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EDITORIAL COMMENT

The Changing Landscape of Atrial Fibrillation

Time to Target Heart Failure Prevention*

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Atrial fibrillation (AF) is common in older adults, is increasing in incidence and prevalence globally, and is associated with adverse cardiovascular outcomes including stroke, systemic thromboembolism, heart failure (HF), myocardial infarction, sudden cardiac death, and death. Survival among patients with AF has improved by 25% over the last 50 years, in part due to advancement in stroke prophylaxis and universal adaptation of clinical stroke prediction models, leading to 74% reduction in AF-related stroke during the same time period (1). Nevertheless, the risk of death among anticoagulated patients with AF remains high at 4.6% per year (2), and further improvement in mortality among patients with AF has been hindered by lack of an effective strategy for prevention of cardiovascular outcomes beyond stroke.

In contemporary AF cohorts, cardiac complications, including HF, myocardial infarction, and sudden death, are the leading causes of death, accounting for 46% of all-cause mortality (2). Among cardiac complications, the burden of HF is substantial. In a cohort of Medicare beneficiaries age 65 years or older, 14% of patients with incident AF were hospitalized or were treated in an emergency department for HF within 5 years (3). In contemporary AF trials, HF accounted for 15% of all deaths in AF, outpacing death due to stroke in the modern anticoagulation era (2). In AF patients, development of HF increases risks of hospitalization, bleeding, cardiovascular mortality, and all-cause mortality (4,5). Despite its substantial morbidity and mortality, there have been no evidence-based strategies for HF prevention in AF. Indeed, reports from Olmsted County, Minnesota, demonstrated that the incidence rate of HF after AF diagnosis did not improve between 1980 and 2000 (44 per 1,000 person-years) and 2000 and 2013 (58 per 1,000 person-years), and there was no temporal trend in the incidence rate within each study period (6,7).

SEE PAGE 552

In this issue of *JACC: Heart Failure*, Chatterjee et al. (8) sought to identify modifiable risk factors for incident HF in patients with AF in the Women's Health Study. The analytic sample included 1,495 women who developed incident AF and were without prevalent HF at the time of AF diagnosis. During a median follow-up of 6.8 years, 187 women developed incident HF at a rate of 17.4 cases per 1,000 person-years. In multivariable models incorporating time-varying covariates, the authors found that diabetes, current smoking, obesity, and elevated systolic blood pressure were associated with incident HF with a combined 62% population-attributable fraction for incident HF. Similar to prior data, there was a 2-fold increased risk for all deaths and 3-fold increased risk for cardiovascular deaths among

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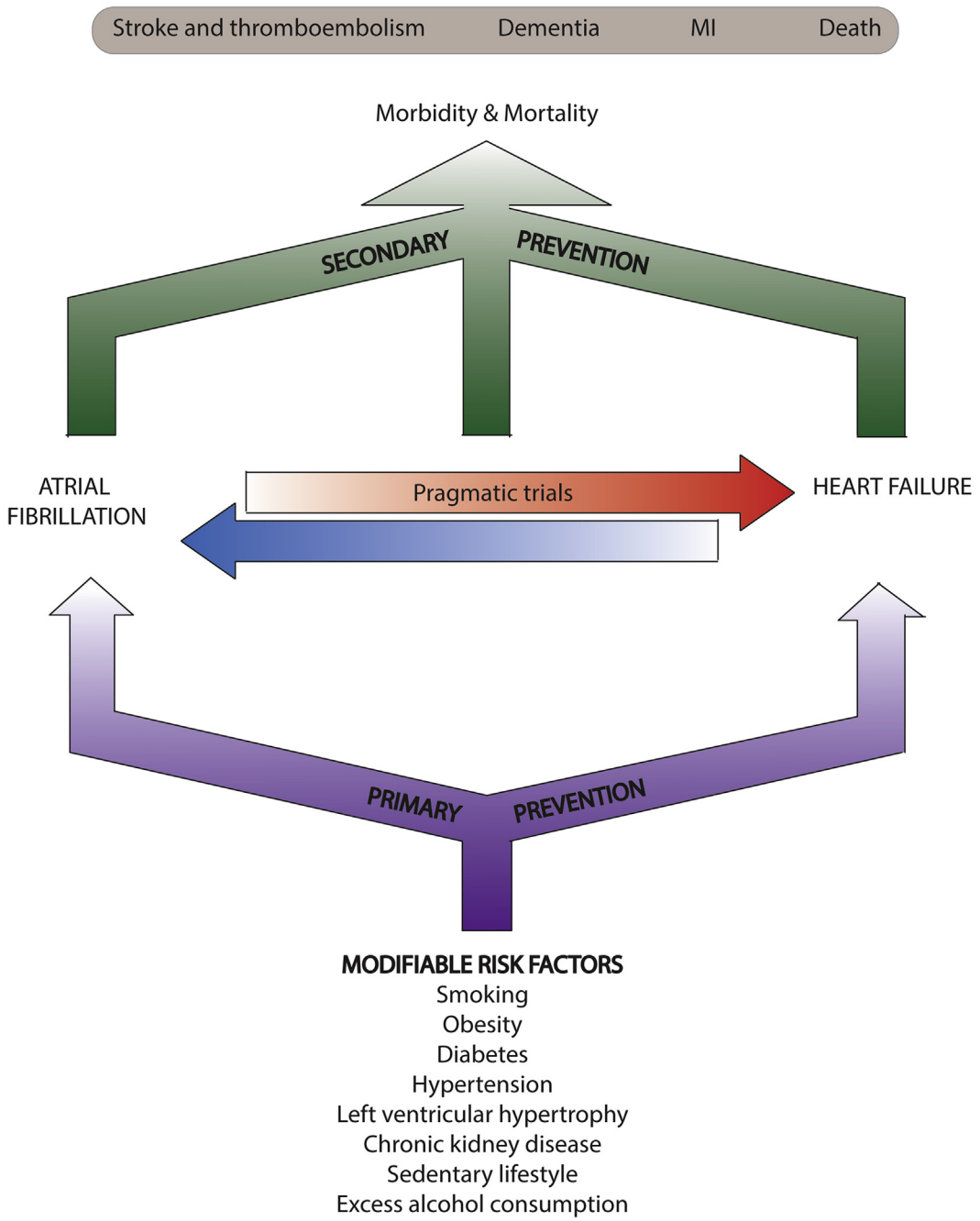
FIGURE 1 Modifiable Risk Factors and AF



The relations between AF and HF are bidirectional. Modifiable risk factors play a critical role in the incidence and complications of AF and HF. Targeting the modifiable risk factors for both primary and secondary prevention of AF and HF can lead to further improvement of the public health burden of the diseases. Pragmatic trials are needed to generate evidence-based strategies for prevention of incident HF in individuals with AF. AF = Atrial fibrillation; HF = heart failure; MI = myocardial infarction.

women who developed HF. Incident HF accounted for 18% of cardiovascular mortality and 10% of all-cause mortality.

The study by Chatterjee et al. (8) has several major strengths. It rigorously validated AF and HF using pre-specified criteria and carefully excluded prevalent HF at the time of AF diagnosis. Use of time-varying risk factors enhanced the ability to account for confounding in the associations between the risk factors and incident HF. The prospective nature of the study and relatively large size of the study sample with AF were additional strengths. Limitations of the study acknowledged by the authors were that the generalizability to men and minorities is uncertain. In addition, determining whether population attributable risk estimates will translate into efficacy of disease prevention if modifiable risk factors are treated will require randomized studies.

The study by Chatterjee et al. (8) is an addition to the emerging literature that has established both modifiable and nonmodifiable risk factors for incident HF in AF (Online Supplement 1). The studies come at a time when the landscape of AF morbidity and mortality is changing rapidly. Stroke and thromboembolism are no longer the leading causes of mortality in AF, a testament to the efficacy and safety of modern anticoagulation treatments. HF is now the leading cardiovascular complication related to AF. There is a vital clinical need for evidence-based strategies of HF prevention in patients with AF.

In small preliminary trials, aggressive risk factor modification for hypertension, obesity, sedentary lifestyle, hyperlipidemia, diabetes mellitus, obstructive sleep apnea, cigarette smoking, and alcohol use, among others, have been shown to improve long-term freedom from AF and quality of life (Online Supplement 2). Assuming a disease continuum (**Figure 1**), the risk factors prospectively identified and validated in the study by Chatterjee et al. (8) and prior publications provide excellent intervention targets.

In order to generate the evidence base for HF prevention, comparative effectiveness research based on randomized controlled trials examining risk factor modification is needed. To date, there have been nearly 35 stroke prevention randomized controlled trials in AF, dating back to 1989. By contrast, there has not been a single prevention trial with incident HF as the primary outcome in patients with AF. Conducting a traditional, explanatory trial in patients with AF for the secondary prevention of HF that is well-powered and has longitudinal follow-up presently is too labor- and cost-intensive to be feasible. For example, assuming an incidence rate of 20 HF cases per 1,000 person-years, about 5,400 participants followed 5 years would be required to detect a relative effect of 0.70 with 80% power (Online Tables 1 and 2).

A pragmatic randomized trial in which patients are recruited at the point of care, and outcome data are extracted from already-existing electronic medical record databases (9), may ameliorate some of the feasibility issues. Careful screening of patients with AF to exclude those with prevalent HF or moderate-to-severe valvular heart disease, and rigorous adjudication of HF outcomes would be needed to ensure internal study validity. In addition, HF with reduced and preserved ejection fraction will need to be subtyped as different endpoints, given their different mechanisms and the potential for variation in effective prevention strategies. Another innovative design, the cohort multiple randomized controlled trial, could leverage existing AF cohorts by randomly selecting some eligible participants and offering the interventions. The HF outcomes of these selected participants would then be compared with the outcomes of eligible patients not selected (10).

There is now convincing evidence that HF prevention is an important management priority for patients with AF (3). Efforts to reduce HF incidence are critical to reduce the public health burden of AF. Several large, prospective observational studies have identified potential therapeutic targets of intervention. Pragmatic randomized controlled trials are needed to generate effective evidence-based strategies.

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APPENDIX For supplemental references and tables, please see the online version of this paper.