Prevalence and Prognostic Significance of Heart Failure Stages

Application of the American College of Cardiology/American Heart Association Heart Failure Staging Criteria in the Community

Khawaja Afzal Ammar, MD; Steven J. Jacobsen, MD, PhD; Douglas W. Mahoney, MS; Jan A. Kors, PhD; Margaret M. Redfield, MD; John C. Burnett, Jr, MD; Richard J. Rodeheffer, MD

Background—Heart failure (HF) is a progressive disorder associated with frequent morbidity and mortality. An American Heart Association/American College of Cardiology staging classification of HF has been developed to emphasize early detection and prevention. The prevalence of HF stages and their association with mortality are unknown. We sought to estimate HF stage prevalence in the community and to measure the association of HF stages with mortality.

Methods and Results—A population-based, cross-sectional, random sample of 2029 Olmsted County, Minnesota, residents aged ≥45 years was identified. Participants were classified by medical record review, symptom questionnaire, physical examination, and echocardiogram as follows: stage 0, healthy; stage A, HF risk factors; stage B, asymptomatic cardiac structural or functional abnormalities; stage C, HF symptoms; and stage D, severe HF. In the cohort, 32% were stage 0, 22% stage A, 34% stage B, 12% stage C, and 0.2% stage D. Mean B-type natriuretic peptide concentrations (in pg/mL) increased by stages: stage 0=26, stage A=32, stage B=53, stage C=137, and stage D=353. Survival at 5 years was 99% in stage 0, 97% in stage A, 96% in stage B, 75% in stage C, and 20% in stage D.

Conclusions—The present study provides prevalence estimates and prognostic validation for HF staging in a community cohort. Of note, 56% of adults ≥45 years of age were classified as being in stage A (risk factors) or B (asymptomatic ventricular dysfunction). HF staging underscores the magnitude of the population at risk for progression to overt HF. **(*Circulation*. 2007;115:1563-1570.)**

Key Words: heart failure ■ epidemiology ■ prevention ■ ventricular dysfunction

Current evidence indicates that heart failure (HF) is usually a progressive condition that begins with risk factors for cardiac dysfunction, proceeds to asymptomatic changes in cardiac structure and function, and then evolves into clinically overt HF, disability, and death.[1,2] In recognition of the importance of this concept, a joint statement from the American Heart Association (AHA) and the American College of Cardiology (ACC) proposed a novel HF model that classifies HF into stages: stage A, HF risk factors; stage B, asymptomatic cardiac structural or functional abnormalities; stage C, symptomatic HF; and stage D, end-stage HF (Table 1).[1] This model emphasizes progressive pathophysiology and underscores the importance of early detection and prevention of symptomatic HF.

Clinical Perspective p 1570

The prevalence of the proposed HF stages in the community has not been determined. The prognostic implications of such a classification are unknown. Our objectives were to (1) estimate the prevalence of HF stages in a population-based cohort of 2029 adults aged ≥45 years, (2) provide neurohumoral validation of the staging model by measuring the association between B-type natriuretic peptide (BNP) concentration and HF stages, and (3) determine the prognostic significance of HF stages.

Methods

The Mayo Foundation and Olmsted Medical Center Institutional Review Boards approved the present study, and subjects gave informed consent.

Study Setting

In 2000, 90% of the 112 255 residents of Olmsted County, Minnesota, were white, 81% were urban, and 11% were ≥65 years of age. Since 1966, the Rochester Epidemiology Project has maintained an infrastructure for conducting population-based research, including a unified and indexed medical record system for inpatient and outpatient care.[3,4]

Received March 9, 2006; accepted December 18, 2006.

From the Division of Cardiovascular Diseases (K.A.A., M.M.R., J.C.B., R.J.R.) and Division of Epidemiology (S.J.J., D.W.M.), Mayo Clinic and Foundation, Rochester, Minn; and the Department of Medical Informatics (J.A.K.), Erasmus University Medical Center, Rotterdam, the Netherlands.

Correspondence to Khawaja Afzal Ammar, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail ammar.khawaja@mayo.edu

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.666818**

TABLE 1. Stages of HF

HF Stage	AHA/ACC Guideline Description	As Operationally Defined in the Present Study
0		Without HF risk factors or abnormal ventricular structure or function; SAS class I
A	Patients at high risk of developing HF because of the presence of a condition strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.	Hypertension,* diabetes mellitus,*† obesity,* coronary artery disease (excluding myocardial infarction)† without abnormal ventricular structure or function; SAS class I
B	Patients with structural heart disease that is strongly associated with the development of HF but without HF signs or symptoms	SAS class I with any of the following abnormalities: history of MI,† systolic dysfunction,*† echocardiographically determined LVH,*† LV enlargement,*† ECG-determined LVH,*† DD,* echocardiographic valvular heart disease,*† and LV regional wall-motion abnormality*†
C	Patients with current or prior symptoms of HF associated with underlying structural heart disease	LV structural or functional abnormality plus symptoms: stage C_1 had SAS class II to III symptoms but did not fulfill Framingham HF criteria; stage C_2 fulfilled Framingham criteria.
D	Patients with advanced structural heart disease and refractory symptoms of HF requiring specialized interventions	History of HF and SAS class IV functional status

MI indicates myocardial infarction; LVH, left ventricular hypertrophy; and DD, diastolic dysfunction. Adapted from Hunt et al.[1]
*Inclusion recommended by literature review.[2]
†Inclusion recommended in AHA/ACC guidelines.[1]
*†Inclusion recommended by both literature review and AHA/ACC guidelines.[1,2]

Population Sampling and Data Collection

A random sample of Olmsted County residents ≥45 years of age on January 1, 1997, was identified. A population sampling fraction of 7% was applied within each gender and age-specific (5 years) stratum. Of the 4203 subjects invited, 2042 (49%) participated. Participation bias was evaluated: Medical record abstraction of 500 randomly selected participants and 500 randomly selected nonparticipants showed no difference in cardiovascular disease prevalence between the groups.[5] The 2042 subjects in the present study cohort are the subject of previous publications.[6–12] Thirteen participants were excluded from analysis due to indeterminate prior myocardial infarction status or missing information on Goldman Specific Activity Scale, which left 2029 subjects.

Enrollment began January 1, 1997, and ended September 30, 2000. Each subject completed a self-administered questionnaire that included the Goldman Specific Activity Scale (SAS) and had a physical examination, 12-lead ECG, and echocardiogram. Medical records were abstracted by trained nurse abstractors, as described previously.[6] The median length of participant medical record archive was 36 years. Confirmed HF was diagnosed if Framingham criteria were fulfilled.[13–19] Diabetes was based on the presence of physician diagnosis and treatment in the medical record. Myocardial infarction and hypertension were diagnosed with criteria from the World Health Organization and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, respectively.[20,21] Plasma BNP concentration was measured by the Biosite method.[7]

Determination of Symptoms and Functional Status

The Goldman SAS questionnaire was used to ascertain symptoms and their associated functional limitation.[22] This self-administered questionnaire evaluates symptoms during 21 specific activities that have known metabolic equivalents (METS) of energy expenditure. It categorizes functional status into 4 ordinal classes: class I=able to perform activity equivalent to ≥7 METS exercise capacity without limiting symptoms; class II=5 to 7 METS; class III=2 to 5 METS; and class IV to <2 METS. A modification of the SAS was made to determine functional limitation from dyspnea or fatigue. Fluid retention was defined as treatment for edema or shortness of breath that caused ≥10-lb weight loss over 5 days.

Echocardiographic Analysis

All subjects underwent echocardiography according to a standardized protocol as described previously.[6,11,12] A single echocardiologist (M.M.R.), masked as to the clinical status of each patient, interpreted all echocardiograms.

Defining HF Stages

Using the proposed HF stages as a template, stage 0 was defined as healthy and without HF risk factors[1] (Table 1). Stage A was defined by the presence of HF risk factors without cardiac structural or functional abnormality. Only risk factors that have been predictive of HF in longitudinal studies were used (hypertension, diabetes mellitus, obesity [defined as body mass index ≥30 kg/m^2], and coronary artery disease; Table 1).[1,2] Age >65 years and male sex are also well-established risk factors for HF[2]; they are not modifiable, however, and their inclusion would (1) lead to an overestimate of the size of the pool of stage A subjects and (2) reduce the ability to measure the impact of age and sex on the association of HF stages and mortality. Therefore, age and sex were not used to assign stage A but were used to stratify and adjust multivariable analyses.

Stage B, asymptomatic ventricular dysfunction, was defined with clinical, ECG, and echocardiographic abnormalities shown to be predictive of incident HF: prior myocardial infarction, left ventricular hypertrophy (LVH), valvular heart disease, regional wall-motion abnormality, left ventricular (LV) enlargement, and systolic and diastolic dysfunction.[2,23–26] The asymptomatic state was defined as being SAS class I (able to exercise at ≥7 METS without fatigue or dyspnea). To generate normative reference data for LVH, a healthy subset of 653 participants was derived by excluding those with cardiac disease by medical record review, valvular heart disease, hypertension, or body mass index ≥30 kg/m^2 and those taking cardiac drugs. LVH was defined by ventricular mass/height >2 SDs above the mean in this disease-free subset, ie, >145.7 g/m in men and >125.2 g/m in women.

LV enlargement was defined by indexing LV end-diastolic dimension (LVEDD) to height. Height is obesity independent, and indexing LVEDD by height has been shown to be predictive of HF.[25] LV enlargement was present in men if LVEDD (in mm) >27+(16.6×height [in meters]) and in women if LVEDD (in mm) >28.3+(13.9×height [in meters]).

Ejection fraction (EF) was measured by M-mode, biplane Simpsons, and 2-dimensional visual estimate. EF (mean [SD]) among participants without cardiovascular disease was similar by M-mode (63.5% [6.5%]), biplane Simpsons (63.9% [6.7%]), and 2-dimensional visual estimate (63.3% [5.4%]) methods; the prevalence of EF <50% in the entire cohort was 6.5% by M-mode or

TABLE 2. Characteristics of the Cohort

	Stage 0	Stage A	Stage B	Stage C	Stage C_1	Stage C_2	Stage D	Total, n
Women	339 (53)	216 (48)	346 (50)	151 (63)	132 (68)	19 (43)	2 (40)	1054
Men	301 (47)	238 (52)	345 (50)	88 (37)	63 (32)	25 (57)	3 (60)	975
Myocardial infarction	0	0	55 (8)	42 (18)	23 (12)	19 (43)	4 (80)	101
Diabetes mellitus	0	53 (12)	59 (9)	37 (15)	25 (13)	12 (27)	4 (80)	153
Hypertension	0	197 (43)	256 (37)	138 (58)	110 (56)	28 (63)	4 (80)	595
HF*	0	0	0	44 (18)	0	44 (100)	5 (100)	49
Coronary artery disease	0	42 (9)	116 (17)	83 (35)	50 (26)	33 (75)	3 (60)	244
BMI >30 kg/m^2	0	309 (68)	234 (34)	112 (47)	93 (48)	19 (43)	3 (60)	658

Data are presented as number of persons (column percent). BMI indicates body mass index.
*HF defined by Framingham criteria.

biplane Simpsons and 6.0% measured by 2-dimensional visual estimate.[5] Because the correlation among methods was so high, and a visual estimate was available in 99.7% of participants, the visual estimate was used in the analysis. Systolic dysfunction was defined as EF $<50\%$.[1,5] As described previously, diastolic dysfunction (DD) was assessed by pulsed-wave Doppler examination of mitral flow (before and during Valsalva maneuver) and pulmonary venous inflow, as well as Doppler tissue imaging of the mitral annulus.[6,10] DD was graded on a 4-point ordinal scale: normal; mild DD=abnormal relaxation without increased LV end-diastolic filling pressure (decreased E/A ratio <0.75); moderate or "pseudonormal" DD=abnormal relaxation with increased LV end-diastolic filling pressure (E/A 0.75 to 1.5, deceleration time >140 ms, and 2 other Doppler indices of elevated LV end-diastolic filling pressure); or severe DD=advanced reduction in compliance, with restrictive filling (E/A ratio of >1.5, deceleration time <140 ms, and Doppler indices of elevated LV end-diastolic filling pressure). For subjects in atrial fibrillation, diastolic function was classified as indeterminate unless restrictive physiology (E/A >1.5, deceleration time <140 ms) was present. Echocardiographic diastolic function could be determined in 1774 subjects. Asymptomatic valvular heart disease was determined if an SAS class I subject had moderate to severe echocardiographic valvular disease or valvular disease diagnosed on medical record review.

To account for all subjects who described exertional dyspnea and fatigue (SAS score II to III=exercise capacity 2 to 7 METS), it was necessary for stage C to include C_1 "mild" and C_2 "advanced" substages (Table 1). Stage C_1 was defined as structural or functional abnormality and exercise limitation from dyspnea or fatigue (SAS score of class II to III) but not fulfilling the more specific Framingham HF criteria.[12,16] Stage C_2 subjects had an SAS score of class II to III and fulfilled the Framingham HF criteria. Stage D "end-stage" HF subjects were defined as having an SAS score of class IV, indicating severe functional limitation of <2 METS.

Mortality Data

In the Rochester Epidemiology Project, mortality data are collected by reviewing community medical records, death certificates, and obituary notices. Participants were assessed for mortality by November 1, 2004, at which time they were censored. This provided 11 210 person-years of follow-up (median 5.5 years) with 129 deaths. Active surveillance of the first 974 persons recruited to participate in follow-up identified no additional deaths.

Statistical Analysis

Categorical data are summarized as a percent of the group total with corresponding 95% CIs based on the normal approximation, and comparison between groups were based on the χ^2 test for association. Continuous variables are summarized as mean$\pm$SD, and comparisons between groups were based on ANOVA models. Post-ANOVA comparisons of continuous variables were based on the t test, but no adjustments for multiple comparisons were made. Time to death was summarized with the Kaplan-Meier estimate. Comparisons between groups were based on the log-rank test for univariate analyses and Cox proportional hazards regression models when adjusting for confounders such as age and gender. The assumption of proportional hazards was tested for the model, and no significant departure was found. Two-sided probability values <0.05 were considered significant. Analyses were performed on JMP version 5 (SAS Institute, Cary, NC).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Prevalence of HF Stages

Participant characteristics are provided in Table 2. In the present study cohort, 640 persons (31.5%; 95% CI, 19.0% to

TABLE 3. Prevalence of HF Stages, Stratified by Age

HF Stage	45–54 y	55–64 y	65–74 y	≥75 y	Total
0	281 (46.9)	225 (36.0)	107 (20.9)	27 (9.3)	640 (31.5)
A	167 (27.9)	157 (25.1)	94 (18.3)	36 (12.3)	454 (22.4)
B	138 (23.0)	202 (32.3)	237 (46.2)	114 (39.0)	691 (34.1)
C	13 (2.2)	41 (6.6)	74 (14.4)	111 (38.0)	239 (11.8)
C_1	9 (1.5)	32 (5.1)	65 (12.7)	89 (30.5)	195 (9.6)
C_2	4 (0.7)	9 (1.4)	9 (1.8)	22 (7.5)	44 (2.2)
D	0 (0)	0 (0)	1 (0.2)	4 (1.4)	5 (0.2)
Total	599	625	513	292	2029

Data are presented as number of persons (column percent).

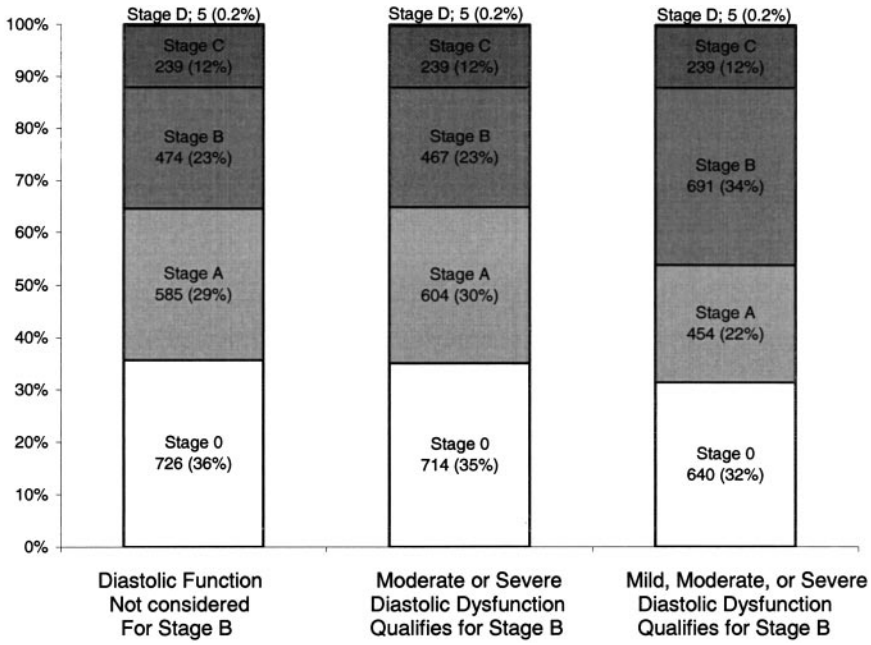

Figure 1. The effect of including diastolic ventricular dysfunction as a qualifying abnormality for stage B HF on HF stage prevalence.

34.0%) were classified as normal (stage 0; Table 3). Stage A (HF risk factors) included 454 persons and accounted for 22.4% (95% CI, 20.6% to 24.2%) of the cohort. Stage B, with asymptomatic structure or function, comprised 691 persons and accounted for 34.1% (95% CI, 32.0% to 36.0%) of the cohort. Because stage B is a clinically silent group not likely to undergo clinical evaluation, we examined the range of asymptomatic abnormalities that resulted in stage B assignment: 60% (n=364) had DD, 34% (n=188) had LV enlargement, 5% (n=36) had echocardiographically moderate or severe valvular heart disease, 24% (n=133) had echocardiographic LVH, 10% (n=66) had systolic dysfunction, 8% (n=55) had a history of myocardial infarction, 7% (n=51) had regional wall-motion abnormalities, and 2% (n=16) had ECG LVH. Because 217 individuals entered stage B based only on DD, we further evaluated the impact of DD on stage B prevalence (Figure 1). Stage B prevalence decreased from 34% to 23% if only moderate or severe DD was considered as abnormal and remained 23% if DD was not considered as a stage B–qualifying abnormality. Fifty-eight subjects in stage B had physical signs of HF (edema, increased jugular venous pressure, or third heart sound) but not Goldman SAS class II to III symptom limitations that would classify them as stage C. This group had similar all-cause mortality to stage B subjects without physical signs of HF (data not shown) and were classified as stage B rather than stage C.

Stage C, which comprised 239 persons with symptomatic HF, accounted for 11.8% (95% CI, 10.5% to 13.3%) of the cohort. Within stage C, 195 persons were classified as early stage C_1, with dyspnea and fatigue limitations on the SAS questionnaire but not meeting the Framingham HF criteria, which accounted for 9.6% (95% CI, 8.0% to 11.0%) of subjects. Forty-four stage C_2 subjects (2.2%; 95% CI, 1.6% to 2.9%) met the Framingham HF criteria. Stage C_1 subjects had fewer abnormalities of cardiac structure and function than stage C_2 subjects (Table 4). Five stage D persons with end-stage HF represented 0.2% (95% CI, 0.1% to 0.6%) of the cohort.

The prevalence of stages B through D increased with advancing age (Table 3). The age distribution of HF stages was similar in men and women (data not shown).

BNP Levels in HF Stages

Mean plasma BNP concentration increased from stage 0 (26 pg/mL; CI 20 to 32 pg/mL) to stage A (32 pg/mL; 95% CI, 25 to 40 pg/mL), stage B (53 pg/mL; 95% CI, 47 to 59 pg/mL), stage C_1 (117 pg/mL; 95% CI, 106 to 128 pg/mL), stage C_2 (222 pg/mL; 95% CI, 199 to 245 pg/mL), and stage D (353 pg/mL; 95% CI, 279 to 428 pg/mL; $P<0.0001$ by ANOVA). Post-ANOVA comparisons of BNP levels at each stage revealed that BNP was significantly ($P<0.05$) greater in each successive stage from B through D. BNP in advanced stage C_2 was significantly higher than mild C_1. Stage 0 and stage A BNP levels were not different from each other but were significantly lower than BNP levels in stage B.

Survival Analysis

HF stages were associated with progressively worsening 5-year survival rates (Figure 2): stage 0 98.9% (95% CI, 98.0% to 99.0%), stage A 97.0% (95% CI, 94.3% to 98.8%), stage B 95.7% (95% CI, 94.2% to 97.3%), stage C (C_1+C_2)

TABLE 4. Frequency of Echocardiographic Abnormalities in Mild C_1 and Advanced C_2 Subgroups

	C_1	C_2
EF <50%	14%	52%
EF <40%	5%	34%
DD	74%	90%
LV wall-motion abnormalities	11%	41%
LA volume index, cm^2/m^2	29±0.7	50±1.5

LA indicates left atrial.

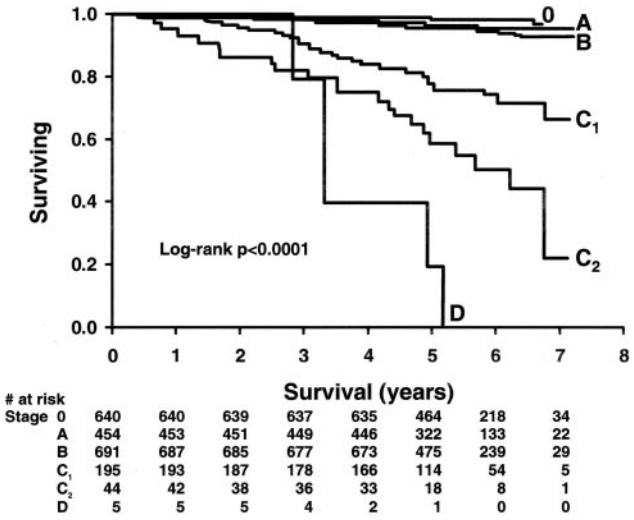

Figure 2. Survival curves according to HF stage.

74.6% (95% CI, 68.9% to 80.4%), early stage C_1 78.0% (95% CI, 72.0% to 84.0%), advanced stage C_2 60.0% (95% CI, 40.0% to 75.0%), and stage D 20.0% (95% CI, 15.0% to 55.0%). HF stages A through D were associated with progressively increasing all-cause mortality hazard ratios (HRs) compared with stage 0, both with (Table 5) and without (results not shown) adjustment for age and sex. Deterioration from stage B to C and from stage C to D was associated with significant incremental increases in HR: stage B versus A, HR=1.7 (95% CI, 0.9 to 3.3; P=0.1); stage C versus B, HR=9.6 (95% CI, 6.8 to 13.6; P<0.0001); and D versus C, HR=5.3 (95% CI, 1.9 to 12.1; P=0.004). Cox proportional hazards analysis, stratified by gender, showed that men had a higher HR than women at any stage and a 4- to 6-fold higher risk in stages B and C (Table 6).

Discussion

This study applies ACC/AHA HF staging in a community population to clarify our understanding of the burden of ventricular dysfunction and HF in adults >45 years of age. The analysis provides a coherent cross-sectional picture of HF from its preclinical risk factors to its advanced manifestations in a single uniformly evaluated, randomly selected, population-based cohort. Although 32% of subjects were healthy (stage 0), 22% carried the burden of HF risk factors (stage A), 34% demonstrated asymptomatic abnormalities of cardiac structure or function (stage B), and 12% manifested structural and functional abnormalities and overt HF symptoms (stages C and D). HF stages were associated with progressively increasing plasma BNP concentration and progressively higher 5-year mortality rates.

TABLE 5. Cox Proportional Hazard Analyses for 5-Year All-Cause Mortality According to HF Stage, Adjusted for Age and Sex

	Deaths/Persons in Stage, n	HR (95% CI)	P*
Age >65 vs <65 y		1.09 (1.06–1.10)	<0.0001
Male sex		2.4 (1.7–3.4)	<0.0001
Stage A	13/454	1.6 (0.7–3.9)	0.23
Stage B	33/691	1.8 (0.9–4.0)	0.08
Stage C	68/239	8.7 (4.4-18.8)	<0.0001
Stage C_1	47/195	7.3 (3.6–15.9)	<0.0001
Stage C_2	21/44	15.0 (6.9–34.7)	<0.0001
Stage D	5/5	31.5 (9.5–92.3)	<0.0001

*Each stage compared with stage 0 HF, in which there were 10 deaths among 640 persons.

HF as a Progressive Condition

Longitudinal studies show that cardiac injury causes progressive chamber remodeling.[26–32] Increased chamber size and decreased ventricular function lead to symptomatic HF, with its attendant morbidity and mortality. Early diagnosis and intervention are advocated to prevent disease progression.[33]

Stage A: HF Risk Factors

The selection of HF risk factors to define stage A was intentionally conservative. Risk factors prospectively demonstrated to predict incident cases of HF were used: hypertension, diabetes mellitus, obesity, and coronary artery disease.[2] Inclusion of less rigorously established risk factors would have further increased the size of stage A at the expense of stage 0. Even so, the presence of HF risk factors in 22% of persons highlights the number of persons in whom risk factor management is indicated.

Stage B: Asymptomatic Cardiac Dysfunction

The magnitude of stage B prevalence depends on the cardiac structure and function abnormalities used to select persons for this category and on the criteria chosen to distinguish asymptomatic from symptomatic persons. Only echocardiographic abnormalities shown to predict incident HF cases or mortality were chosen: increased LV mass, LVEDD, LV DD, or decreased LV EF.[2,6,26–32] Inclusion of other echocardiographic parameters could have further increased the relative size of stage B. To be considered asymptomatic, subjects had to be SAS class I, indicating the ability to perform activities requiring ≥7 METS of exercise capacity without fatigue or dyspnea limitations.

A 34% prevalence of stage B asymptomatic ventricular dysfunction among persons ≥45 years of age suggests the size of the population in whom early identification of abnormal ventricular structure and function may be important. This HF stage also describes a group in whom clinical trials of early pharmacological intervention for systolic and diastolic dysfunction are appropriate.

A unique aspect of the present study is the ability to include a graded measurement of diastolic function in the definition of stage B. Recent studies have shed light on the substantial contribution that DD plays in HF with preserved EF,[6,34,35] the prognostic significance of diastolic HF,[6,35] and the increasing proportion of HF patients who manifest primarily diastolic HF. The current ACC/AHA criteria[1] reflect an increased recognition of the role of DD in the evolution of HF, and a comprehensive HF staging scheme is enhanced if it can take into account the role of DD in the progression to HF with normal EF.

TABLE 6. Cox Proportional Hazard Analysis of All-Cause Mortality for CHF Staging in Men and Women

	Men			Women		
Stage	Deaths/Persons in Stage, n	HR* (95% CI)	*P*	Deaths/Persons in Stage	HR* (95% CI)	*P*
A	6/238	1.9 (0.5–6.9)	0.32	7/216	1.6 (0.5–4.9)	0.42
B	25/345	4.0 (1.3–11.9)	0.0110	8/346	0.9 (0.3–2.7)	0.84
C	37/88	26.0 (8.9–75.9)	<0.0001	31/151	6.6 (2.6–16.5)	<0.0001
C_1	24/63	22.0 (7.3–66.1)	<0.0001	23/132	5.5 (2.1–14.1)	<0.0001
C_2	13/25	38.4 (12.1–121.9)	<0.0001	8/19	14.7 (4.9–44.3)	<0.0001
D	3/3	60.4 (12.8–286.1)	<0.0001	2/2	48.7 (9.3–254.9)	<0.0001

*Each stage compared with stage 0 HF. Results of the model adjusted for age, sex, stage, and interactions between age and sex with stage. The interaction between sex and stage was significant ($P=0.0293$). Individual testing indicated that most of the sex differences came from differences in responses between male and female stage B ($P=0.0466$) and stage C ($P=0.0494$) patients.

Stage C: Overt HF

To be classified as stage C, subjects had to have abnormality of LV structure or function and score as class II to III on the Goldman SAS (functional limitation from dyspnea or fatigue at an exercise level of 2 to 7 METS). The 12% prevalence of stage C is considerably higher than the prevalence of overt HF previously reported in population cohorts, including this one, that have used a clinical definition such as the Framingham criteria to identify HF.[13,16,19] In the present study, application of the Framingham criteria (stage C_2) identified 2.2% of the population, a prevalence comparable to other studies of HF prevalence in this age range.[5,16,19] However, in recognition of persons with echocardiographic ventricular dysfunction who have functional limitation from fatigue or dyspnea but do not yet fulfill the Framingham criteria, the present study included all persons with ventricular dysfunction who were Goldman SAS class II to III in its definition of stage C symptomatic HF. This broader definition of symptomatic HF identified a larger group, stage C_1, which accounted for 9.6% of the population. The validity of this broader definition of symptomatic HF is borne out by the doubling of plasma BNP from stage B (53 pg/mL) to stage C_1 (117 pg/mL). There is also a substantial decrease in 5-year survival between stage B and stage C_1 (from 96% to 78%), which suggests that C_1 subjects with ventricular dysfunction and functional limitation who do not yet fulfill the Framingham HF criteria should be considered to have overt HF.

Plasma BNP and HF Stages

Plasma BNP concentrations have been shown to be associated with LV dysfunction and to have independent prognostic value for hospitalization and mortality events.[36] In the present study, plasma BNP concentrations rose incrementally and significantly from HF stages A through D, providing a neurohormonal correlate across the stages.

Association of HF Stages With Mortality

Five-year survival decreased most sharply at the transition from stage B asymptomatic LV dysfunction to stage C symptomatic HF, from 96% to 75%. Stage B was a significant mortality predictor in an unadjusted model and continued to be a significant predictor after adjustment for sex; however, after adjustment for age, it lost statistical significance, which implies a strong association between stage B abnormalities and age.

Clinical Implications

The development of stage B is associated with increased mortality risk in men. Transition from stage B to stage C_1 is associated with a 5-fold increase in mortality risk in both men and women, which suggests that the development of even mild exercise limitations portends a significant increase in risk. These findings underscore the importance of identifying persons as early as stage B (asymptomatic), and certainly at stage C_1 (mildly symptomatic), for early diagnosis and intervention.

Strengths and Limitations

The strengths of the present study include its randomly selected population-based sample, the availability of medical records with a 36-year median length of archive, uniform collection of cross-sectional data, and standardized echocardiographic measurements. A unique strength is the Doppler-echocardiographic assessment of diastolic function. The use of the Goldman SAS for classification of functional status impairment based on a series of specific questions reduces bias that may result from an unstructured interview technique such as the New York Heart Association HF classification.

In our attempt to use only HF risk factors prospectively proven to be predictive of HF, we may have generated an excessively conservative prevalence estimate of stage A. Future studies may need to include more clinical or echocardiographic risk factors if they are prospectively proven to be independent predictors of HF.

The cross-sectional nature of the study limits the ability to eliminate survivor bias, to assess time-dependent changes, and to make cause-effect inferences. Long-term follow-up will be necessary to fully assess the risk of progression from stage A to stage C. The small number of stage D subjects limits the power to make meaningful observations about end-stage HF. Owing to the small number of deaths, the mortality risk ratio CIs are wide, which indicates a relative lack of power for sex-specific mortality analysis.

Retrospective assignment of HF stage classification to participants could lead to misclassification. However, because data were collected prospectively, without knowledge of the forthcoming ACC/AHA staging definitions, class assignment bias was avoided.

This predominantly white cohort includes only persons ≥45 years of age, so conclusions cannot be generalized to the entire US population. Participation bias has been evaluated: Medical record abstraction of a random selection of 500 participants and 500 invited nonparticipants showed no difference in cardiovascular disease.[4] However, 5-year all cause mortality was 94% among participants and 87% among nonparticipants, which suggests an element of participation bias.

Conclusions

This study shows that the proposed classification of HF into stages A through D is conceptually, biohormonally, and prognostically sound. The high prevalence of stages A and B and the worsening prognosis associated with progression to stage C signal a need for the development of diagnostic and treatment strategies to prevent progression from asymptomatic ventricular dysfunction to symptomatic HF.

Acknowledgment

We thank Tammy S. Burns for expert manuscript preparation.

Sources of Funding

This study was supported by grants from the Public Health Service (National Institutes of Health [NIH] HL 555902 to Dr Rodeheffer, NIH AR30582 to Dr Jacobsen, NIH HL 62381 to Dr Redfield, and NIH HL 36634 to Dr Burnett) and by the Mayo Clinic Foundation.

Disclosures

None.

References

1. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Circulation*. 2005;112:1825–1852.
2. Kenchaiah S, Narula J, Vasan RS. Risk factors for heart failure. *Med Clin North Am*. 2004;88:1145–1172.
3. Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am*. 1981;245:54–63.
4. Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996;71:266–274.
5. Jacobsen SJ, Mahoney DW, Redfield MM, Bailey KR, Burnett JC Jr, Rodeheffer RJ. Participation bias in a population-based echocardiographic study. *Ann Epidemiol*. 2004;14:579–584.
6. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.
7. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40:976–982.
8. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation*. 2004;109:3176–3181.
9. Costello-Boerrigter LC, Boerrigter G, Redfield MM, Rodeheffer RJ, Urban LH, Mahoney DW, Jacobsen SJ, Heubelin DM, Burnett JC. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community. *J Am Coll Cardiol*. 2006;47:345–353.
10. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol*. 2005;45:87–92.
11. Munagala VK, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Association of newer diastolic function parameters with age in healthy subjects: a population-based study. *J Am Soc Echocardiogr*. 2003;16:1049–1056.
12. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age-and gender-related ventricular-vascular stiffening: a community-based study. *Circulation*. 2005;112:2254–2262.
13. Kannel WB, Belanger AJ. Epidemiology of heart failure. *Am Heart J*. 1991;121:951–957.
14. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971;285:1441–1446.
15. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347:1397–1402.
16. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol*. 1992;20:301–306.
17. Mosterd A, Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, Grobbee DE. Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol*. 1997;13:491–502.
18. Senni M, Tribouilloy CH, Rodeheffer RJ, Evans JM, Jacobsen SJ, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation*. 1998;98:2282–2289.
19. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. *Am J Cardiol*. 2000;86:1090–1096.
20. Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. *Am Heart J*. 1984;108:150–158.
21. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (published correction appears in *Arch Intern Med* 1998;158:573). *Arch Intern Med*. 1997;157:2413–2446.
22. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation*. 1981;64:1227–1234.
23. Gardin JM, Siscovick D, Anton-Culver H, Lynch JC, Smith VE, Klopfenstein HS, Bommer WJ, Fried L, O'Leary D, Manolio TA. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly: the Cardiovascular Health Study. *Circulation*. 1995;91:1739–1748.
24. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol*. 1987;59:956–960.
25. Lauer MS, Larson MG, Levy D. Gender-specific reference M-mode values in adults: population-derived values with consideration of the impact of height. *J Am Coll Cardiol*. 1995;26:1039–1046.
26. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation*. 2003;108:977–982.
27. St. John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S, Menapace FJ Jr, Parker PO, Lewis S, Sestier F, Gordon DF, McEwan P, Bernstein V, Braunwald E. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction: the protective effects of captopril. *Circulation*. 1994;89:68–75.
28. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med*. 1997;336:1350–1355.
29. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, Shelton B. Left ventricular function/congestive heart failure: effects of long-term enalapril therapy on cardiac structure and function in

patients with left ventricular dysfunction: results of the SOLVD Echocardiography Substudy. *Circulation*. 1995;91:2573–2581.
30. Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). *Am J Cardiol*. 1992; 70:1180–1184.
31. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. *Circulation* 1993;87:VI-17–VI-23.
32. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.
33. Cohn JN. The prevention of heart failure: a new agenda. *N Engl J Med*. 1992;327:725–727.
34. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2001;37:1042–1048.
35. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259.
36. Rodeheffer RJ. Measuring plasma B-type natriuretic peptide in heart failure: good to go in 2004? *J Am Coll Cardiol*. 2004;44:740–749.

CLINICAL PERSPECTIVE

Heart failure (HF), a major form of cardiac disease associated with high morbidity and mortality, is increasing in prevalence. The American Heart Association and American College of Cardiology proposed the concept of heart failure staging to emphasize the progression from HF risk factors to asymptomatic cardiac dysfunction to clinically overt HF. The prevalence of HF stages in the community is unknown. This cross-sectional, population-based, community study of 2029 persons ≥45 years old provides prevalence estimates for HF stages: 22% of persons had risk factors for HF (stage A), 34% had asymptomatic abnormalities of cardiac structure/function (stage B), 12% had HF symptoms associated with abnormalities of cardiac structure/function (stage C), and 0.2% had end-stage HF (stage D). HF stages were associated with a progressive increase in plasma B-type natriuretic peptide concentration and with progressively severe 5-year mortality rates. In total, 56% of adults ≥45 years of age have HF risk factors or asymptomatic cardiac dysfunction and constitute a target population for HF prevention efforts. Longitudinal community studies will be necessary to clarify the rate of progression through the HF stages and to assess the impact of prevention and treatment strategies on HF progression.