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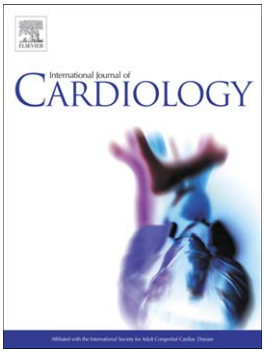

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Diabetes mellitus and risk of ischemic stroke in patients with heart failure and no atrial fibrillation

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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.

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. Professor Søgaard has served as a consultant for BIOTRONIK, a speaker for GE Healthcare and BIOTRONIK, and received research grants from GE Healthcare and EBR Systems. 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.

Keywords: Heart failure, diabetes, stroke, systemic thromboembolism, death, risk stratification.

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%; systemic 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); systemic 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, systemic 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, systemic 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.

Abbreviations:

AF: Atrial fibrillation

COPD: Chronic obstructive pulmonary disease

HF: Heart failure

TE: Thromboembolic event

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.

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Titles and Legends to Figures

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 systemic thromboembolic event; C) Adjusted cumulative incidence curve of all-cause death.

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 any stroke/TIA	12.0 (3,884)	17.1 (1,215)
Previous myocardial infarction	24.0 (7,723)	29.8 (2,118)
Previous systemic 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, systemic 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)
SYSTEMIC 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

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. 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
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 (Systemic thromboembolic event)	I63.0-I63.9, I64
Transient ischemic attack (Systemic thromboembolic event)	G45.0-G45.9 (Not inclusive G45.3 (Amaurosis fugax))
Systemic embolism (Systemic thromboembolic event)	I74.0-I74.9
Acute myocardial infarction (Systemic 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	C10
Non steroidal anti-inflammatory drugs (NSAIDs)	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).

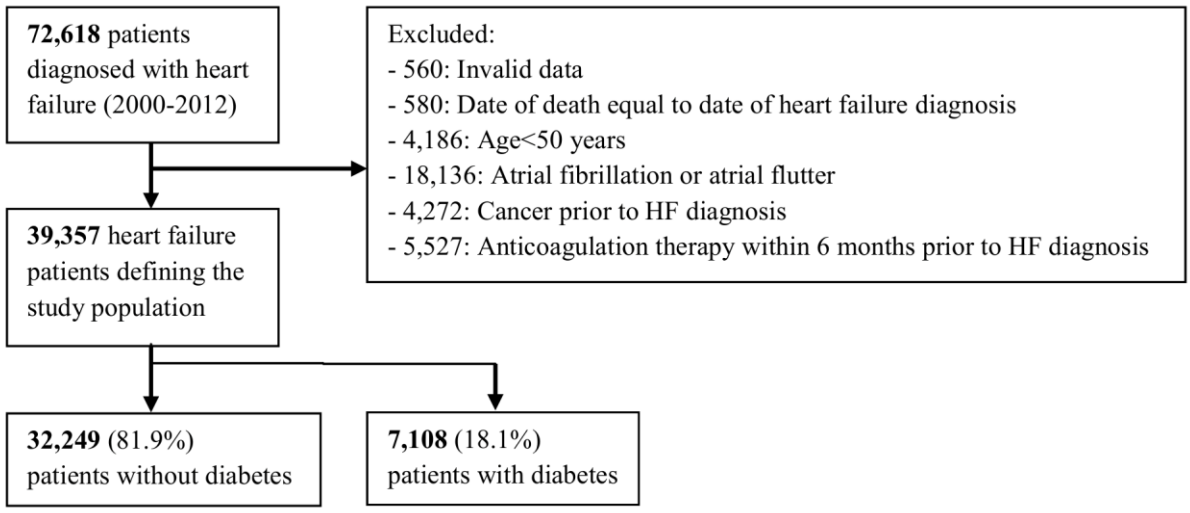

FIGURE 1

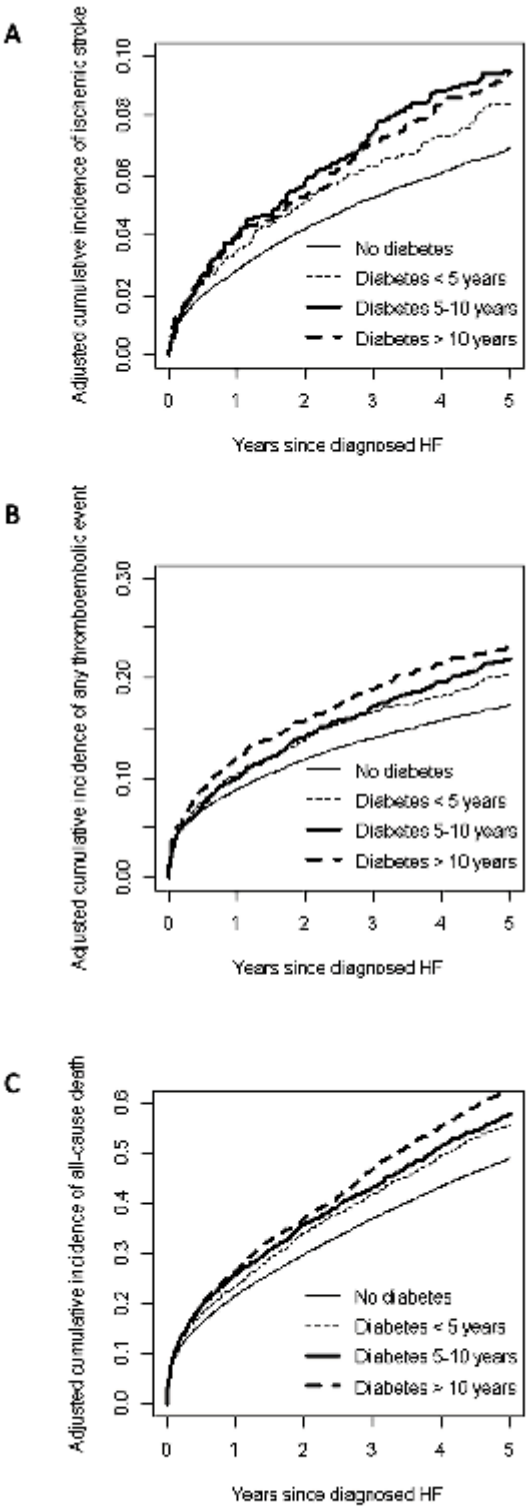

FIGURE 2