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ORIGINAL PAPER

Sex differences in risk of incident venous thromboembolism in heart failure patients

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Abstract

Background In patients with incident heart failure, the risk of venous thromboembolism (VTE), defined as pulmonary embolism (PE) and/or deep venous thrombosis (DVT), is sparsely described, especially potential sex differences. We conducted an observational study to evaluate risk of VTE among male and female heart failure patients.

Methods Population-based cohort study of patients diagnosed with incident heart failure during 2000–2015, identified by record linkage between nationwide registries in Denmark. Using a pseudo-value approach, we calculated relative risks [RR] of VTE at 1 and 3 years of follow-up. Crude VTE risk for males and females are reported and contrasted after adjustment for established clinical risk factors for VTE.

Results A total of 32,330 heart failure patients were included, of which 15,238 (47%) were females. For the combined endpoint of VTE, female sex was associated with a higher risk (1-year adjusted RR: 1.30, 95% confidence interval [CI]: 0.97–1.73; 3-year adjusted RR: 1.34, 95% CI: 1.07–1.67) compared to male patients. For the individual endpoints of PE and DVT after 1-year of follow-up, female sex was only associated with a higher risk of PE and not DVT, compared to male patients. However, female sex was associated with a higher risk of both PE and DVT after 3 years of follow-up.

Conclusions Among incident heart failure patients, female sex is associated with a higher risk of VTE, mainly driven by an excess risk of PE. This finding may help improve clinical decision-making regarding VTE prophylaxis in patients with heart failure.

Keywords Heart failure · Sex · Venous thromboembolism · Deep vein thrombosis · Pulmonary embolism

Abbreviations

CI Confidence interval
DVT Deep vein thrombosis
HF Heart failure
PE Pulmonary embolism
RR Relative risk
VTE Venous thromboembolism

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Introduction

Heart failure (HF) is associated with a higher risk of thromboembolic events [1]. Although many studies have focused on arterial endothelial dysfunction, venous dysfunction is also present in HF, and contribute to a prothrombotic state in HF patients [2]. Venous thromboembolism (VTE), defined as a diagnosis of pulmonary embolism (PE) or deep vein thrombosis (DVT) [3], often occur secondary to clinical conditions such as HF [4, 5]. Several guidelines recommend that all hospitalized patients with HF receive VTE prophylaxis with anticoagulant medication if the risk–benefit ratio is favorable and the patient is not already anticoagulated [6, 7]; however, there is evidence that thromboprophylaxis is underused in the HF patient group, possibly due to the difficulties in accurately assessing the individual patient's risk [8].

Several studies have investigated the association between VTE and HF, but no study has focused on the association between sex and the risk of VTE in HF patients [9, 10]. Previous studies assessing the association between sex and risk of VTE, not specifically in HF patients, have demonstrated inconsistent findings, but most studies found an excess risk among males [11–13]. In the HF population, potential sex differences in risk of VTE has not been investigated, but two studies demonstrated that HF appears to be a stronger risk factor for both PE and DVT in females than in males [9, 10]. However, one of these studies focused on the association between ejection fraction and thromboembolic risk; the study did not include DVT as an endpoint and had a low proportion of females [9]. The other study only examined VTE risk in HF patients during hospitalization [10].

Establishing potential sex-related differences in risk of VTE could improve the possibility of tailoring thromboprophylactic strategies in the HF population. Therefore, we performed an observational cohort study to assess the risk of VTE in HF patients according to sex, using Danish nationwide administrative registries.

Methods

Data sources

This observational cohort study used data from three nationwide registries: (1) The Danish Civil Registration System, which holds information on sex, date of birth, vital and emigration status of all persons living in Denmark [14]; (2) the Danish National Patient Registry [15], which has registered dates of hospital admission and discharge, and discharge diagnoses classified according to the 10th revision of the International Classification of Diseases (ICD) for more than 99% of hospital admissions in Denmark since 1994; (3) 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. Data were linked via a unique personal identification number used across all Danish national registries. Information from the three registries was retrieved until December 31, 2015. These registries have previously been validated [14–16], and the diagnoses of HF and VTE were found to have sufficiently high validity to conduct epidemiological investigations in cohorts consisting of patients with these records [17–21].

Study population

We used the Danish National Patient Registry to identify all patients diagnosed with a primary discharge diagnosis of incident (first-time hospital diagnosis) HF in the period January 1, 2000–December 31, 2015 (see e-Table 1 in the supporting materials). Patients who had previously experienced a VTE were excluded to examine the risk of first-time VTE. Since cancer patients represent a subgroup with high VTE risk [22] and specialized thromboprophylactic treatment regimens, we excluded patients with a diagnosis of cancer within 3 years before HF diagnosis. Using the Danish National Prescription Registry, we identified and excluded patients with a claimed prescription of anticoagulant therapy within 12 months prior to the HF diagnosis to avoid potential effect modification by anticoagulation.

Additional comorbidities were assessed at the date of discharge from the incident HF diagnosis and identified using the Danish National Patient Registry and the Danish National Prescription Registry. Ascertainment of baseline medication status (other than oral anticoagulants) was based on prescriptions claimed between 60 days before and 10 days after hospital discharge from incident HF to express the status in the follow-up period. The 10-day period after discharge was included to give a more accurate estimate of the baseline medication status as many patients may redeem a prescription within the first days after hospital discharge. ICD-codes and ATC-codes used to define comorbidities and medical therapy are provided in the supporting materials (see e-Table 1 in the supporting materials). As diagnoses from the emergency room commonly represent working diagnoses with a documented low validity, these diagnoses were not included in our study [23].

Outcomes

The main endpoint was a primary diagnosis of VTE, defined as pulmonary embolism (PE) and/or deep venous thrombosis (DVT) (for ICD-codes see e-Table 1 in the supporting materials). Besides the main combined endpoint of VTE, PE and DVT were analyzed as separate endpoints. For all study outcomes, only primary in-hospital codes were obtained, excluding emergency room and ambulatory diagnoses, likewise to ensure higher validity of the outcomes [23].

Statistical methods

Patient baseline characteristics were presented separately for men and women using means and standard deviation for continuous measures and proportions for categorical measures. We applied time-to-event survival analyses to describe the association between sex and risk of endpoints. Follow-up began at the date of discharge from the HF diagnosis. Patients were followed for 1 and 3 years until the outcome of interest, date of death, emigration, or end of study (December 31, 2015), whichever came first.

Absolute risks of all endpoints according to sex were estimated based on Aalen-Johansen [24] estimator for the cumulative incidence function assuming death as a competing risk and adjusted for well-established risk factors of VTE and potential confounders [age, atrial fibrillation, hypertension, vascular disease, diabetes, and chronic obstructive pulmonary disease [25, 26], as well as statin and aspirin therapy (as these therapies may influence the association between sex and VTE risk)]. Adjustment was obtained applying an inverse probability of treatment weights approach [27]. For the main analysis, a pseudo-value approach was used to compare relative risk (RR) of the endpoints at 1 and 3 years follow-up according to sex, using male patients as reference, to account for competing risk of death [28, 29]. The pseudo-values were analyzed by generalized linear regression analysis with log-link function and with sex as exposure and adjusted by the pre-specified potential confounders [25, 26].

In a secondary analysis, the role of age on the association between sex and risk of VTE was examined. The study population was stratified into three age groups (< 60 years, 60–80 years, and > 80 years) and the adjusted RR calculations were repeated. The youngest age group (< 60 years) was eliminated from the secondary analysis due to few events. To maintain robust estimates of the adjusted RR in this stratified analysis, we fitted a logistic regression model to calculate a propensity score based on the previously described risk factors for VTE. This approach was selected due to a potential mismatch between the number of identified risk factors for VTE, and the limited number of events within strata [30].

Analyses were performed using Stata version 14 (Stata Corporation, College Station, TX, USA). Results are reported with 95% confidence intervals (CI).

Ethical considerations

No ethical approval is required for studies based on data from administrative Danish registries. The study was approved by the Danish Data Protection Agency (J. No. File No. 2015-57-0001).

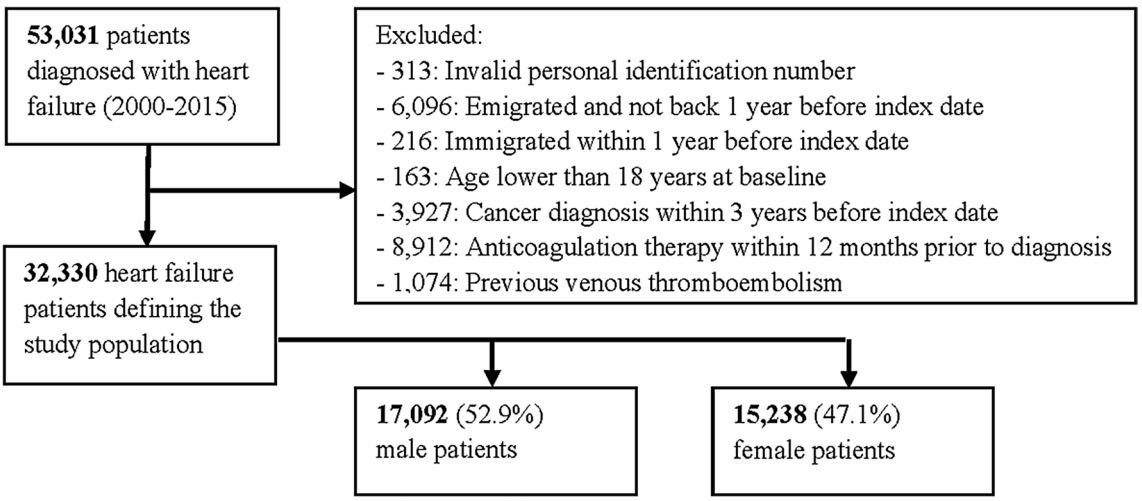

Fig. 1 Flowchart of patients included in the final study population

Table 1 Baseline characteristics of study population according to sex

Clinical characteristics	Overall	Males	Females
N, % (*n*)	32,330	52.9 (17,092)	47.1 (15,238)
Mean age, years (SD)	75.4 (13.3)	72.3 (13.3)	78.9 (12.4)
Age < 60 years, % (*n*)	13.6 (4398)	18.0 (3073)	8.7 (1325)
Age 60–80 years, % (*n*)	43.4 (14,036)	49.9 (8526)	36.2 (5510)
Age > 80 years, % (*n*)	43.0 (13,896)	32.1 (5493)	55.1 (8403)
Comorbidity, % (*n*)			
Atrial fibrillation	22.7 (7331)	21.8 (3732)	23.6 (3599)
Diabetes	14.6 (4725)	15.9 (2722)	13.1 (2003)
Hypertension	33.8 (10,933)	32.1 (5491)	35.7 (5442)
Vascular disease (previous myocardial infarction or peripheral artery disease)	24.3 (7870)	27.5 (4702)	20.8 (3168)
Previous myocardial infarction	17.1 (5516)	19.6 (3348)	14.2 (2168)
Renal disease	6.4 (2082)	7.3 (1256)	5.4 (826)
Liver disease	0.4 (141)	0.6 (104)	0.2 (37)
Chronic obstructive pulmonary disease	18.4 (5939)	18.0 (3083)	18.7 (2856)
Previous ischemic stroke	9.6 (3097)	9.8 (1668)	9.4 (1429)
Previous intracranial hemorrhage	1.0 (317)	1.0 (165)	1.0 (152)
Pacemaker/implantable cardioverter-defibrillator	5.0 (1623)	5.8 (984)	4.2 (639)
Medication, % (*n*)			
ACE-inhibitors	39.9 (12,891)	44.9 (7679)	34.2 (5212)
Angiotensin receptor blocker	6.8 (2213)	6.3 (1080)	7.4 (1133)
Beta-blockers	37.1 (11,983)	39.4 (6741)	34.4 (5242)
Aldosterone antagonists	19.0 (6158)	20.9 (3568)	17.0 (2590)
Non-loop diuretics	33.8 (10,922)	33.4 (5706)	34.2 (5216)
Loop diuretics	65.3 (21,115)	64.8 (11,081)	65.8 (10,034)
Statins	21.1 (6833)	24.7 (4221)	17.1 (2612)
NSAIDs	13.7 (4425)	12.7 (2172)	14.8 (2253)
Aspirin	39.3 (12,706)	40.5 (6920)	38.0 (5786)
Thienopyridines	7.1 (2311)	8.2 (1393)	6.0 (918)

ACE angiotensin-converting enzyme, *NSAIDs* non-steroidal anti-inflammatory drugs, *SD* standard deviation

Results

We identified 32,330 incident HF patients, of which 15,238 (47.1%) were females [Fig. 1]. The median follow-up time for the primary endpoint of VTE was 4.0 years (inter-quartile range 0.9–6.0). Baseline patient characteristics are summarized in Table 1. Mean age was higher among female patients than among male patients, 78.9 (SD 12.4) and 72.3 years (SD 13.3), respectively. The prevalence of vascular disease (including prior myocardial infarction) and diabetes was lower in female patients compared to male patients, but the prevalence of hypertension was higher in female patients. Male patients were more often using angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, statins, and aspirin compared to the female patients.

The number of events and absolute risks of VTE, DVT, and PE in each patient group at 1 and 3 years of follow-up are shown in Table 2. After 3 years of follow-up, the absolute risk of VTE was 2.0% for the female patients and 1.5% for the male patients, corresponding to incidence rates per 1000 person-years of 7.4 and 4.9, respectively. Especially, female patients had a high risk of PE (1.1%) compared to the male patients (0.8%), whereas the risk of DVT was similar between the female and male patients at 1-year follow-up, but higher among females after 3 years of follow-up. Adjusted cumulative incidence curves for VTE, DVT, and PE demonstrate a steady increase during follow-up, as seen in Figs. 2 and 3.

Multivariable analysis

For the combined endpoint of VTE, female sex was associated with a higher risk [1-year adjusted RR: 1.30, 95% confidence interval (CI): 0.97–1.73; 3-year adjusted RR: 1.34, 95% CI: 1.07–1.67] compared to male patients [Fig. 4]. After 1-year of follow-up, for the individual

Table 2 Event numbers and weighted cumulative incidences of all endpoints after 1 and 3 years of follow-up, according to sex

Endpoint	1 year of follow-up		3 years of follow-up	
	Number of events	Weighted cumulative incidence (%)	Number of events	Weighted cumulative incidence (%)
VTE				
Male patients	98	0.7	176	1.5
Female patients	122	0.9	222	2.0
DVT				
Male patients	46	0.3	86	0.7
Female patients	43	0.3	91	0.9
PE				
Male patients	52	0.4	92	0.8
Female patients	83	0.6	136	1.1

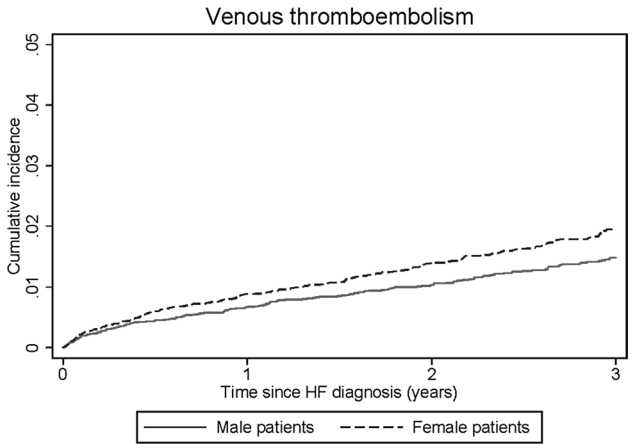

Fig. 2 Adjusted cumulative incidence of venous thromboembolism according to sex. *HF* heart failure. Adjusted for age (continuous), hypertension (binary), vascular disease (binary), diabetes (binary), chronic obstructive pulmonary disease (binary), statin therapy (binary), and aspirin therapy (binary)

endpoints of PE and DVT, female sex was only associated with a higher risk of PE (adjusted RR: 1.62, 95% CI: 1.10–2.38) and not DVT (adjusted RR: 1.05, 95% CI: 0.61–1.83) compared to male patients. However, female sex was associated with a higher risk of both PE and DVT after 3 years of follow-up. Results were similar also when censoring patients who initiated oral anticoagulation during follow-up (data not shown).

In the age-stratified analysis, female sex was associated with a higher risk of VTE (specifically a higher risk of PE), in the age groups "60–80 years" and ">80 years"; though, statistical significance was not reached (Fig. 5).

In the age-stratified analyses, female sex was associated with an overall higher risk of VTE in comparison to males: among patients at age 60–80 years, females had a 15% higher risk and 43% higher risk among patients aged > 80 years (Fig. 5). Importantly, the higher risk of VTE in females was mainly driven by higher risk of PE in both strata.

Discussion

In this nationwide cohort study of HF patients, we examined the difference in risk of VTE between male and female patients. We found a higher risk of VTE in female patients compared to male patients. This association was mainly driven by a higher risk of PE in female patients.

The mechanism by which HF is associated with a higher risk for VTE is not precisely determined [31]. In the general Danish population, VTE incidence is much lower than in the present heart failure population, but in contrast with our findings more frequent among men than women [32]. Multiple mechanisms lead to a high risk of VTE in this patient group, such as increased pulmonary pressure and decreased ejection fraction leading to increased venous stasis in the lower extremities [2, 33]. As ejection fraction decreases, exercise tolerance decreases resulting in poor mobility, which leads to a significantly higher risk for VTE [34]. HF is also associated with endothelial dysfunction, decreased microcirculatory blood flow, and increased blood levels of prothrombotic molecules, which all lead to a hypercoagulable state [2, 33].

Whether male and female patients have different physiological mechanisms that may explain the higher risk of PE among female patients has not been determined. In our study, female HF patients had a higher mean age, but a lower prevalence of vascular disease (such as prior myocardial infarction) and diabetes. Older age is a well-known risk factor of PE [35, 36] and could be part of the explanation for the difference in PE risk between the male and female patients. We performed a secondary analysis, stratifying the study population into two age groups (60–80 years and > 80 years), and found a clear trend for a higher risk of PE among female patients in both age groups. Another possible explanation could be that males and females do not share the same risk factors for VTE and especially for PE. For example, we did not have information about risk factors such as smoking, body mass index, and recent immobilization, which could

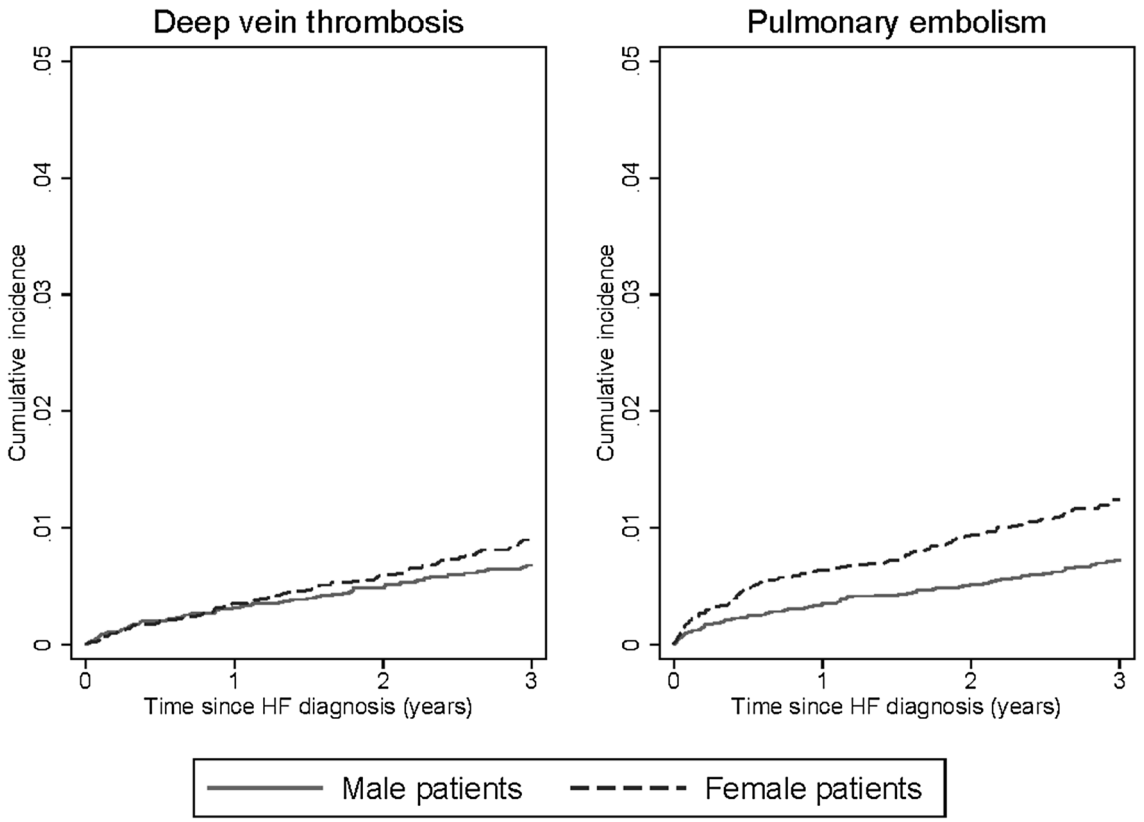

Fig. 3 Adjusted cumulative incidence of deep vein thrombosis and pulmonary embolism according to sex. *HF* heart failure. Adjusted for age (continuous), hypertension (binary), vascular disease (binary), diabetes (binary), chronic obstructive pulmonary disease (binary), statin therapy (binary), and aspirin therapy (binary)

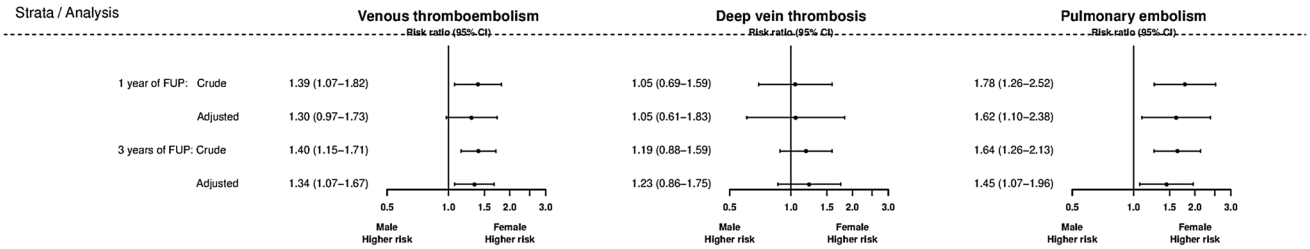

Fig. 4 Relative risks of all endpoints after 1 and 3 years of follow-up, according to sex (reference group: male patients). *FUP* follow-up, *95% CI* 95% confidence interval. Analysis adjusted for age (continuous), hypertension (binary), vascular disease (binary), diabetes (binary), chronic obstructive pulmonary disease (binary), statin therapy (binary), and aspirin therapy (binary)

be related to the risk of PE, but we do not expect that this missing information will completely explain our findings. In addition, females are uniquely exposed to well-known risk factors of VTE, such as hormone replacement therapy, estrogen containing oral contraceptives, pregnancy and the postpartum period [37, 38] as opposed to males. However, some of these unique risk factors might not be of much relevance in our older HF population or at least of perceived very little bearing. We had no access to information about ejection fraction, New York Heart Association (NYHA) class, or the specific aetiology of heart failure in our study population and could, therefore, not explore how such clinical characteristics would have influenced the observed sex disparities. In the general HF population, females more often have HF with preserved ejection fraction, whereas males more often have HF with reduced ejection fraction [39, 40], just as men often are more symptomatic as measured by NYHA class [41]. However, few studies have found an association between reduced ejection fraction and higher risk of VTE [9, 34], so this does not provide an explanation for

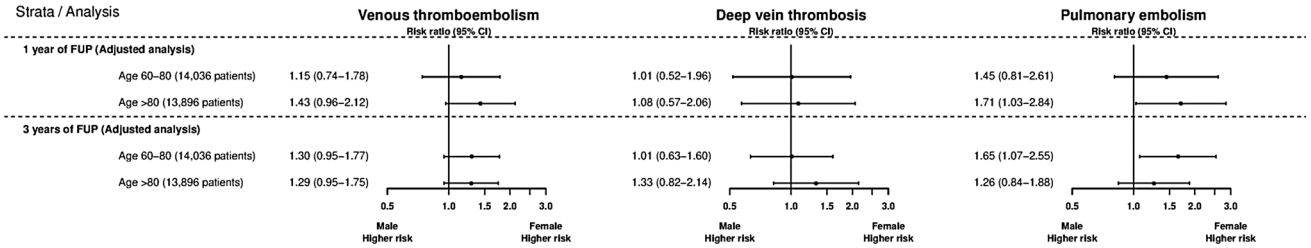

Fig. 5 Relative risks of all endpoints after 1 and 3 years of follow-up, according to sex (reference group: male patients), and stratified into two age groups. *FUP* follow-up, *95% CI* 95% confidence interval. Analysis adjusted for a propensity score based on age (continuous), hypertension (binary), vascular disease (binary), diabetes (binary), chronic obstructive pulmonary disease (binary), statin therapy (binary), and aspirin therapy (binary)

the higher risk of VTE observed among women compared with men. In addition, although the baseline prevalence of chronic obstructive pulmonary disease was similar between sexes, we had no information on severity on this disease, which is known to be specifically associated with PE [42]. More males than females were using statins and antiplatelets at baseline in our study; probably reflecting the difference in vascular disease and diabetes history. This difference could potentially influence the outcome estimates; however, we included these medications in the adjusted analysis. Thus, future studies are needed to explain the etiological relation between female sex and PE risk, and whether the prognostic value of sex is consistent across different aetiologies of heart failure as well as within categories of ejection fraction.

Clinical importance

Several guidelines recommend that all hospitalized patients with HF receive VTE prophylaxis with anticoagulant medication if the risk–benefit ratio is favourable and the patient is not already anticoagulated [6, 7]. Recent evidence shows a large gap between these guidelines and clinical practice [43], and there is evidence that thromboprophylaxis is underused in the HF patient group, possibly due to the difficulties in accurately assessing the individual patient's risk [8]. However, current guidelines only recommend anticoagulation to HF patients for long-term thromboprophylaxis if the patient has concomitant atrial fibrillation or another indication for anticoagulation [44, 45]. Given the bleeding risk associated with thromboprophylactic therapy, identification of high-risk subjects with an assumed benefit from treatment is essential. We found a higher risk of PE among female HF patients compared to male HF patients; thus, female HF patients may be a subgroup that deserves more attention in clinical practice. More focus on modifiable PE risk factors in the female HF population is warranted and specific thromboprophylactic strategies in women may be necessary to possibly reduce the burden of PE in these patients.

It should be noted that there are no completed randomized trials investigating the effect of long-term anticoagulation on VTE prevention specifically in patients with heart failure. However, previous trials of extended duration of anticoagulation in acute medically ill patients have yielded conflicting results, with some demonstrating a benefit of prolonged treatment [46, 47], while in others the antithrombotic effect was offset by bleeding risk [48]. Another trial is still ongoing [49].

Strengths and limitations

The large sample size uniquely possible with this type of cohort study minimized the risk of random error. Selection into the study was not an issue, since we investigated a nationwide population cohort of incident HF patients using administrative data, which also implies virtually no loss to follow-up.

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% [18, 50]; thus, we may have underestimated the true population HF prevalence, and also cannot be certain that all included patients had definite HF. Nonetheless, this most likely applies equally to both men and women and the risk of observational bias due to misclassification is, therefore, not a likely explanation for the observed associations. In addition, we included only patients with a primary discharge diagnosis of HF to optimize the probability of including only correctly identified patients with HF.

In Denmark, almost every patient presenting with VTE symptoms is admitted to and examined in a hospital setting. Hence, the accuracy of our findings depends on proper ICD-10 coding. Recent Danish validation studies comparing VTE diagnoses obtained from the Danish National Patient Registry with medical records have revealed positive predictive values of 75–88% for first-time VTE [19, 23]. Additionally, the positive predictive value for first-time VTE is similar

between sexes, 78–86 and 71–88% for men and women, respectively [19, 23].

Generalizability of the study results

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. Furthermore, the study was carried out as a nationwide study in the Danish population, which is ethnically fairly homogeneous; thus, future studies are needed to evaluate if our findings hold in more ethnically diverse HF populations.

In conclusion, we examined the difference in risk of VTE between male and female HF patients.

Among incident HF patients, female sex is associated with a higher risk of VTE, mainly driven by an excess risk of PE. These findings may help improve clinical decision-making regarding VTE prophylaxis in patients with HF.

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Compliance with ethical standards

Conflict of interest Professor Lip: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Associate Professor Larsen: An investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim. Speaker for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. Peter Brønnum Nielsen: Speaker for Boehringer Ingelheim and Bayer Pharma AG; research Grant from BMS/Pfizer. Flemming Skjøth: Consultancy fees from Bayer. Other authors—none declared. Profs Lip and Larsen are guarantors of this paper.

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