafting the article, or revising it critically for important intellectual content and approved the final version to be published.

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Table 1. Baseline characteristics of study population, stratified according to presence of diabetes.

Clinical characteristics	**No diabetes**	**Diabetes**
N, % (n)	81.9 (32,249)	18.1 (7,108)
Sex (females), % (n)	45.7 (14,722)	38.3 (2,723)
Mean age at baseline, years (SD)	74.5 (11.5)	72.1 (10.5)
Baseline comorbidity, % (n)		
Previous stroke/TIA	12.0 (3,884)	17.1 (1,215)
Previous myocardial infarction	24.0 (7,723)	29.8 (2,118)
Previous thromboembolism*	32.3 (10,415)	41.2 (2,929)
Vascular disease	29.8 (9,608)	39.8 (2,828)
Hypertension	27.4 (8,827)	49.8 (3,541)
Renal Disease	4.6 (1,492)	8.5 (605)
Liver Disease	0.4 (127)	0.7 (49)
Hyperthyroidism	2.6 (830)	2.7 (191)
COPD	13.2 (4,254)	13.9 (989)
Baseline medication, % (n)		
ACE-inhibitors	50.4 (16,245)	55.4 (3,941)
Angiotensin receptor blocker	9.0 (2,915)	16.9 (1,200)
Beta-blockers	42.8 (13,808)	48.2 (3,424)
Aldosterone antagonists	22.1 (7,119)	27.1 (1,923)
Non-loop diuretics	37.8 (12,194)	43.8 (3,113)
Loop diuretics	63.7 (20,548)	73.0 (5,185)
Statins	27.6 (8,912)	44.9 (3,189)
NSAIDs	13.9 (4,473)	14.8 (1,053)
Aspirin	46.4 (14,973)	54.3 (3,859)
Thienopyridines	10.3 (3,332)	13.2 (941)
Insulins and analogues	-	28.2 (2,003)
Blood glucose lowering drugs	-	54.7 (3,890)

Abbreviations: COPD= Chronic obstructive pulmonary disease; NSAIDs= Non-steroidal anti-inflammatory drugs; SD=Standard deviation; TIA=Transient ischemic attack.

* Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

Table 2. Absolute and relative risks of ischemic stroke, thromboembolism, and all-cause death after 1-year follow-up, stratified according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
No. of patients	39,357	32,249	7,108
ISCHEMIC STROKE			
Event number	1,116	839	277
Absolute risk, %	3.0	2.8	4.1
Crude relative risk	-	1.00 (ref.)	1.49 (1.30-1.70)
Adjusted relative risk*	-	1.00 (ref.)	1.27 (1.07-1.51)
THROMBOEMBOLISM†			
Event number	3,473	2,659	814
Absolute risk, %	9.9	8.6	11.9
Crude relative risk	-	1.00 (ref.)	1.38 (1.28-1.49)
Adjusted relative risk*	-	1.00 (ref.)	1.20 (1.11-1.30)
ALL-CAUSE DEATH			
Event number	7,980	6,499	1,481
Absolute risk, %	21.5	21.4	22.1
Crude relative risk	-	1.00 (ref.)	1.03 (0.98-1.08)
Adjusted relative risk*	-	1.00 (ref.)	1.17 (1.11-1.23)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction

Figure 1: Flowchart of patients included in the final study population.

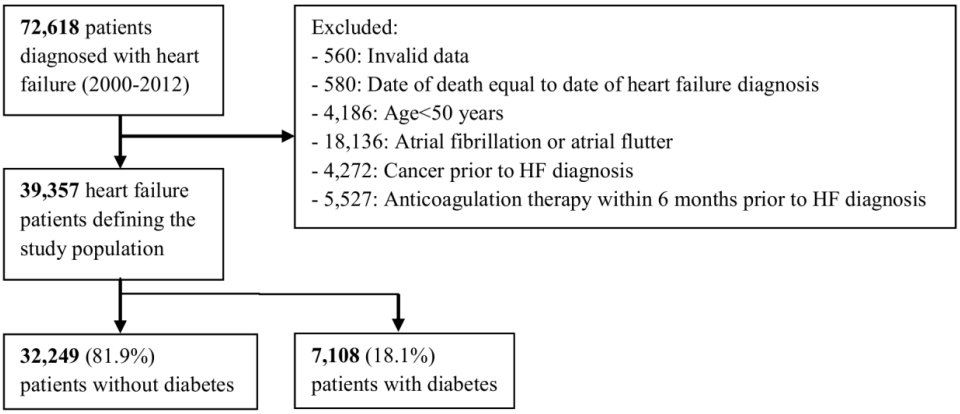
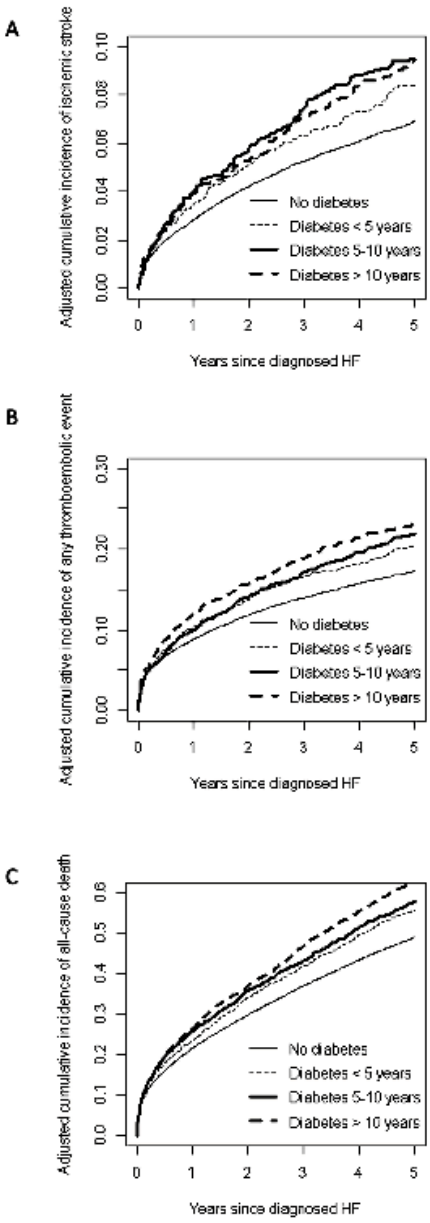


Figure 2: Adjusted cumulative incidence curve of the three endpoints according to duration of diagnosed diabetes. A) Adjusted cumulative incidence curve of ischemic stroke; B) Adjusted cumulative incidence curve of any thromboembolic event; C) Adjusted cumulative incidence curve of all-cause death.



Supplementary materials

eTable 1. ICD10-codes and ATC-codes used in the study.

eTable 2. Sensitivity analysis (using only diagnosis codes in diabetes definition): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-years follow-up, according to presence of diabetes.

eTable 3. Sensitivity analysis (excluding patients with prior stroke): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

eTable 4. Sensitivity analysis (excluding patients with an AF diagnosis within 30 days after the HF diagnosis): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

eTable 5. Sensitivity analysis (censoring patients developing AF during follow-up): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

eTable 6. Sensitivity analysis (using the combination of diagnosis codes and ATC-codes in diabetes definition): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

eTable 7. Figure 2 – raw numerical values: Absolute risks of ischemic stroke, systemic thromboembolism, and all-cause death after 1-year follow-up, stratified according to duration of diabetes.

eTable 8. Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 5-years follow-up, according to presence of diabetes.

eTable 9. Absolute risks of each component of the systemic thromboembolic end point (besides ischemic stroke) after 1-year follow-up, stratified according to duration of diabetes.

eTable 1. ICD10-codes and ATC-codes used in the study.

ICD 10-Codes and ATC-Codes used in the Study	
Main diagnosis	**ICD 10-Codes**
Congestive heart failure	I50.0-I50.9, I11.0, I13.0, I13.2
Diabetes mellitus	E10.0-E10.9, E11.0-E11.9 + (24900, 24909, 25008, 25009 (ICD-8)) + (ATC: A10)
Endpoints	**ICD 10-Codes**
Stroke (ischemic)	I63.0-I63.9, I64
Ischemic stroke (Thromboembolic event)	I63.0-I63.9, I64
Transient ischemic attack (Thromboembolic event)	G45.0-G45.9 (Not inclusive G45.3 (Amaurosis fugax))
Systemic embolism (Thromboembolic event)	I74.0-I74.9
Acute myocardial infarction (Thromboembolic event)	I21.0-I21.9, I23.0-I23.9
Comorbidities	**ICD 10-Codes**
Prior stroke (ischemic or hemorrhagic)	I60.0-I60.9, I61.0-I61.9, I62.0-I62.9, I63.0-I63.9, I64.9
Acute myocardial infarction	I21.0-I21.9, I23.0-I23.9
Vascular disease	I21.0-I21.9, I23.0-I23.9, I70.0, I70.2-I70.9, I71.0-I71.9, I73.9
Hypertension	I10.0-I10.9, I11.0-I11.9, I12.0-I12.9, I13.0-I13.9, I15.0–I15.9
Renal disease	I12.0-I12.9, I13.0-I13.9, N00-N07, N11.0-N11.9, N14.0-N14.4, N17.0-N17.9, N18.0-N18.9, N19, Q61.0-Q61.9
Liver disease	B15.0-B15.9, B16.0-B16.9, B17.0-B17.9, B18.0-B18.9, B19.0-B19.9, K70.4, K72.0-K72.9, K76.6
Hyperthyroidisme	E05.0-E05.9, E06.0-E06.9
Chronic obstructive pulmonary disease (COPD)	J44.0-J44.9
Atrial fibrillation and flutter (exclusion criteria)	I48
Cancer any type (exclusion criteria)	C00-C97
Concomitant medication	**ATC-Codes**
Warfarin (exclusion criteria)	B01AA03
Phenprocoumon (exclusion criteria)	B01AA04
Glucose-lowering medication	A10
ACE-inhibitors	C09AA
Angiotensin receptor blockers	C09CA
Beta-blockers	C07
Non-loop diuretics	C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G,C09BA, C09DA, C09XA52
Aldosterone antagonists	C03DA
Loop diuretics	C03C
Statins Non steroidal anti-inflammatory drugs (NSAIDs)	C10 M01A
Aspirin	B01AC06
Thienopyridines	B01AC04, B01AC22, B01AC24
Insulins and analogous	A10A
Blood glucose lowering drugs	A10B

eTable 2. Sensitivity analysis (using only diagnosis codes in diabetes definition): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
ISCHEMIC STROKE			
Event number	1,116	891	225
Absolute risk, %	3.0	2.8	4.3
Crude relative risk	-	1.00 (ref.)	1.53 (1.32-1.77)
Adjusted relative risk*	-	1.00 (ref.)	1.29 (1.08-1.54)
SYSTEMIC THROMBOEMBOLISM†			
Event number	3,757	3,065	692
Absolute risk, %	9.9	9.5	13.0
Crude relative risk	-	1.00 (ref.)	1.37 (1.27-1.48)
Adjusted relative risk*	-	1.00 (ref.)	1.18 (1.09-1.28)
ALL-CAUSE DEATH			
Event number	7,980	6,830	1,150
Absolute risk, %	21.5	21.4	22.0
Crude relative risk	-	1.00 (ref.)	1.03 (0.97-1.09)
Adjusted relative risk*	-	1.00 (ref.)	1.17 (1.10-1.23)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

eTable 3. Sensitivity analysis (excluding patients with prior ischemic stroke): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
ISCHEMIC STROKE			
Event number	722	569	153
Absolute risk, %	2.1	2.0	2.6
Crude relative risk	-	1.00 (ref.)	1.28 (1.07-1.53)
Adjusted relative risk*	-	1.00 (ref.)	1.19 (0.98-1.45)
SYSTEMIC THROMBOEMBOLISM†			
Event number	2,835	2,235	600
Absolute risk, %	8.3	7.9	10.1
Crude relative risk	-	1.00 (ref.)	1.28 (1.17-1.39)
Adjusted relative risk*	-	1.00 (ref.)	1.12 (1.02-1.23)
ALL-CAUSE DEATH			
Event number	6,929	5,715	1,214
Absolute risk, %	20.5	20.5	20.7
Crude relative risk	-	1.00 (ref.)	1.01 (0.96-1.07)
Adjusted relative risk*	-	1.00 (ref.)	1.16 (1.10-1.23)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

eTable 4. Sensitivity analysis (excluding patients with an AF diagnosis within 30 days after the HF diagnosis): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
ISCHEMIC STROKE			
Event number	1,063	794	269
Absolute risk, %	2.9	2.6	4.0
Crude relative risk	-	1.00 (ref.)	1.52 (1.32-1.74)
Adjusted relative risk*	-	1.00 (ref.)	1.30 (1.09-1.54)
SYSTEMIC THROMBOEMBOLISM†			
Event number	3,327	2,540	787
Absolute risk, %	9.0	8.4	11.7
Crude relative risk	-	1.00 (ref.)	1.39 (1.29-1.50)
Adjusted relative risk*	-	1.00 (ref.)	1.21 (1.11-1.31)
ALL-CAUSE DEATH			
Event number	7,817	6,359	1,458
Absolute risk, %	21.4	21.3	22.0
Crude relative risk	-	1.00 (ref.)	1.03 (0.98-1.09)
Adjusted relative risk*	-	1.00 (ref.)	1.17 (1.11-1.23)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

eTable 5. Sensitivity analysis (censoring patients developing AF during follow-up): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
ISCHEMIC STROKE			
Event number	1,061	788	273
Absolute risk, %	2.9	2.6	4.1
Crude relative risk	-	1.00 (ref.)	1.55 (1.36-1.78)
Adjusted relative risk*	-	1.00 (ref.)	1.33 (1.11-1.58)
SYSTEMIC THROMBOEMBOLISM†			
Event number	3,377	2,579	798
Absolute risk, %	9.1	8.5	11.9
Crude relative risk	-	1.00 (ref.)	1.39 (1.29-1.50)
Adjusted relative risk*	-	1.00 (ref.)	1.21 (1.12-1.32)
ALL-CAUSE DEATH			
Event number	7,566	6,147	1,419
Absolute risk, %	20.8	20.7	21.5
Crude relative risk	-	1.00 (ref.)	1.04 (0.99-1.10)
Adjusted relative risk*	-	1.00 (ref.)	1.18 (1.12-1.24)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

eTable 6. Sensitivity analysis (using the combination of diagnosis codes and ATC-codes in diabetes definition): Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 1-year follow-up, according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
ISCHEMIC STROKE			
Event number	1,116	934	182
Absolute risk, %	3.0	2.8	4.3
Crude relative risk	-	1.00 (ref.)	1.51 (1.29-1.76)
Adjusted relative risk*	-	1.00 (ref.)	1.28 (1.06-1.54)
SYSTEMIC THROMBOEMBOLISM†			
Event number	3,473	2,937	536
Absolute risk, %	9.2	8.8	12.5
Crude relative risk	-	1.00 (ref.)	1.42 (1.30-1.54)
Adjusted relative risk*	-	1.00 (ref.)	1.18 (1.08-1.30)
ALL-CAUSE DEATH			
Event number	7,980	7,051	929
Absolute risk, %	21.5	21.5	22.1
Crude relative risk	-	1.00 (ref.)	1.03 (0.97-1.09)
Adjusted relative risk*	-	1.00 (ref.)	1.21 (1.14-1.28)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

eTable 7. Figure 2 – raw numerical values: Absolute risks of ischemic stroke, systemic thromboembolism, and all-cause death after 1-year follow-up, stratified according to duration of diabetes.

Duration of diabetes	<5 years		5-10 years		>10 years	
Absolute risk, % (95% CI)						
Ischemic stroke	3.6	(2.8-4.3)	4.3	(3.5-5.2)	4.5	(3.6-5.4)
Systemic thromboembolism	11.0	(9.8-12.2)	11.3	(9.9-12.6)	13.7	(12.2-15.2)
All-cause death	19.6	(18.1-21.2)	22.9	(21.0-24.7)	24.3	(22.4-26.2)

eTable 8. Absolute and relative risks of ischemic stroke, systemic thromboembolic event, and all-cause death after 5-years follow-up, according to presence of diabetes.

Endpoint	Overall	No diabetes	Diabetes
ISCHEMIC STROKE			
Event number	2,421	1,845	576
Absolute risk, %	7.3	6.8	9.6
Crude relative risk	-	1.00 (ref.)	1.42 (1.30-1.55)
Adjusted relative risk*	-	1.00 (ref.)	1.23 (1.10-1.36)
SYSTEMIC THROMBOEMBOLISM†			
Event number	6,193	4,751	1,442
Absolute risk, %	18.1	16.9	23.3
Crude relative risk	-	1.00 (ref.)	1.38 (1.31-1.46)
Adjusted relative risk*	-	1.00 (ref.)	1.20 (1.14-1.27)
ALL-CAUSE DEATH			
Event number	15,638	12,665	2,973
Absolute risk, %	48.7	47.8	52.4
Crude relative risk	-	1.00 (ref.)	1.10 (1.06-1.13)
Adjusted relative risk*	-	1.00 (ref.)	1.16 (1.14-1.19)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary)

†Composite endpoint of ischemic stroke, transient ischemic attack, systemic embolism, acute myocardial infarction.

eTable 9. Absolute risks of each component of the systemic thromboembolic end point (besides ischemic stroke) after 1-year follow-up, stratified according to duration of diabetes.

Endpoint	Overall	No diabetes	Diabetes
TRANSIENT ISCHEMIC ATTACK			
Event number	226	184	42
Absolute risk, %	0.6	0.6	0.6
Crude relative risk	-	1.00 (ref.)	1.02 (0.73-1.43)
Adjusted relative risk*	-	1.00 (ref.)	0.83 (0.52-1.33)
SYSTEMIC EMBOLISM			
Event number	67	49	18
Absolute risk, %	0.2	0.2	0.3
Crude relative risk	-	1.00 (ref.)	1.65 (0.96-2.84)
Adjusted relative risk*	-	1.00 (ref.)	1.42 (0.65-3.13)
ACUTE MYOCARDIAL INFARCTION			
Event number	2,268	1,739	529
Absolute risk, %	6.0	5.6	7.7
Crude relative risk	-	1.00 (ref.)	1.37 (1.25-1.51)
Adjusted relative risk*	-	1.00 (ref.)	1.15 (1.03-1.27)

*Adjusted for: sex (binary), age (continuous), hypertension (binary), vascular disease (binary), previous stroke/transient ischemic attack (binary), chronic obstructive pulmonary disease (binary), and renal disease (binary).

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