RESEARCH LETTER

Prognostic importance of atrial fibrillation in heart failure according to time elapsed since diagnosis

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Atrial fibrillation (AF) is a common comorbidity in patients with heart failure (HF) that may compromise cardiac contractility and exacerbate the HF syndrome.[1] Multiple studies point to increased mortality in HF complicated by AF (compared to HF with sinus rhythm), regardless of the time of AF onset in relation to HF syndrome.[2] Mortality rates for HF patients generally are greatest early after onset and tend to decrease with time elapsed since the diagnosis; however, whether the presence of AF alters such a clinical course is unknown. Given the uncertainty regarding optimal management strategies for patients with both diagnoses, it would be important to examine the mortality risks of HF patients with and without AF based on timing and duration of both conditions.[3]

This study was exempt from ethical board approval. The Declaration of Helsinki was not relevant given its registry-based setup in which individuals could not be identified; consent was waived for the same reason. Through the Danish nationwide administrative registries, we followed all patients with a first diagnosis of HF (any diagnosis, regardless of left ventricular ejection fraction, both inpatient and outpatient, ICD-8 codes 427.09–427.11, 427.19, 424.49, ICD-10 codes I42, I43, and I50) for all-cause mortality over the years 1998–2018. Mean follow-up was 6.2 ± 5.8 years. Details of the study population have been previously reported.[2] We identified and grouped AF (ICD-8 codes 427.93–427.94, ICD-10 code I48) as occurring antecedent, concomitant with (diagnosed the same day), or after the HF diagnosis. Exposure groups were defined at the start of each year since HF onset for the landmark analysis.[4] We used time-dependent Poisson regression models, adjusted for age, sex, calendar year, hypertension, diabetes, acute myocardial infarction, ischemic heart disease, dilated cardiomyopathy, aortic valve replacement, mitral valve repair or replacement, prior stroke, chronic obstructive pulmonary disease, cancer, renal disease, liver disease, anticoagulation therapy, angiotensin-converting enzyme inhibitor and angiotensin II receptor blockers, calcium channel blockers, beta-blockers, statin, aspirin, and the presence of a pacemaker and implantable cardioverter-defibrillator throughout follow-up (time-dependently) to estimate the mortality rate ratios associated with AF, using "no AF" as the referent. Two-tailed $P < .05$ was considered significant. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

A total of 252,988 HF patients (45% women; mean age 74 ±13 years) were included in the study. Of these patients, 54,064 (21%) had AF before HF onset and 27,651 (11%) had AF diagnosed concomitantly with HF. During follow-up, an additional 30,565 patients developed AF. Patients with AF

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KEY FINDINGS

- Although mortality risk seems to decline over time in heart failure (HF) patients with and without concomitant atrial fibrillation (AF), the presence of AF significantly reduces the rate at which this risk declines.
- The prognostic implications of our findings on concomitant AF and HF may impact management decisions (eg, rate vs rhythm control) for patients with these 2 comorbid conditions.

that occurred before HF onset were older and had a higher prevalence of comorbidities at baseline compared to patients with concomitant AF and AF that occurred after HF onset (full baseline characteristics previously reported[2]). Regardless of the sequence of presentation, cumulative mortality associated with AF was high and remained increased even after several years (Figure 1A). HF patients with AF experienced substantially less declines in mortality rates as time elapsed since HF diagnosis compared to the no AF group ($P < .0001$ for interaction with HF duration) (Figure 1B), rendering AF of greater prognostic importance later in the clinical course of HF (Figure 1C).

Among this unselected cohort of HF patients, we observed a more than 2-fold increased mortality across all subgroups with AF compared to HF patients without AF. Furthermore, although it is well known that the mortality associated with HF declines over time, few data on the mortality trends in HF complicated by AF have been available. Our study suggests that although mortality risk seems to decline over time in HF patients with and without concomitant AF, the presence of AF significantly reduces the rate at which this risk declines (Figure 1). Thus, HF patients with AF are not as protected by the same natural "survival of the fittest" phenomenon as otherwise seen with HF,[5] and AF continues to be a strong risk factor for mortality among patients with HF for at least 10 years after the initial diagnosis. Future studies aiming to address the outcomes of sinus rhythm restoration in patients with AF and HF may warrant consideration of the time since HF diagnosis. A major strength associated with this study is the large sample size (252,988 individuals) with long follow-up. Study limitations include a racially homogeneous population, shortcomings of ICD coding criteria (including a lack of data on left ventricular ejection fraction), and limited data on certain confounders of AF.

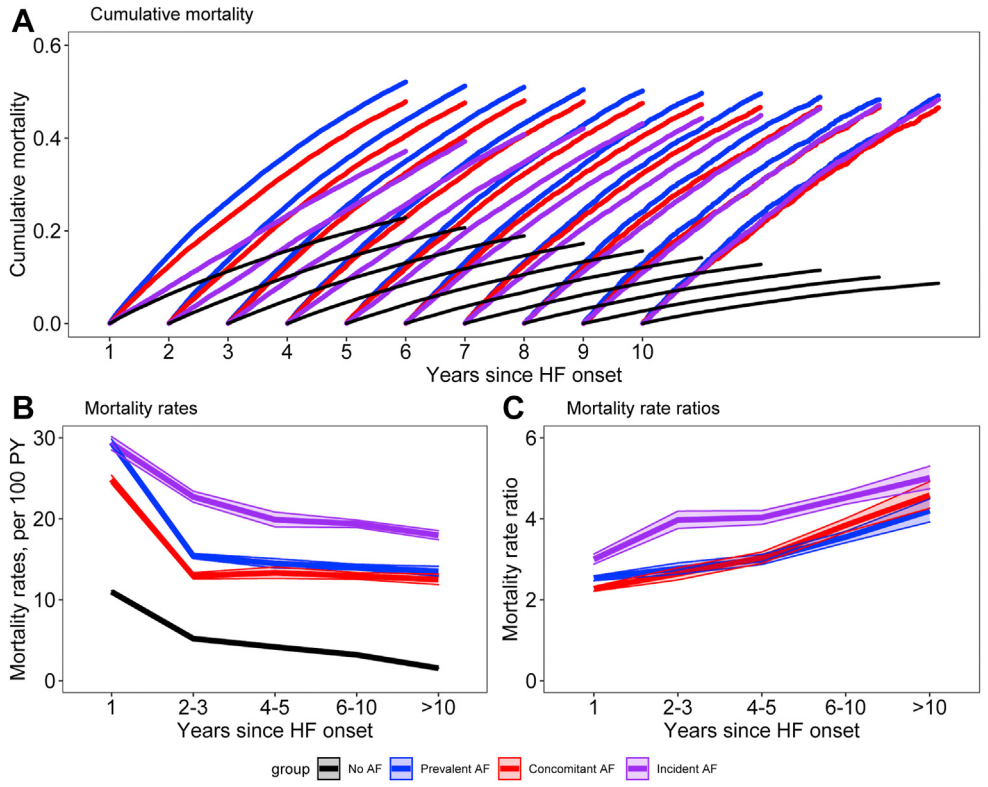

Figure 1 Mortality in patients with heart failure (HF) according to time elapsed since diagnosis of atrial fibrillation (AF). **A:** Five-year cumulative mortality for HF patients at years 1 to 10 after HF. **B:** Mortality rates for years 1 to >10 after HF diagnosis. **C:** Mortality rate ratios ("no AF" referent) for years 1 to >10 after HF diagnosis. Prevalent AF *(blue)* is AF diagnosed before HF, concomitant AF *(red)* is AF diagnosed with HF, and incident AF *(purple)* is AF diagnosed after HF. *Shaded areas* represent 95% confidence intervals. PY = person-year.

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Patient Consent: Consent was waived due ot the use of de-identified data.

Ethics Statement: This study was exempted from ethical board approval, as the data from the registry used in this study were de-identified.

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