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

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

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

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

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

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

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

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

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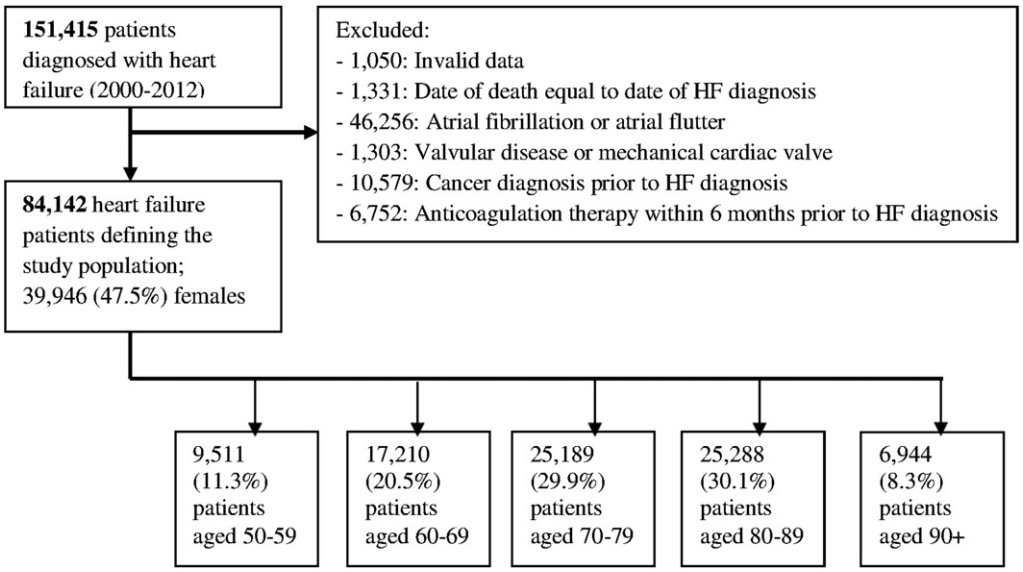
Figure 1



Flowchart of patients included in the final study population.

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

Methods

Registry data sources

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

Study population

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

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

Outcomes

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

Statistical methods

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