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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;4:808–15)

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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

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

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TABLE 1 Clinical Characteristics of Study Samples

	Sample 1* (Primary Analyses)		Sample 2 (Biomarker Sample)	
	Women (n = 3,657)	Men (n = 3,113)	Women (n = 1,807)	Men (n = 1,609)
Age, yrs	51 ± 16	51 ± 16	59 ± 10	59 ± 10
Body mass index, kg/m^2	26.7 ± 6.1	28.3 ± 4.7	27.3 ± 5.7	28.5 ± 4.4
Obesity, %	24.2	29.1	25.6	30.3
Systolic blood pressure, mm Hg	120 ± 18	124 ± 15	127 ± 20	130 ± 17
Diastolic blood pressure, mm Hg	72 ± 9	77 ± 10	74 ± 9	77 ± 9
Hypertensive, %	29.8	38.5	38.4	44.8
Antihypertensive medication, %	23.1	27.2	25.4	30.8
Total cholesterol	190 ± 35	185 ± 37	212 ± 39	199 ± 41
HDL cholesterol	62 ± 17	48 ± 13	58 ± 16	43 ± 12
Lipid-lowering medication, %	18.6	25.6	0.9	1.2
Dyslipidemia, %	31.0	52.3	35.5	50.9
Fasting glucose, mg/dl	97 ± 20	103 ± 22	100 ± 26	107 ± 28
Diabetes, %	5.5	9.1	8.0	11.9
Diabetes medication, %	4.0	5.8	4.1	6.5
Smokers, %	13.2	14.3	15.8	14.6
Dyspnea, %	2.5	1.5	21.1	17.6
Edema, %	20.1	6.3	10.3	4.0
Valvular heart disease, %	2.2	3.2	3.7	6.4
LV mass	135 ± 29	194 ± 41	140 ± 31	192 ± 43
LV hypertrophy by ASE criteria, %	17.0	29.3	23.8	33.2
Regional wall motion abnormality, %	1.5	5.3	2.7	11.9
LV enlargement, %	3.3	1.9	3.7	5.3
LV systolic dysfunction, %	1.3	5.0	3.6	13.0
History of coronary artery disease, %	0.1	0.3	0.0	0.0
History of myocardial infarction, %	1.3	4.3	1.6	7.4
History of HF, %	0.8	1.6	0.7	1.4
HFPEF	55.2	21.6	53.8	18.2
HFREF	27.6	56.9	38.5	63.6
Undefined	17.2	21.5	7.7	18.2
HF stage frequencies, %				
Healthy	42.1	33.6	33.2	25.5
Stage A	38.6	33.9	42.5	39.0
Stage B	18.5	30.9	23.6	34.1
Stage C/D	0.8	1.6	0.7	1.4
Biomarkers†				
Aldosterone, ng/dl	-	-	11 (7, 15)	9 (7, 13)
B-type natriuretic peptide, pg/ml	-	-	10.0 (4.1, 20.3)	6.6 (4.0, 16.7)
C-reactive protein, mg/l	-	-	2.4 (1.0, 5.8)	1.8 (0.9, 3.8)
High-sensitivity cardiac troponin I, pg/ml	-	-	1.2 (0.8, 1.9)	1.6 (1.1, 2.7)
Growth differentiation factor-15, ng/l	-	-	1023 (813, 1305)	1064 (820, 1417)
Renin, mU/l	-	-	11 (6, 19)	14 (8, 25)
ST-2, ng/ml	-	-	18.8 (15.3, 23.2)	23.6 (19.2, 29.1)

Values are mean ± SD, %, or median (Q1, Q3). *Sample 1 includes participants from both Offspring and Third Generation cohorts (Online Table 4). †Aldosterone, C-reactive protein, renin, and ST-2 were considered only in secondary analyses.

HDL = high-density lipoprotein; HF = heart failure; HFPEF = HF with preserved ejection fraction; HFREF = HF with reduced ejection fraction; LV = left ventricular.

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 or diastolic blood pressure of ≥90 mm Hg or using antihypertension medication. Diabetes mellitus was defined as either having a fasting blood glucose value of ≥126 mg/dl or using glucose-lowering medication. Obesity was defined as having a BMI ≥30 kg/m^2. Coronary artery disease was defined as having a myocardial infarction (8). We measured circulating concentrations of biomarkers representing inflammation (C-reactive protein [CRP]), neurohormonal activation (BNP, renin, and aldosterone), and cardiac stress (hsTnI, ST-2, and GDF-15). These biomarkers were chosen because they have been associated to incidence of HF in a previous report from our group (3). BNP was measured with the Shionogi assay, ST2 with a high-sensitivity second-generation, enzyme-linked immunosorbent assay (Critical Diagnostics, San Diego, California; detection limit 2 ng/ml), hsTnI was measured with an ultrasensitive immunoassay using a novel, single-molecule counting technology (Singulex, with a detection limit is 0.2 pg/ml; range: 0.5 to 70 pg/ml), GDF15 levels were measured with a precommercial automated electrochemoluminescent immunoassay (Roche Elecsys, Basel, Switzerland; with a detection limit of <10 ng/l) (3). High-sensitivity CRP levels were measured with a Dade Behring BN100 nephelometer. Serum aldosterone levels were measured with a radioimmunoassay applied to extracted and fractionated serum (Quest Diagnostics, Cambridge, Massachusetts). Plasma renin concentrations were measured with an immunochemiluminometric assay (Nichols assay, Quest Diagnostics). The interassay coefficients of variation for each biomarker are as follows: CRP (2.2%); BNP (12.2%); aldosterone (4.0% for high concentrations and 9.8% for low concentrations); renin (2.0% for high concentrations and 10.0% for low concentrations); GDF-15 (8% to 10%); ST2 (<4%); and hsTnI(8%).

ECHOCARDIOGRAPHIC MEASUREMENTS. All study participants underwent standardized 2-dimensional transthoracic echocardiography with Doppler color flow imaging. A sonographer or a cardiologist (experienced in echocardiography) read all echocardiograms; all readers were blinded to biomarker results and clinical information. We averaged digital M-mode measurements from 3 or more cardiac cycles and estimated the LV internal dimensions in end-diastole and systole, and the diastolic thicknesses of the LV posterior wall and the interventricular septum. All measurements were made using the leading edge technique and following the American Society of

Echocardiography guidelines for echocardiographic measurements (9). Excellent reproducibility of echocardiographic measurements has been previously reported (10). The interobserver variability ranged from 0.9% to 5% for LV diastolic dimensions, 2% to 2.9% for LV posterior wall thickness in diastole, 3.6% to 6.5% for the interventricular septum in diastole, and 0.8% to 4% for LV mass. The intraobserver variability was measured from 0.3% (LV diastolic dimensions) to 4% (interventricular septal thickness). Abnormal LV systolic function was defined as having a fractional shortening value of <0.29 or qualitative assessment of borderline/mild ejection fraction (mild systolic dysfunction), or having a fractional shortening <0.22 or qualitative assessment of moderate/severe ejection fraction (moderate/severe systolic dysfunction).

OUTCOME EVENTS. The outcome of interest was all-cause mortality during follow-up after the eighth examination cycle. All deaths were verified using information from medical records, local obituaries, and national death registries. Heart failure was defined based on the Framingham criteria (11).

STATISTICAL ANALYSIS. We used a categorical variable to classify participants into the healthy category or 1 of the 3 HF stages, as reported by the AHA/ACC (5): 1) healthy: healthy participants with no HF risk factors, or symptoms of dyspnea or physical sign of edema; 2) stage A: participants with at least 1 HF risk factors (hypertension; diabetes; obesity; coronary artery disease defined by myocardial infarction, angina pectoris, or coronary insufficiency), but with no cardiac structural/functional abnormality on imaging studies; 3) stage B: participants with any of the following: prior myocardial infarction, valvular heart disease, or echocardiographic evidence of asymptomatic LV systolic dysfunction, hypertrophy by American Society of Echocardiography criteria, enlargement or any regional wall motion abnormality; and 4) stage C/D: participants with prevalent HF. In secondary analyses, stage C/D was further classified based on ejection fraction measured near the time of HF: HF with preserved ejection fraction, HF with reduced ejection fraction, and HF with unknown ejection fraction.

We described the prevalence of HF stages by sex using samples 1 and 2 separately. For analysis, we considered the following age groups: <55 years, 55 to <65, 65 to <75 years, and ≥75 years for an easier comparison with the prevalence of HF stages in Olmsted County as reported by Ammar et al. (2).

Using sample 1, we examined cross-sectional associations of the HF stages (dependent variables) with age and sex (predictor variables) using 3 separate logistic regression models corresponding to the definition of the variable representing the HF stages (i.e, ≥stage A vs. healthy, ≥stage B vs. ≤stage A, and stage C/D vs. others).

Using sample 2, we examined cross-sectional association of log-transformed biomarkers (dependent variables, separate model for each biomarker) with HF stages using analysis of covariance, adjusting for age and sex, and further adjusting for BMI in separate models. HF stage was modeled as a continuous variable to test for trend across HF stages and also as categorical variable, treating healthy as the reference group. Primary analyses included circulating BNP, GDF-15, and hsTnI, whereas ST-2, CRP, aldosterone, and renin were included in secondary analyses, given their association with HF in select reports. Additionally, we graphically presented the least square means of the log-transformed standardized biomarkers adjusting for age, sex, and further adjusting for BMI. Furthermore, we plotted the means of biomarkers across the numbers of risk factors, and also created Cox proportional hazards regression models among those in stage B to evaluate whether participants having stage B and also highest biomarker levels were at highest risk of developing overt HF (stage C/D). Finally, we have created tertiles of the biomarkers GDF-15, BNP, and hsTnI, and we have categorized individuals belonging in stage B (n = 976) into 3 groups: 1) those having all biomarker values in the lowest tertiles; 2) those having at least 2 biomarkers in the highest tertile; and 3) all other participants. We used this grouping variable to create Cox proportional hazards regression models to compare the groups with regards to risk of developing HF (stage C/D).

FIGURE 1 Prevalence of Heart Failure Stages by Age Group

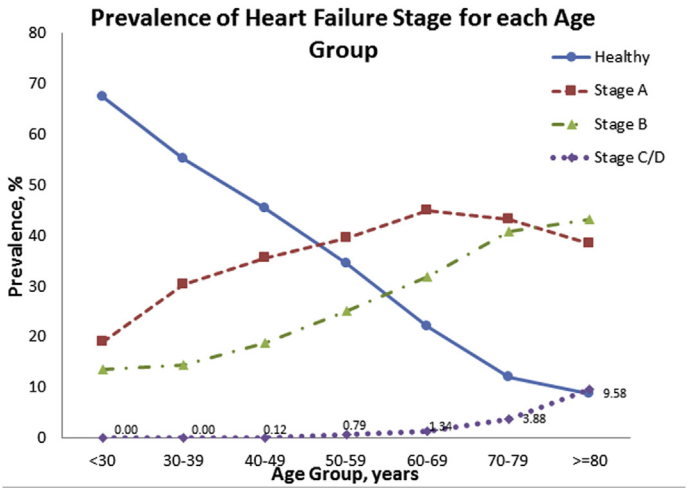
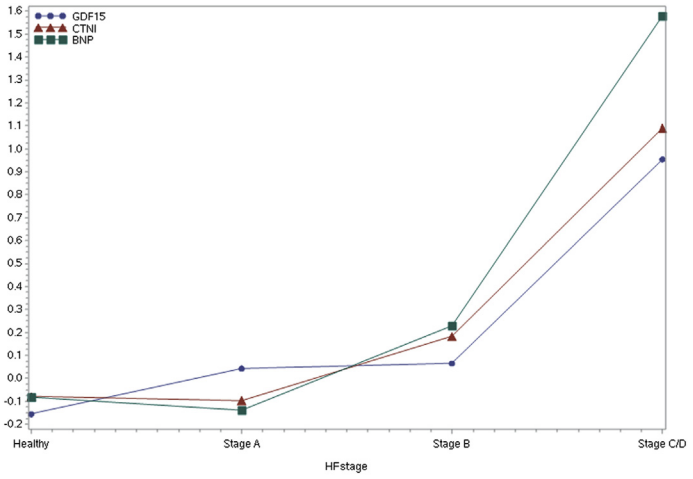


FIGURE 2 Age- and Sex-Adjusted Standardized Biomarker Means by HF Stage



BNP = B-type natriuretic peptide; GDF = growth differentiation factor; HF = heart failure.

Last, we evaluated the association between the HF stages and all-cause mortality using age- and sex-adjusted Cox proportional hazards regression models (12), after confirming that the proportionality of hazards assumption was met. We adjusted for familial associations to account for potential correlations between parents, children, and siblings. We also evaluated the interactions of HF stage with age and sex including the corresponding interaction terms in separate models. We also related HF stages 0-B to the incidence of overt HF by calculating incidence rates.

Statistical significance was assessed based on a 2-sided p value of <0.05. The SAS software, version 9.3 (Cary, North Carolina), was used for all analyses.

RESULTS

The baseline characteristics of both study samples are shown in **Table 1**. Participants were middle-aged to older, with a mean BMI in the overweight range. About 60% of individuals in our sample had preclinical HF (stage A or B) (Online Table 1), of which nearly 24% had stage B HF and the remaining 36% had stage A HF. The prevalence of stages B and C/D and HF with reduced ejection fraction was substantially higher in men versus women, whereas HF with preserved ejection fraction was more prevalent among women. We also observed an increasing trend in the prevalence of stages A, B, and C/D as age increased (**Figure 1**); this was confirmed in sex-adjusted models in which we observed a statistically significant association between advancing age and the greater odds of having preclinical or clinical HF using 3 different reference categories (Online Table 2). Compared with women, men had 1.6-fold higher odds of having prevalent preclinical or clinical HF (Online Table 2). Notably, age- and sex-adjusted concentrations of circulating biomarkers rose with increasing HF stage ($p < 0.0001$ for BNP, GDF-15, and hsTnI) (**Figure 2**, Online Table 3, Online Figure 1), findings that remain mostly unchanged upon additional adjustment for BMI. Additionally, biomarker levels increased across the number of risk factors (in stage A), as shown in Online Figure 2. Finally, in age- and sex-adjusted Cox proportional hazard regression models, individuals belonging in stage B and also having highest levels of biomarkers were at 4 times the hazard of developing overt HF (stage C/D) as compared with those having lowest values of biomarkers (hazard ratio: 4.03, $p = 0.02$). Notably, among the individuals in stage B, those with biomarker values in the highest tertiles were at higher risk of HF compared with those with biomarker values in the lowest tertiles. In prospective analyses, there were 232 deaths (43% women) over a mean follow-up period of approximately 7 years (maximum 10 years). Incidence rates of death rose across the HF stages (**Table 2**). Higher HF stages were associated with a greater risk of death compared to Healthy, adjusting for age and sex (hazard ratio: 1.63 (95% confidence interval: 1.37 to 1.93) **Figure 3**. Additionally, 88 deaths (of the total 232) were observed among those in stage B, and it is noteworthy that 69% of those deaths were due to non-CVD causes. We did not observe a

TABLE 2 Mortality Rates Associated With HF Stages in the Community

HF Stage	No. Events/No. at Risk	Person-Years at Risk	Crude Incidence Rate*	Age- and Sex-Adjusted Death Rate (95% CI)†	HR (95% CI)	p Value for HR
Healthy	23/2,585	17,934	0.128	2.92 (0.12-4.50)	Referent	Referent
Stage A	90/2,468	15,506	0.580	4.11 (2.82-5.35)	1.97 (1.24-3.13)	0.0042
Stage B	88/1,637	9,992	0.881	4.80 (2.97-6.53)	2.07 (1.29-3.34)	0.0027
Stage C/D	31/80	362	8.564	12.52 (7.67-16.72)	7.83 (4.61-13.28)	<0.0001

*Data shown are number per 100 person-years. †Risk of death over 8 years.
CI = confidence interval; HF = heart failure; HR = hazard ratio.

statistically significant interaction between sex and HF stage on the incidence of death. Finally, we observed increasing rates for incidence of HF across HF stages (**Table 3**, Online Figure 3).

DISCUSSION

PRINCIPAL FINDINGS. Our findings are 3-fold. First, we observed that a very high proportion (~60%) of middle-aged and older adults had preclinical HF defined as stage A or B according to the AHA/ACC classification schema. A higher proportion of men were classified into more advanced HF stages compared with women. As expected, the prevalence of HF stages increased with age. Of note, nearly 38% of people between ages 65 to 75 years and 43% of those older than age 75 years had evidence of preclinical HF stage B. Additionally, 32% of people <55 years were classified as stage A HF. Second, higher HF stages were associated with greater circulating concentrations of cardiac stress biomarkers, and demonstrated evidence of systemic inflammation and neurohormonal activation. Of note, stage B HF was associated with a 2-fold mortality hazard and stage C/D with a 8-fold risk compared with healthy individuals. Interestingly, 69% of deaths occurring among participants with stage B were due to non-CVD causes, which is likely from the presence of comorbidities leading to death before progressing to HF. Finally, we observed increasing incidence rates for HF across the HF stages 0, A, and B.

COMPARISON WITH THE PUBLISHED LITERATURE. The comparison of HF stages between our sample and the one used by Ammar et al. (6) showed significant differences in the prevalence of all stages, notably among those with stages A and B (**Table 4**). Contrary to the study by Ammar et al. (6), we did not observe a statistically significant interaction between sex and HF stage on the incidence of death.

We observed a high prevalence of preclinical HF in our sample, similar to an earlier report (2) from the Olmsted County. Ammar et al. also reported increasing circulating BNP concentrations with higher HF stages (2). Our study confirmed these results for blood BNP levels, and expanded the biomarker profile to include 7 biomarkers reflecting inflammation, neurohormonal activation, and cardiac stress. Of note, we observed that participants in stage B had a 2-fold mortality hazard compared with those who were healthy. The Mayo Clinic report (2) demonstrated such an association only among men in their sample (hazard ratio: 4.0). To our knowledge, this finding of increased mortality in both sexes with stage B HF has not been reported previously. The differences between the present investigation and the Mayo Clinic report may stem from several important differences between the 2 studies. The participants in the sample from the Olmsted County were older. Moreover, the categorization in the age groupings are very different (notably 60%, 17%, 14%, and 9% in the Framingham Heart Study cohort vs. 30%, 31%, 25%, and 14% in the Olmsted County cohort for the <54, 55 to 64, 65 to 74, and >75 years categories, respectively). The mean follow-up in our study was longer (7 years) compared with the Mayo Clinic study (median follow-up 5.5 years). Our sample was larger and included a wider age range compared with the smaller Mayo clinic sample. Additionally,

FIGURE 3 Survival of Participants According to Heart Failure Stages

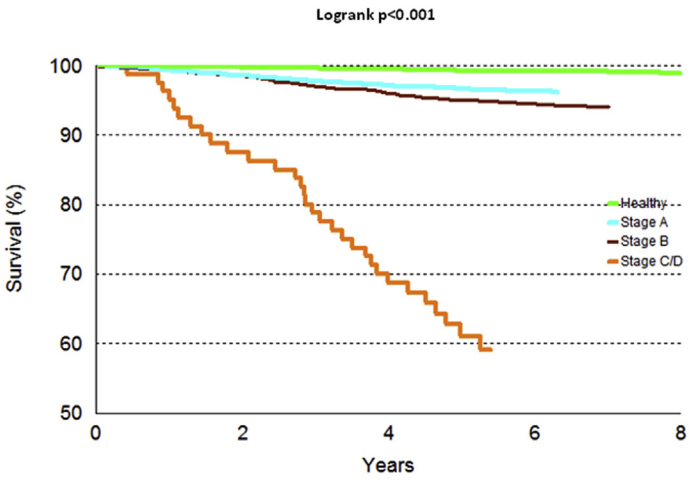


TABLE 3 HF Incidence Rates Associated With HF Stages in the Community

HF Stage	Women			Men			Pooled		
	No. Events/ No. at Risk	Person-Years at Risk	Incidence Rate	No. Events/ No. at Risk	Person-Years at Risk	Incidence Rate	No. Events/ No. at risk	Person-Years at Risk	Incidence Rate
Healthy	0/476	2,807	0.00	0/234	1,379	0.00	0/710	4,186	0.00
Stage A	19/772	4,180	0.45	14/559	3,063	0.46	33/1,331	7,242	0.46
Stage B	15/450	2,395	0.63	35/575	3,059	1.14	50/1,025	5,454	0.92

Values are number per 100 person-years.
HF = heart failure.

TABLE 4 Comparison of Prevalence of HF Stages in FHS and Mayo Clinic

	FHS*					Mayo Clinic Study				
HF Stage	**≤54 yrs**	**55–64 yrs**	**65–74 yrs**	**≥75 yrs**	**Total**	**45–54 yrs**	**55–64 yrs**	**65–74 yrs**	**≥75 yrs**	**Total**
Healthy	2,050 (50.1)	332 (28.5)	146 (15.9)	57 (9.5)	2,585 (38.2)	281 (46.9)	225 (36.0)	107 (20.9)	27 (9.3)	640 (31.5)
A	1,317 (32.2)	500 (42.9)	407 (44.4)	244 (40.7)	2,468 (36.4)	167 (27.9)	157 (25.1)	94 (18.3)	36 (12.3)	454 (22.4)
B	719 (17.6)	315 (27.1)	346 (37.7)	257 (42.9)	1637 (24.2)	138 (23.0)	202 (32.3)	237 (46.2)	114 (39.0)	691 (34.1)
C/D	4 (0.1)	17 (1.5)	18 (2.0)	41 (6.9)	80 (1.2)	13 (2.2)	41 (6.6)	75 (14.6)	115 (39.4)	244 (12.0)
Total	4,090	1,164	917	599	6,770	599	625	513	292	2,029

Values are frequencies (%). *Participants from Offspring Exam 8 and Generation 3 Exam 1.

there were minor differences in the constituent criteria for the different HF stages in the 2 reports; for example, the definitions of LV hypertrophy varied across these studies and the Mayo report used the Goldman SAS questionnaire, which was not used in our study.

Additionally, Wang et al. have reported that higher circulating biomarker levels mirroring cardiac stress are associated with the incidence of HF (3). Other investigators have also reported higher circulating concentrations of neurohormones and CRP in individuals with precursors of HF such as LV systolic dysfunction and LV hypertrophy (4,5). The present study compares the biomarker profile across the HF stages using a comprehensive panel of biomarkers.

STRENGTHS AND LIMITATIONS. The use of a large community-based sample including the echocardiographic database with comprehensive phenotyping for LV hypertrophy, and systolic dysfunction, and evaluation of an extensive panel of putative biomarkers implicated in preclinical and overt HF strengthen our investigation. Additionally, we combined cross-sectional prevalence data with longitudinal prognostic information to truly capture the community burden of preclinical and overt HF. A few limitations merit comment. Our sample was predominantly white and middle-aged, which limits the generalizability of our results to other ethnicities and age groups not evaluated. Although our follow-up was longer than that in the Mayo Clinic report, we may underestimate the true risk of mortality associated with preclinical HF stages over a longer period of follow-up. Furthermore, individuals with stages A and B HF likely progress over time to overt HF, and the mortality risk in these stages may reflect disease progression itself. We did not specifically evaluate this premise. Finally, separate samples were used for the evaluation of incidence of death and biomarker analyses, based on the availability of data.

CONCLUSIONS

In our large community-based sample, a substantial proportion of individuals (nearly 60%) had prevalent preclinical HF (stages A and B). A staggering 83% of people older than age 65 years have preclinical HF, and preclinical stage B HF doubled the mortality hazard relative to healthy people. These observations may serve as forebodings of a substantial rise in the morbidity and mortality resulting from HF in the community in the future. Consistent with our hypotheses, higher HF stages were associated with increased biomarker levels, consistent with activation of different biological pathways across the disease continuum. The likelihood that most individuals with stage B HF will die of non-CVD causes before they experience overt HF underscores the importance of targeting prevention efforts at comorbidities at the earlier HF stages to avoid death.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The AHA/ACC classify HF into 4 stages, 2 of which are preclinical. Nearly 60% of middle-aged to older individuals in the community has preclinical HF, higher circulating concentrations of key HF biomarkers, and experiences a substantially elevated risk of death.

TRANSLATIONAL OUTLOOK: Preclinical HF stages may be characterized by elevation of pro-inflammatory, stress and neurohormonal biomarkers as well as with higher risk of death, underscoring the importance of targeting prevention efforts at comorbidities at the earlier HF stages to avoid death.

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APPENDIX For supplemental tables and figures, please see the online version of this article.