JACC: HEART FAILURE VOL. ■, NO. ■, 2016
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER http://dx.doi.org/10.1016/j.jchf.2016.05.001

Prevalence, Neurohormonal Correlates, and Prognosis of Heart Failure Stages in the Community

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ABSTRACT

OBJECTIVES The purpose of this study was to describe the prevalence and prognosis of HF stages in the community; to evaluate if preclinical HF stages are characterized by elevation of pro-inflammatory (C-reactive protein), neurohormonal activation (B-type natriuretic peptide, renin and aldosterone), and cardiac stress biomarkers (high-sensitivity troponin I, ST-2, and growth differentiation factor-15).

BACKGROUND The American Heart Association/American College of Cardiology heart failure (HF) classification has 3 stages. Knowledge regarding the community burden of HF stages is limited, and data on the biomarker profile associated with HF stages are scarce, although higher concentrations of certain biomarkers are associated with preclinical HF.

METHODS We evaluated 6,770 participants (mean age 51 years; 54% women) from the Framingham Study, defining 4 stages: 1) healthy: no risk factors; 2) stage A: presence of HF risk factors (hypertension, diabetes, obesity, coronary artery disease), no cardiac structural/functional abnormality; 3) stage B: presence of prior myocardial infarction, valvular disease, left ventricular (LV) systolic dysfunction, LV hypertrophy, regional wall motion abnormality, or LV enlargement; 4) stage C/D: prevalent HF.

RESULTS The prevalence of HF stages A and B were 36.5% and 24.2%, respectively, rising with age (odds ratio: 1.70 [95% confidence interval: 1.64 to 1.77] per decade increment). In age- and sex-adjusted models, we observed a gradient of increasing biomarker levels across HF stages ($p < 0.05$; $n = 3,416$). Adjusting for age and sex, mortality rose across HF stages (232 deaths, mean follow-up 7 years), with 2- and 8-fold mortality risks for stages B and C/D, respectively, compared with healthy.

CONCLUSIONS Approximately 60% of our sample has preclinical HF, and those in stage B had higher concentrations of HF biomarkers and experienced a substantial mortality risk. (J Am Coll Cardiol HF 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AHA/ACC = American Heart Association/American College of Cardiology

BMI = body mass index

BNP = B-type natriuretic peptide

CRP = C-reactive protein

CVD = cardiovascular disease

GDF = growth differentiation factor

HF = heart failure

hsTnI = high-sensitivity troponin I

LV = left ventricular

Given the high morbidity and mortality, and health care costs associated with heart failure (HF), prevention of HF is a public health priority. In this context, knowledge of the burden of preclinical precursors of HF in the community is a fundamental prerequisite to screen for and prevent the condition. The American Heart Association/American College of Cardiology (AHA/ACC) have categorized HF into 3 stages (A, B, C/D) (1) with 2 of these stages (A and B) being preclinical phases, i.e., they are characterized by elevated risk of HF without the overt syndrome (see the following section). Information regarding the burden of HF stages in the community and the mortality risk associated with these stages is quite limited (2). Additionally, investigators have reported that higher levels of biomarkers mirroring cardiac stress (such as B-type natriuretic peptide [BNP], growth differentiation factor [GDF]-15, high-sensitivity troponin I [hsTnI], and ST2) are associated with higher incidence of HF (3). Data on the biomarker profile associated with HF stages are limited, however, although some of the aforementioned biomarkers have been related individually to select preclinical HF phenotypes (such as left ventricular [LV] hypertrophy or systolic dysfunction) (4,5). More specifically, the prevalence of HF stages and their association with mortality has not been described in a non-hospital-based community sample. Additionally, the associations between HF stages and biomarkers of neurohormonal stress have not been comprehensively reported. Moreover, the relations of the HF stages with cardiovascular disease (CVD) and non-CVD mortality have not been reported. Accordingly, we estimated the prevalence of the various HF stages in the community, assessed the biomarker profile associated with these stages, and evaluated their prognosis using a large community-based sample. We hypothesized that: 1) the prevalence of preclinical HF stages increases with age and is higher in men versus women; 2) there is a gradient of increasing circulating concentrations of BNP, GDF-15, and hsTnI levels across the stages from healthy to preclinical to overt HF; and 3) preclinical HF is associated with considerable mortality risk, which is intermediate between the risk observed for 'healthy individuals and that observed among those with overt HF.

METHODS

STUDY SAMPLE. The description of the design, selection criteria, and sampling methods of the Framingham Offspring and Third Generation Studies has been reported (6,7). For the present investigation, we used 2 distinct samples. For assessing prevalence of the HF stages and for evaluating the prognostic significance of these stages, 3,021 participants of the Framingham Offspring cohort who attended the eighth examination cycle (2005 to 2008) and 4,095 participants of the Framingham Third Generation cohort attending the first examination (2002 to 2005) were eligible. Participants were excluded for the following reasons: renal insufficiency as indicated by serum creatinine levels ≥2 mg/dl (n = 21), missing components of HF stage classification (n = 48), and missing family classification (n = 277), resulting in a total sample of 6,770 participants (sample 1). Participants with renal insufficiency were excluded because the specificity of the Framingham Heart Study HF criteria may be limited in the presence of fluid overload states such as renal failure, and biomarker values could be inflated. For comparing levels of various biomarkers across the HF stages, we evaluated 3,532 participants of the Framingham Offspring cohort who attended the sixth examination cycle (1995 to 1998). Participants in this subsample were excluded for the following reasons: serum creatinine levels ≥2 mg/dl (n = 15), missing HF stage classification (n = 19), missing body mass index (BMI) (n = 38), and missing data on biomarkers of interest (n = 44), yielding a final sample of 3,416 participants (sample 2). We used 2 different samples for this investigation, driven by the availability of biomarker measurements in Offspring examination cycle 6, and the availability of components defining all heart failure stages in Offspring examination cycle 8 and Third generation examination cycle 1. The Boston University Medical Center Institutional Review Board approved all study protocols. Written informed consent was provided by all participants.

CLINICAL AND BIOMARKER MEASUREMENTS. Blood was drawn on all Heart Study participants in the morning after an overnight fast (typically between 7:30 AM and 9:00 AM), and the biosamples were stored at -80°C until assayed. Hypertension was defined as either having a systolic blood pressure of ≥140 mm Hg

significant consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Amgen, and Novartis. John R. Teerlink, MD, served as Guest Editor for this paper.

Manuscript received December 7, 2015; revised manuscript received March 22, 2016, accepted May 2, 2016.

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