RESEARCH ARTICLE

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.

Abbreviations: **AF**, atrial fibrillation; **COPD**, chronic obstructive pulmonary disease; **HF**, heart failure; **MI**, myocardial infarction; **PAD**, peripheral artery disease.

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 atrial fibrillation (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 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 represents 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 supporting materials [please see table in 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 text in S1 Text in the supporting materials 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 supporting materials). 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 supporting materials).

We performed 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]. Additionally, crude cumulative incidence curves for both end points according to vascular disease were constructed based on the Aalen-Johansen estimator for competing risks data.

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.
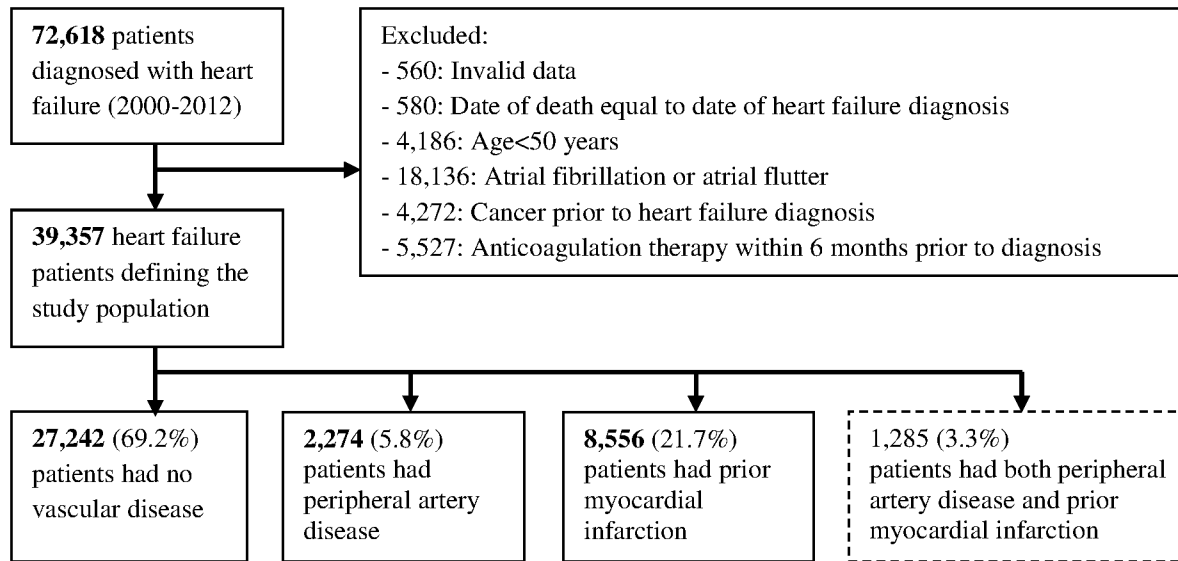
Ethical Considerations

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 heart failure 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 Fig 1]. 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. 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. For patients with no vascular disease, PAD, or prior MI, the absolute

| 72,618 patients diagnosed with heart failure (2000-2012) | Excluded:
- 560: Invalid data
- 580: Date of death equal to date of heart failure diagnosis
- 4,186: Age<50 years
- 18,136: Atrial fibrillation or atrial flutter
- 4,272: Cancer prior to heart failure diagnosis
- 5,527: Anticoagulation therapy within 6 months prior to diagnosis |

| 39,357 heart failure patients defining the study population |

| 27,242 (69.2%) patients had no vascular disease | 2,274 (5.8%) patients had peripheral artery disease | 8,556 (21.7%) patients had prior myocardial infarction | 1,285 (3.3%) patients had both peripheral artery disease and prior myocardial infarction |

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

doi:10.1371/journal.pone.0152269.g001

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)

doi:10.1371/journal.pone.0152269.t001

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

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

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

doi:10.1371/journal.pone.0152269.t002

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 table in S2 Table in the supporting materials.

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 to 1.65) and all-cause death (adjusted HR: 1.47, 95% CI: 1.35 to 1.59), whereas prior MI was not (adjusted HR: 1.00, 95% CI: 0.86 to 1.15 and 0.94, 95% CI: 0.89 to 1.00, for ischemic stroke and all-cause death, respectively), as shown in Table 3. 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 to 1.72 and 1.53, 95% CI: 1.40 to 1.68, for ischemic stroke and all-cause death, respectively). Similar results were obtained after 5-years follow-up [please see table in S3 Table in the supporting materials]. Cumulative incidence curves for both end points demonstrate a steady increase during follow-up [please see figure in S1 Fig in the supporting materials].

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. Regardless of antiplatelet therapy

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

(Abbreviations: 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)

doi:10.1371/journal.pone.0152269.t003

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

(Abbreviations: 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)

doi:10.1371/journal.pone.0152269.t004

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 table in S4 Table in the supporting materials].

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 tables in S7 and S8 Tables in the supporting materials. 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 table in S5 Table in the supporting materials]. 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 table in S6 Table in the supporting materials].

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 prognostic value of PAD and prior MI in relation to 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.

Patients with PAD are likely to have concomitant coronary artery disease or cerebrovascular disease, which from an etiological perspective could influence the association between vascular disease and stroke risk; however, since the focus of the study was on the *prognostic value* of PAD and prior MI in relation to ischemic stroke, and not to elucidate a potential causal role, confounding is per definition not an issue of concern. Hence, our observations of a higher stroke risk in patients with PAD versus no vascular disease cannot exclusively be attributed to an *effect* of PAD, but is likely to be explained also by other concomitant stroke risk factors, such as lifestyle factors (e.g., smoking), coexisting cerebrovascular disease, and etiology and subtype of HF. For example, coronary artery disease is an important cause of HF, and we therefore possibly compared patient populations with different underlying substrates for HF. If our aim had been to examine the *effect* of vascular disease on stroke risk, this would have required a different study design with use of a more broad definition of vascular disease, taking into account possible confounding stroke risk factors, but this was beyond the scope of this study which had focus on stroke risk stratification in the HF population.

Clinical implications

Reduced secondary prevention in PAD patients compared to patients with coronary artery disease has been observed in several studies[26,27]; notwithstanding 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 mortality 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 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.

Supporting Information

S1 Fig. Cumulative incidence of ischemic stroke and all-cause death: A) Ischemic stroke; B) All-cause death.
(DOCX)

S1 Table. ICD-10 codes and ATC-codes used in the cohort study.
(DOCX)

S2 Table. Event numbers and absolute risks of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.
(DOCX)

S3 Table. Hazard rate ratios of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.
(DOCX)

S4 Table. Hazard rate ratios of ischemic stroke and all-cause death after 5-year follow-up, stratified by antiplatelet therapy at baseline.
(DOCX)

S5 Table. 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.
(DOCX)

S6 Table. Sensitivity analysis excluding patients with a history of stroke: Hazard rate ratios of incident stroke after 1-year follow-up, according to vascular disease.
(DOCX)

S7 Table. Relative risks of ischemic stroke and all-cause death after 1-year follow-up, according to vascular disease.
(DOCX)

S8 Table. Relative risks of ischemic stroke and all-cause death after 5-years follow-up, according to vascular disease.
(DOCX)

S1 Text. Methodological details- Analysis on a risk-scale.
(DOCX)

Acknowledgments

Author Contributions

Conceived and designed the experiments: LM AGR LHR GYHL TBL. Performed the experiments: LM AGR LHR GYHL TBL. Analyzed the data: LM AGR LHR GYHL TBL. Contributed reagents/materials/analysis tools: LM AGR LHR GYHL TBL. Wrote the paper: LM AGR LHR GYHL TBL.

References

1. Lip G, Rasmussen L, Skjøth F, Overvad K, Larsen T. Stroke and mortality in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. BMJ Open. 2012; 2:1–10.

2. Anandasundaram B, Lane D, Apostolakis S, Lip GYH. The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. J Thromb Haemost. 2013; 11:975–87. doi: 10.1111/jth.12177 PMID: 23441593

3. Alberts MJ, Bhatt DL, Mas J-L, Ohman EM, Hirsch AT, Röther J, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. Eur Heart J. 2009; 30:2318–26. doi: 10.1093/eurheartj/ehp355 PMID: 19720633

4. Gronewold J, Hermann DM, Lehmann N, Kröger K, Lauterbach K, Berger K, et al. Ankle–brachial index predicts stroke in the general population in addition to classical risk factors. Atherosclerosis. 2014; 233:545–50. doi: 10.1016/j.atherosclerosis.2014.01.044 PMID: 24530962

5. Hermann DM, Gronewold J, Lehmann N, Moebus S, Jockel K-H, Bauer M, et al. Coronary Artery Calcification Is an Independent Stroke Predictor in the General Population. Stroke. 2013; 44:1008–13. doi: 10.1161/STROKEAHA.111.678078 PMID: 23449263

6. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA2DS2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. JAMA. 2015; 314:1030–8. doi: 10.1001/jama.2015.10725 PMID: 26318604

7. Hebert K, Lopez B, Michael C, Franco E, Dias A, Trahan P, et al. The prevalence of peripheral arterial disease in patients with heart failure by race and ethnicity. Congest Hear Fail. 2010; 16:118–21.

8. Hwang S-J, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2014; 63:2817–27. doi: 10.1016/j.jacc.2014.03.034 PMID: 24768876

9. Olesen JB, Lip GYH, Lane DA, Køber L, Hansen ML, Karasoy D, et al. Vascular Disease and Stroke Risk in Atrial Fibrillation: A Nationwide Cohort Study. Am J Med. 2012; 125:826.e13–826.e23.

10. Rasmussen LH, Larsen TB, Due KM, Tjønneland A, Overvad K, Lip GYH. Impact of vascular disease in predicting stroke and death in patients with atrial fibrillation: the Danish Diet, Cancer and Health cohort study. J Thromb Haemost. 2011; 9:1301–7. doi: 10.1111/j.1538-7836.2011.04308.x PMID: 21535388

11. Lynge E, Sandegaard J, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011; 39:30–3. doi: 10.1177/1403494811401482 PMID: 21775347

12. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011; 39:38–41. doi: 10.1177/1403494810394717 PMID: 21775349

13. Pedersen CBC. The Danish Civil Registration System. Scand J Public Health. 2011; 39:22–5. doi: 10.1177/1403494810387965 PMID: 21775345

14. Krarup L, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007; 28:150–4. PMID: 17478969

15. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, et al. Accuracy of a heart failure diagnosis in administrative registers. Eur J Heart Fail. 2008; 10:658–60. doi: 10.1016/j.ejheart.2008.05.006 PMID: 18539522

16. Thygesen S, Christiansen C, Christensen S, Lash T, Sørensen H. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011; 11:83. doi: 10.1186/1471-2288-11-83 PMID: 21619668

17. Zöller B, Ji J, Sundquist J, Sundquist K. Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden. Eur J Cancer. 2012; 48:1875–83. doi: 10.1016/j.ejca.2012.01.005 PMID: 22296948

18. Ambrogi F, Biganzoli E, Boracchi P. Estimates of clinically useful measures in competing risks survival analysis. Statis Med. 2008; 27:6407–25.

19. Andersen PK, Geskus RB, De witte T, Putter H. Competing risks in epidemiology: Possibilities and pitfalls. Int J Epidemiol. 2012; 41:861–70. doi: 10.1093/ije/dyr213 PMID: 22253319

20. Lip G, Nieuwlaat R, Pisters R, Lane D, Crijns H. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010; 137:263–72. doi: 10.1378/chest.09-1584 PMID: 19762550

21. Van Staa T, Setakis E, Di Tanna G, Lane D, Lip G. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011; 9:39–48. doi: 10.1111/j.1538-7836.2010.04085.x PMID: 21029359

22. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke. 1994; 25:333–7. PMID: 8303740

23. Pullicino P, McClure L, Howard V, Wadley V, Safford M, Meschia J, et al. Identifying a high stroke risk subgroup in individuals with heart failure. J Stroke Cerebrovasc Dis. 2013; 22:620–6. doi: 10.1016/j.jstrokecerebrovasdis.2011.10.012 PMID: 22142776

24. Lip G, Piotrponikowski P, Andreotti F, Anker S, Filippatos G, Homma S, et al. Thromboembolism and antithrombotic therapy for heart failure in sinus rhythm: an executive summary of a joint consensus document from the ESC Heart Failure Association and the ESC working group on thrombosis. Thromb Haemost. 2012; 108:1009–22. PMID: 23093044

25. Marín F, Lip GYH. Oral anticoagulation for heart failure in sinus rhythm: from evidence to clinical recommendations, or not? Eur J Heart Fail. 2013; 15:3–4. doi: 10.1093/eurjhf/hfs198 PMID: 23204212

26. Mcdermott MM, Hahn EA, Greenland P, Cella D, Ockene JK, Brogan D, et al. Atherosclerotic Risk Factor Reduction in Peripheral Arterial Disease. J Gen Intern Med. 2002; 17:895–904. PMID: 12472925

27. Zeymer U, Parhofer KG, Pittrow D, Binz C, Schwertfeger M, Limbourg T, et al. Risk factor profile, management and prognosis of patients with peripheral arterial disease with or without coronary artery disease: results of the prospective German REACH registry cohort. Clin Res Cardiol. 2009; 98:249–56. doi: 10.1007/s00392-009-0754-1 PMID: 19221687

28. Nakamura Y, Kunii H, Yoshihisa A, Takiguchi M, Shimizu T, Yamauchi H, et al. Impact of Peripheral Artery Disease on Prognosis in Hospitalized Heart Failure Patients. Circ J. 2015; 79:785–93. doi: 10.1253/circj.CJ-14-1280 PMID: 25739573

29. Loh E, Sutton MS, Wun CC. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med. 1997; 336:251–7. PMID: 8995087

30. Chen Z, Jiang L, Chen Y, Xie J, Pan H, Peto R. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366:1607–21. PMID: 16271642

31. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34:2949–3003. PMID: 23996286

32. Tendera M, Aboyans V, Bartelink M-L, Baumgartner I, Clément D, Collet J-P, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011; 32:2851–906. PMID: 21873417

33. Cokkinos D V, Haralabopoulos GC, Kostis JB, Toutouzas PK. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. Eur J Heart Fail. 2006; 8:428–32. PMID: 16737850

34. Cleland JGF, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J. 2004; 148:157–64. PMID: 15215806

35. Homma S, Thompson JLP, Pullicino P, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm. N Engl J Med. 2012; 366:1859–69. doi: 10.1056/NEJMoa1202299 PMID: 22551105

36. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JGF, Ezekowitz M, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation. 2009; 119:1616–24. PMID: 19289640

37. Nielsen PB, Chao T. The risks of risk scores for stroke risk assessment in atrial fibrillation. Thromb Haemost. 2015; 113:1170–3. doi: 10.1160/TH15-03-0210 PMID: 25759209

38. Sandhu RK, Hohnloser SH, Pfeffer MA, Yuan F, Hart RG, Yusuf S, et al. Relationship Between Degree of Left Ventricular Dysfunction, Symptom Status, and Risk of Embolic Events in Patients With Atrial Fibrillation and Heart Failure. Stroke. 2015; 46:667–72. doi: 10.1161/STROKEAHA.114.007140 PMID: 25628308

39. Badheka AO, Rathod A, Kizilbash MA, Bhardwaj A, Ali O, Afonso L, et al. Comparison of Mortality and Morbidity in Patients With Atrial Fibrillation and Heart Failure With Preserved Versus Decreased Left Ventricular Ejection Fraction. Am J Cardiol. 2011; 108:1283–8. doi: 10.1016/j.amjcard.2011.06.045 PMID: 21855829

40. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. Clin Epidemiol. 2010; 2:235–9. doi: 10.2147/CLEP.S12457 PMID: 21042557