Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Progression of Preclinical Heart Failure

A Description of Stage A and B Heart Failure in a Community Population

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BACKGROUND: The aims of this study are to evaluate the rate of progression of preclinical (Stage A and B) heart failure, identify associated characteristics, and evaluate long-term outcomes.

METHODS: Retrospective review of the Olmsted County Heart Function Study. Individuals categorized as Stage A or B heart failure at initial visit that returned for a second visit 4 years later were included. Logistic regression analyses evaluated group differences with adjustment for age and sex.

RESULTS: At visit 1, 413 (32%) individuals were classified as Stage A and 413 (32%) as Stage B. By visit 2, 146 (35%) individuals from Stage A progressed with the vast majority (n=142) progressing to Stage B. In comparison, a total of 23 (6%) individuals progressed from Stage B. A greater rate of progression was seen for Stage A compared with Stage B (8.7 per 100 person-years [95% CI, 7.4–10.2] versus 1.4 per 100 person-years [95% CI, 0.9–2.1]; $P<0.001$). NT-proBNP correlated with progression for Stage B ($P=0.01$), but not for Stage A ($P=0.39$). A multivariate model found female sex (odds ratio, 1.65 [95% CI, 1.05–2.58]; $P=0.03$), increased E/e' (odds ratio, 1.13 [95% CI, 1.02–1.26], $P=0.02$), and beta blocker use (odds ratio, 2.19 [95% CI, 1.25–3.82], $P=0.006$) were associated with progression for Stage A. There was a signal that cardiovascular mortality was higher in individuals who progressed, although not statistically significant ($P=0.06$ for Stage A and $P=0.05$ for Stage B).

CONCLUSIONS: There is significant progression of preclinical heart failure in a community population, with progression rates higher for Stage A. NT-proBNP correlated with progression for Stage B, but not for Stage A. No statistically significant differences in long-term outcomes were seen. Study results have clinical implications important to help guide future heart failure screening and prevention strategies.

Key Words biomarkers ■ heart failure ■ prevalence

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WHAT IS KNOWN

- There is a high prevalence of preclinical heart failure (Stages A and B).
- Individuals with preclinical heart failure carry an increased risk of progression to clinical heart failure.

WHAT THE STUDY ADDS

- To the authors' knowledge, this is the first study to describe the progression rate of preclinical heart failure in a community population.
- A range of abnormal echocardiographic features were seen in those who progressed; however, left ventricular systolic dysfunction was uncommon and the majority of those who progressed from Stage A to B had moderate/severe diastolic dysfunction.
- The cardiac biomarker, NT-proBNP, was predictive of progression for Stage B individuals but not for Stage A.

In 2001, the American College of Cardiology/American Heart Association introduced a new classification system for heart failure (HF) consisting of 4 stages: Stage A, those with HF risk factors; Stage B, asymptomatic cardiac structural or functional abnormalities; Stage C, symptomatic HF; and Stage D, end-stage HF; to better characterize the progressive nature of the disease.[1,2] Stage A and B HF encompass patients without clinical symptoms; thus, these stages are collectively referred to as preclinical HF.

There has been increasing interest in preclinical HF, and various studies have examined the prevalence. Specifically, Ammar et al utilized the Olmsted County Heart Function Study and provided prevalence estimates of the various HF stages. They reported 56% of adults ≥45 years of age were classified as having preclinical HF (Stage A/B).[3] In addition, multiple studies have demonstrated individuals with preclinical HF carry an increased risk of progression to clinical HF (Stage C/D) and increased mortality.[3–8]

While the prevalence and outcomes of individuals with preclinical HF in the community have been well described, there remains a gap in knowledge about the natural history and rate of progression of persons with preclinical HF. Within the Olmsted County Heart Function Study, there is a unique opportunity to evaluate community individuals at 2 time points to monitor for progression of preclinical HF. The objectives of the current study were to determine the rates of progression of Stage A and B HF in a community population, identify characteristics associated with progression, and evaluate long-term cardiovascular outcomes.

METHODS

The authors declare that all supporting data are available within the article (and its Data Supplement).

Study Design

This study involved a retrospective review of the Olmsted County Heart Function Study. The institutional review boards of Mayo Clinic and Olmsted Medical Center approved this study. Participants provided written informed consent for evaluation and medical record follow-up.

Study Population

The Olmsted County Heart Function Study has previously been well defined.[3,9–12] Briefly, the cohort is a population-based random sample of 2042 Olmsted County, Minnesota residents aged ≥45 years who underwent clinical evaluation, medical record abstraction, and comprehensive Doppler echocardiography at visit 1 (1997–2000). After visit 1, all participants were invited to return, with 82 participants having passed away before visit 2. In total, 1402 of the 1960 surviving visit 1 participants (72%) returned for visit 2. Of those, 826 participants were categorized as either Stage A or B HF at visit 1 and were included in the current analysis. All data collected at visit 1 was again collected at visit 2.

Definition of HF Stages

Stage A was defined as no previous diagnosis of HF and normal echocardiogram with one or more of the following: coronary artery disease (CAD), hypertension, diabetes, or obesity (defined as body mass index, ≥30 kg/m^2). A normal echocardiogram was defined as left ventricular (LV) ejection fraction (EF) ≥50%, no significant valve disease on echocardiogram (defined by less than or equal to moderate in severity), normal LV mass index (LVMI), normal left atrial volume index (LAVI), and normal LV size. As a marker of CAD, individuals with previous myocardial infarction were included in Stage A if they had no history of HF and no evidence of a structural or functional abnormality, as evidenced by a normal echocardiogram.

Stage B was defined as no previous diagnosis of HF and evidence of a structural or functional abnormality including the following: LV EF <50%,[3,12,13] diastolic dysfunction at least moderate in severity, LV hypertrophy (LVMI>134 g/m^2 for men and >110 g/m^2 for women),[14] significant valve disease per echocardiogram (defined as greater than moderate in severity), presence of regional wall motion abnormalities on echocardiogram, enlarged left ventricle (indexed LV end diastolic dimension to height, >27+(16.6×height [in meters]) for men and >28.3+(13.9×height [in meters]) for women, reported in mm),[3,15] or abnormal LAVI (>33 mL/m^2 for men and >30 mL/m^2 for women).[16,17]

Both preclinical diastolic dysfunction and preclinical systolic dysfunction, respectively, have been associated with an increased risk of clinical HF and increased risk of mortality.[8,10,18–23] Accordingly, multiple studies have included preclinical diastolic dysfunction as Stage B, including the present study.[3,5,10,24,25]

Progression and Follow-Up

On average, visit 2 was completed 4 years (range, 2.7–5.2) after visit 1 for all individuals. Based on data collected at visit

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2, individuals were placed into one of the 2 categories. Those who remained in the same HF stage or regressed were classified as Did Not Progress. Individuals who advanced in HF stage were classified as Progressed. Incident heart failure that developed between visit 1 and visit 2 was diagnosed by the Framingham criteria. After visit 2, incident heart failure was diagnosed by *International Classification of Diseases-Ninth Revision* codes, which were assigned by trained coders according to physician diagnoses in outpatient and inpatient records (not by hospital billing records).[10,20,26] Individuals were then followed after visit 2 to assess long-term cardiovascular outcomes, which included all-cause mortality, cardiovascular mortality, and development of clinical HF for Stage A; and all-cause mortality and cardiovascular mortality for Stage B. The median follow-up period for evaluation of long-term outcomes was 8.3 (IQR, 7.6–9.3) years after visit 2.

Echocardiography

Comprehensive echocardiographic assessment was performed using standardized instruments and techniques, as previously reported.[10,27,28] At visits 1 and 2, echocardiography was performed by 1 of 3 registered diagnostic sonographers and reviewed by 2 cardiologists. Clinicians performing studies at visit 2 were masked to both visit 1 clinical and echocardiogram findings. Diastolic function was assessed by pulsed-wave Doppler examination of mitral flow (before and during Valsalva), Doppler tissue imaging of the mitral annulus, and pulmonary venous flow; and then categorized as normal, mild, moderate, or severe.[10]

Additional Data

Demographics, comorbidities, and medication use were obtained from the electronic medical record. Diabetes was based on physician diagnosis and treatment. Myocardial infarction and hypertension were diagnosed according to 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.[29,30] Cardiovascular death was defined using primary coded cause of death (*International Classification of Diseases-Tenth Revision*) from Minnesota death records.

Statistical Analysis

Baseline characteristics are presented as number (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median (interquartile range) for non-normally distributed variables. Progression was defined at visit 2,and continuous baseline characteristics at visit 1 were compared between groups using linear regression analyses on raw or log-transformed continuous variables, as appropriate. Logistic regression analyses were used to compare categorical variables between groups. These analyses include age and sex as covariates to control for differences between groups. The progression rates for Stage A and B HF were compared using Poisson regression.

Further evaluation of biomarkers was performed using logistic regression models to evaluate the association between progression and continuous biomarkers in addition to age and sex. Results from logistic regression analyses are presented as odds ratios (ORs) and 95% CIs. Biomarkers were log-transformed before analyses, and ORs are presented per 1 SD. Results were also summarized using receiver operative characteristic curves, and the area under the curve was compared between models using the DeLong and DeLong test.

Long-term outcome data were defined from visit 2 and is based on the Kaplan-Meier product-limit method, and patients without event were censored at last known follow-up. Cox proportional hazards regression analyses were used to compare outcomes between groups after adjusting for age and sex. Proportional hazards assumptions were examined by plotting scaled Schoenfeld residuals versus time. A formal test was done by testing for correlation between the residual and time. All analyses were performed using SAS version 9.4 (Cary, NC). Two-sided tests were used, and $P<0.05$ was set as the level of significance.

RESULTS

Baseline Characteristics

At visit 1, 413 individuals were classified as Stage A and 413 as Stage B (Table 1). Stage B individuals were older and more likely to be female ($P<0.001$ for both). Higher prevalence of hypertension was seen for Stage A ($P<0.001$). Those in Stage B had lower EF (62% versus 64%, $P<0.001$), with 26 individuals (6%) having EF <50%. Stage B subjects had higher LAVI, E/e', and LVMI compared with Stage A ($P<0.001$ for all, Table 1). Lastly, higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (106.6 versus 50.2 pg/mL, $P<0.001$), HS-Troponin (3.7 versus 2.8 pg/mL, $P<0.001$), and NT-ANP (2556 versus 1931 pg/mL, $P<0.001$) were seen in Stage B compared with Stage A.

Stage A HF: Progressed Versus Did Not Progress

Of individuals classified as Stage A at visit 1 (n=413), 146 (35%) progressed in HF stage by visit 2 (Figure 1). The rate of progression was 8.7 cases per 100 person-years of follow-up, 95% CI (7.4–10.2). Of those who progressed, 142 (34%) individuals progressed to Stage B and 4 (1%) to clinical HF (Stage C/D). Of the 142 individuals who progressed to Stage B, only 4 (2.6%) had EF <50%, and the majority had moderate/severe diastolic dysfunction (Figure 2). In those who progressed to Stage C/D, only 1 individual (25%) had EF<50%.

Comparison of Baseline Characteristics

Individuals who progressed by visit 2 (n=146) were older ($P=0.005$) and more likely to be female ($P=0.01$, Table 2). These individuals were more likely to have hypertension ($P=0.04$) and CAD ($P=0.04$). Individuals who progressed had higher LAVI ($P=0.03$) and higher E/e' ($P=0.008$). NT-ProBNP (71.0 versus 41.4 pg/mL, $P=0.03$) and NT-ANP (2516 versus 1701 pg/mL, $P=0.04$, Table 2) were higher in those who progressed. Greater use of

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Table 1. Baseline Characteristics at Visit 1 (1997–2000)

	Stage A (N=413)	Stage B (N=413)	Age/sex adjusted *P* value
Age, y, mean (SD)	60.8 (8.8)	64.0 (10.2)	<0.001
Female, n (%)	177 (43)	235 (57)	<0.001
BMI, kg/m^2, mean (SD)	31.2 (5.1)	28.9 (5.4)	<0.001
Comorbidities			
Prior myocardial infarction, n (%)	14 (3)	28 (7)	0.04
Diabetes, n (%)	48 (12)	35 (8)	0.08
Hypertension, n (%)	192 (46)	158 (38)	<0.001
Obesity,* n (%)	270 (65)	157 (38)	<0.001
Coronary artery disease, n (%)	56 (14)	74 (18)	0.20
Hyperlipidemia, n (%) (n=781)	82 (21)	106 (27)	0.11
Medication use (n=781)			
Aspirin, n (%)	153 (39)	151 (39)	0.93
Beta blocker, n (%)	73 (19)	99 (26)	0.08
Calcium channel blocker, n (%)	31 (8)	40 (10)	0.52
Diuretic,† n (%)	97 (25)	73 (19)	<0.001
Statin, n (%)	82 (21)	106 (27)	0.11
Angiotensin receptor blocker, n (%)	9 (2)	12 (3)	0.82
ACE inhibitor, n (%)	49 (12)	38 (10)	0.43
Echocardiogram			
EF, %, mean (SD)	64.0 (5.2)	62.4 (7.3)	<0.001
EF<50%, n (%)	…	26 (6)	…
Left atrial volume index, mL/m^2, mean (SD), (n=779)	22.4 (4.5)	29.7 (8.6)	<0.001
E/e', mean (SD) (n=688)	8.20 (2.39)	9.79 (3.32)	<0.001
Left ventricular mass index, g/m^2, mean (SD), (n=666)	92.5 (14.8)	107.0 (22.6)	<0.001
Diastolic dysfunction, mild, n (%) (n=766)	81 (21)	59 (16)	<0.001
Diastolic dysfunction, moderate or severe, n (%) (n=766)	…	115 (31)	…
Significant valve disease, n (%)	…	34 (8)	…
Regional wall motion abnormality, n (%)	…	35 (8)	…
Biomarkers‡			
Creatinine, mg/dL (n=803)	0.9 (0.8–1.0)	0.8 (0.7–0.9)	0.01
NT-proBNP,§ pg/mL (n=735)	50.2 (18.1–103.4)	106.6 (44.4–218.5)	<0.001
HS-troponin,‖ pg/mL (n=774)	2.8 (1.8–4.7)	3.70 (2.2–5.9)	<0.001
NT-atrial natriuretic peptide,¶ pg/mL (n=766)	1931 (1220–2958)	2556 (1666–3801)	<0.001

ACE indicates angiotensin-converting enzyme; BMI, body mass index; EF, ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Defined as BMI ≥30 kg/m^2.

†Loop, thiazide-based, and potassium sparing diuretics included.

‡Numbers shown are median (25th–75th percentile).

§Normal reference range: 10–138 pg/mL for males and 10–263 pg/mL for females.[31–33]

‖Normal reference range ≤40 pg/mL.[34,35]

¶Normal reference range: 365±104 pg/mL for ages 20–30 y and 438±72 pg/mL for ages 55–70 y.[36]

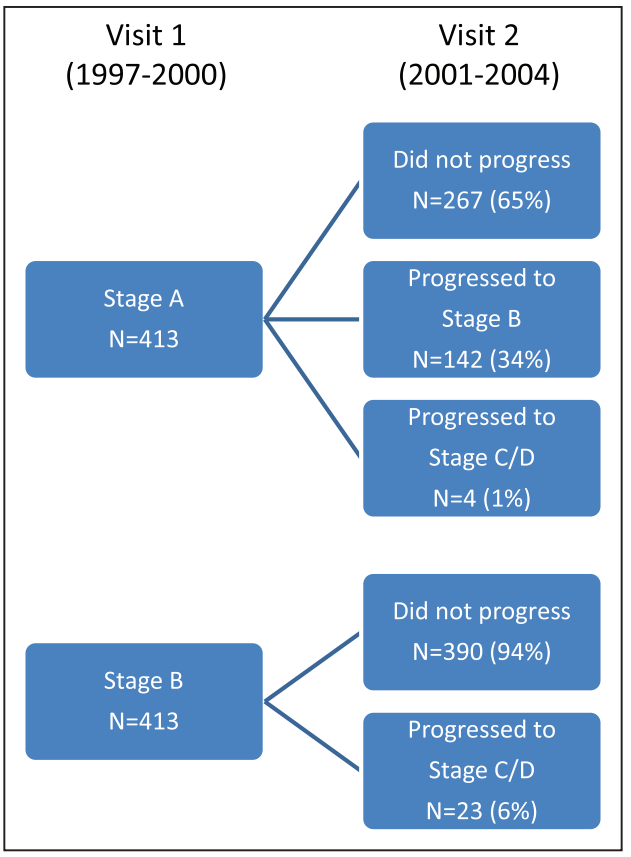

Figure 1. Progression in heart failure stage from Visit 1 (1997–2000) to Visit 2 (2001–2004).
The number (percentage) of those with Stage A and B heart failure at visit 1 who progressed in heart failure stage by visit 2. Rate of progression for Stage A was higher at 8.7 cases per 100 person-years of follow-up (95% CI, 7.4–10.2), compared with 1.4 cases per 100 person-years of follow-up (95% CI, 0.9–2.1) for Stage B (*P*<0.001).

beta blocker therapy was seen in those who progressed from Stage A (*P*<0.001, Table 2).

A multivariable logistic regression model was created including variables which were associated with progression for Stage A. After adjustment, female sex (OR, 1.65 [95% CI, 1.05–2.58], *P*=0.03), increased E/e' (OR, 1.13 [95% CI, 1.02–1.26], *P*=0.02), and beta blocker use (OR, 2.19, 95% CI (1.25, 3.82), *P*=0.006) remained associated with progression for Stage A. Obesity was more common in those who did not progress from Stage A (*P*<0.001, Table 2). In the multivariate model, obesity was associated with lower risk of progression from Stage A (OR, 0.52 [95% CI, 0.32–0.84], *P*=0.008).

Long-Term Outcomes Following Visit 2

When individuals who progressed from Stage A were compared with those who did not progress, differences were seen in cardiovascular mortality with 5 events occurring in those who progressed versus 1 event in those who did not progress; however, this was not statistically significant (hazard ratio [HR], 8.10 [95% CI, 0.92–70.85], *P*=0.06, Figure 3A). There were no differences in the development of clinical (Stage C/D) HF (HR, 1.69

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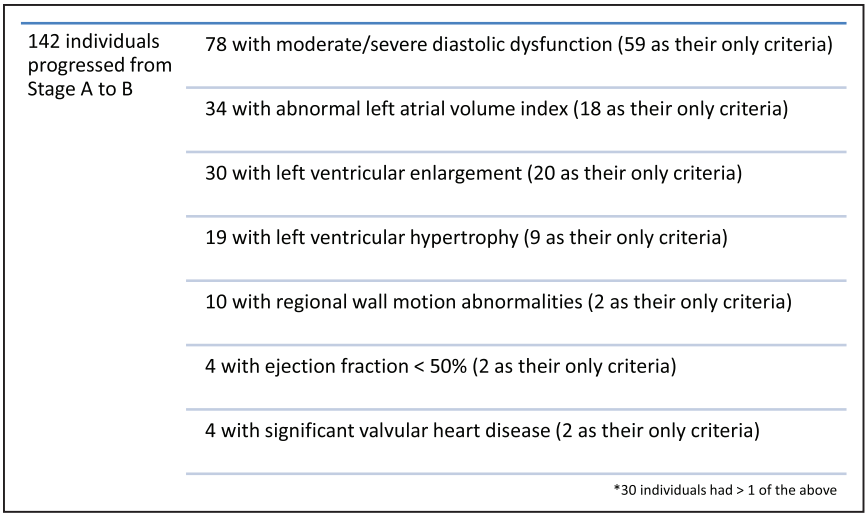

Figure 2. Echocardiographic features of individuals who progressed from Stage A to Stage B heart failure from Visit 1 (1997–2000) to Visit 2 (2001–2004).
A total of 142 individuals progressed from Stage A to Stage B HF from visit 1 to visit 2. This table highlights the echocardiographic features that confirmed progression, and the number of individuals who met those criteria.

[95% CI, 0.76–3.78]; *P*=0.20) or all-cause mortality (HR, 1.28 [95% CI, 0.65–2.50], *P*=0.48) between those who progressed and did not progress.

Stage B HF: Progressed Versus Did Not Progress

By visit 2, 23 (6%) individuals from Stage B had progressed to clinical (Stage C/D) HF (Figure 1). Of those who progressed, only 4 (17%) had reduced EF. The rate of progression was 1.4 cases per 100 person-years of follow-up (95% CI, 0.9–2.1).

Within the individuals who did not progress from Stage B at visit 2, 152 (39%) individuals regressed, with 111 (29%) classified as Stage A and 41 (10%) categorized as normal at visit 2. Individuals who regressed from Stage B had higher EF, smaller LAVI, and lower values of NT-ProBNP and HS-Troponin compared with those who remained stable (Table I in the Data Supplement).

Comparison of Baseline Characteristics

Those who progressed from Stage B by visit 2 were older (*P*<0.001), had lower EF (57% versus 62%, *P*<0.001), higher LAVI (*P*=0.003), and higher LVMI (*P*=0.03, Table 3) at visit 1. Higher NT-ProBNP (461.1 versus 95.8 pg/mL, *P*<0.001) and HS-troponin (10.4 versus 3.5 pg/mL, *P*<0.001, Table 3) were also seen in those who progressed. Medication use was quite similar between groups, and only ACE (angiotensin-converting enzyme) inhibitor use was higher in those who progressed (*P*=0.007, Table 3).

Long-Term Outcomes Following Visit 2

As in Stage A progressors, those who progressed from Stage B had a trend toward increased risk of cardiovascular death, although not statistically significant (HR, 2.66 [95% CI, 1.02–6.94], *P*=0.05, Figure 3B). No difference was seen in all-cause mortality (HR, 1.71 [95% CI, 0.85–3.43], *P*=0.13) for those who progressed from Stage B compared with those who did not progress.

Biomarkers and Progression

Given higher NT-ProBNP levels were seen in those who progressed from Stage A and B, we explored this further with an ROC curve analysis where association with progression was evaluated first for age and sex, then by adding NT-ProBNP. For Stage A, there was not a strong benefit from adding NT-ProBNP over age and sex alone (area under the curve, 0.61 [0.55–0.67] versus area under the curve 0.62 [0.57–0.68]), *P*=0.39). Repeating similar analyses in Stage B, the area under the curve improved from 0.73 (0.63–0.84) with age and sex to 0.86 (0.79–0.93) with the addition of NT-ProBNP (*P*=0.01). The addition of HS-Troponin to NT-ProBNP did not significantly alter the correlation of NT-ProBNP on progression for either stage.

DISCUSSION

In this study of community-based individuals with preclinical (Stage A and B) HF, 20% of those classified as Stage A/B progressed in HF stage over a 4-year period, with a greater rate of progression seen for Stage A. After multivariate analysis, female sex, increased E/e', and beta blocker use were associated with progression for Stage A, while obesity was associated with lower risk of progression. Those who progressed from Stage B were older, had lower EF, higher LAVI and LVMI, and more ACE inhibitor use. There were a range of abnormal echocardiographic features seen in those who progressed from Stage A; however, the development of LV systolic dysfunction was uncommon overall. Individuals who progressed from either stage had higher levels of NT-proBNP. Further analysis demonstrated that NT-proBNP was predictive of progression for Stage B but not Stage A. In follow-up after visit 2, there was a signal that individuals who progressed had increased cardiovascular mortality; however, no statistically significant differences were seen, likely because of small numbers.

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Table 2. Characteristics of Individuals With Stage A Heart Failure Who Progressed vs Did Not Progress by Visit 2 (2001–2004)

	Did not progress (n=267)	Progressed (n=146)	*P* value, age and sex adjusted
Age, y, mean (SD)	59.9 (8.4)	62.5 (9.3)	0.005
Female, n (%)	102 (38)	75 (51)	0.01
BMI, mean (SD), kg/m^2	31.7 (4.8)	30.3 (5.3)	0.04
Comorbidities			
Hypertension, n (%)	110 (41)	82 (56)	0.04
Diabetes, n (%)	29 (11)	19 (13)	0.59
Prior myocardial infarction, n (%)	6 (2)	8 (5)	0.11
Obesity,* n (%)	193 (72)	77 (53)	<0.001
Coronary artery disease, n (%)	29 (11)	27 (18)	0.04
Hyperlipidemia, n (%) (n=393)	46 (18)	36 (26)	0.13
Medication use (n=393)			
Aspirin, n (%)	93 (37)	60 (43)	0.15
Beta blocker, n (%)	32 (13)	41 (29)	<0.001
Calcium channel blocker, n (%)	19 (8)	12 (9)	0.94
Angiotensin receptor blocker, n (%)	5 (2)	4 (3)	0.84
ACE inhibitor, n (%)	30 (12)	19 (14)	0.43
Diuretic,† n (%)	58 (23)	39 (28)	0.89
Statin, n (%)	46 (18)	36 (26)	0.13
Echocardiogram			
EF, %, mean (SD)	63.8 (4.7)	64.3 (5.9)	0.89
Left atrial volume index, mL/m^2, mean (SD) (n=381)	22.0 (4.4)	23.1 (4.5)	0.03
E/e', mean (SD) (n=343)	7.9 (2.2)	8.8 (2.6)	0.008
e', mean (SD) (n=343)	0.09 (0.03)	0.08 (0.08)	0.84
Left ventricular mass index, g/m^2, mean (SD) (n=302)	92.4 (14.6)	92.8 (15.4)	0.28
Diastolic dysfunction, mild, n (%) (n=389)	54 (21)	27 (21)	0.19
Biomarkers‡			
Creatinine, mg/dL (n=398)	0.9 (0.8–1.0)	0.8 (0.7–1.0)	0.64
NT-proBNP,§ pg/mL (n=406)	41.4 (16.0–85.2)	71.0 (28.5–129.7)	0.03
HS-troponin,‖ pg/mL (n=365)	2.60 (1.7–4.3)	3.30 (1.90–5.7)	0.06
NT-atrial natriuretic peptide,¶ pg/mL (n=380)	1701 (1183–2566)	2516 (1318–3417)	0.04

ACE indicates angiotensin-converting enzyme; BMI, body mass index; EF, ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Defined as BMI≥30 kg/m^2.

†Loop, thiazide-based, and potassium sparing diuretics included.

‡Numbers shown are median (25th–75th percentile).

§Normal reference range 10–138 pg/mL for males and 10–263 pg/mL for females.[31–33]

‖Normal reference range ≤40 pg/mL.[34,35]

¶Normal reference range 365±104 pg/mL for ages 20–30 y and 438±72 pg/mL for ages 55–70 y.[36]

Progression of Preclinical Heart Failure

HF occurs on a continuum, as is described by the American College of Cardiology/American Heart Association staging system.[1,13,37] Previous studies have shown a high prevalence of preclinical heart failure and that successive advancement in HF stage increases an individual's mortality risk.[3–8] Adding to the current literature, our study demonstrated that 20% of community patients with preclinical HF progress in HF stage in a follow-up period of only 4 years, with a higher rate of progression for Stage A compared with Stage B (Stage A: 8.7 per 100 person-years [95% CI, 7.4–10.2], Stage B: 1.4 per 100 person-years [95% CI, 0.9–2.1], *P*<0.001).

Our study found many features associated with progression, with some differences for Stage A versus Stage B. Age, female sex, hypertension, CAD, increased LAVI, increased E/e', beta blocker use, and increased NT-proBNP and NT-ANP were seen in those who progressed from Stage A. After multivariate analysis, female sex, increased E/e', and beta-blocker use remained associated with progression from Stage A. Interestingly, obesity was associated with protection against progression from Stage A. For Stage B, age, ACE inhibitor use, lower EF, increased LAVI and LVMI, presence of regional wall motion abnormality, and higher NT-proBNP and HS-Troponin were seen in those that progressed. Unfortunately, given the small size of Stage B progressors (n=23), a reliable multivariable model could not be produced.

By definition, individuals in Stage A have heart failure risk factors. Progression from this stage occurs by the development of asymptomatic structural/functional abnormalities (Stage B), and/or the development of clinical heart failure symptoms (Stage C/D). In our study, the majority of individuals who progressed from Stage A went on to Stage B (Figure 1). In those individuals, a range of abnormal echocardiographic features were seen, with the majority having moderate/severe diastolic dysfunction (Figure 2). The development of LV systolic dysfunction was uncommon, even in those who progressed from Stage B. Heart failure pathophysiology is complex and often structural, systolic, and diastolic functional abnormalities overlap regardless of etiology.[38] While varied, the range of echocardiographic features seen for both Stage A and B progressors is reflective of what has been previously reported, as increased LV mass, increased left atrial size, diastolic dysfunction, and abnormal global longitudinal systolic strain have all previously been associated with HF progression.[39]

In terms of medication use, the current study found more beta blocker use in those who progressed from Stage A. While these individuals also had more CAD and hypertension; beta blocker use remained associated with progression after multivariate analysis. Thus, it is possible that beta blocker use acts as a surrogate for other uncaptured covariates. One possibility which was

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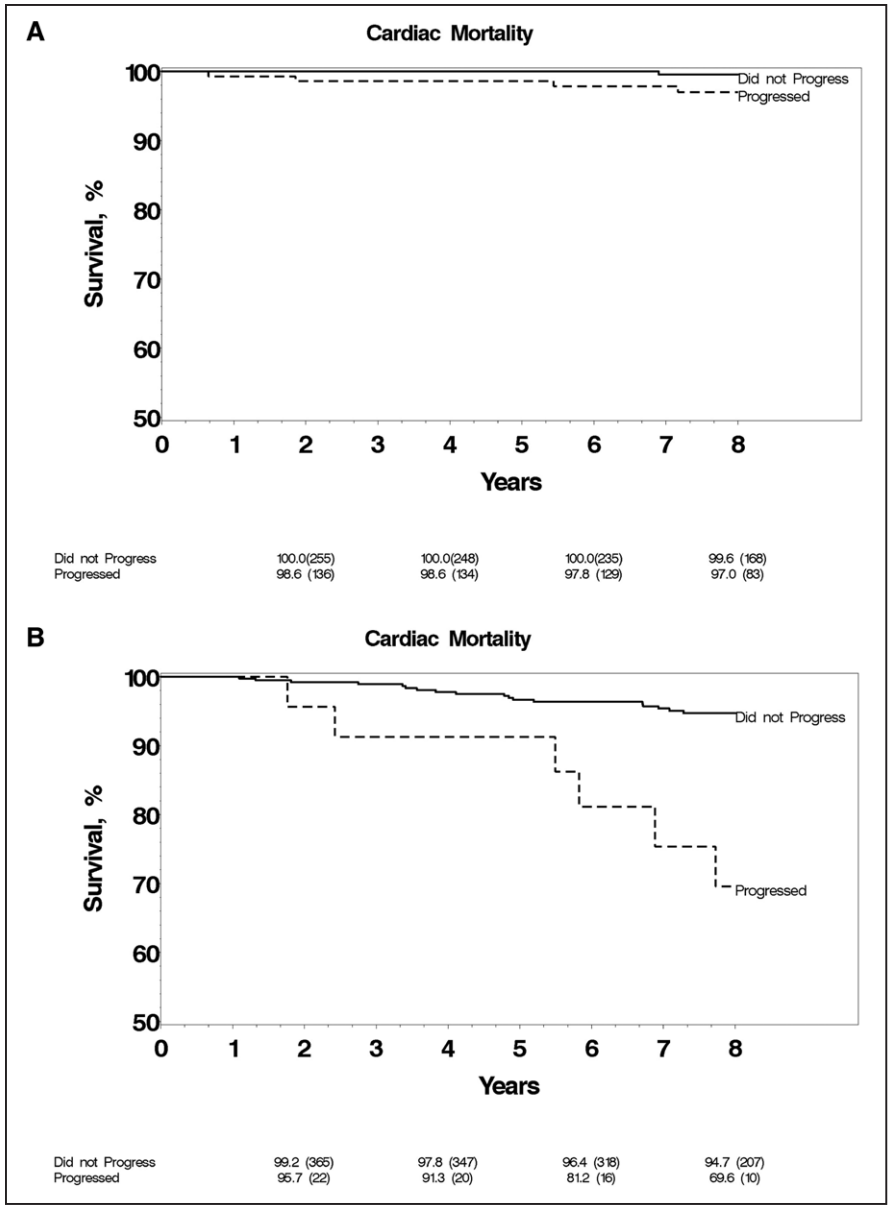

Figure 3. Long-term outcomes: progressed vs did not progress.
The median follow-up period for evaluation of long-term outcomes was 8.3 (interquartile range [IQR], 7.6–9.3) years after visit 2 for Stage A and 8.1 (IQR, 7.0–9.0) years after visit 2 for Stage B. Shown are the unadjusted Kaplan-Meier curves for cardiovascular mortality for individuals who progressed vs did not progress from Stage A (**A**) and Stage B (**B**). Numbers below the curve represent the survival estimate (number at risk).

not fully evaluated in the present study is the presence of arrhythmias for which individuals may be prescribed beta blocker therapy. Atrial fibrillation in particular is common in patients with heart failure.[40] Future studies evaluating progression in heart failure should include atrial fibrillation and other arrhythmias in their assessment. In comparison, more ACE inhibitor use was seen in those who progressed from Stage B, which is anticipated as a component of guideline directed medical therapy for clinical heart failure.

Interestingly, obesity was associated with protection from progression of Stage A. There has been an obesity paradox described for many cardiovascular diseases, including heart failure, wherein overweight and obese individuals have been shown to have a better prognosis when compared with leaner patients.[41,42] There are many purposed reasons for the obesity paradox in HF including greater metabolic reserve, less cachexia, protective cytokines, earlier presentation, and increase in muscle mass and strength.[41,42] Another proposed mechanism, which may be more relevant to the current study, is that overweight and obese individuals tend to have other comorbidities, such as hypertension, and may in fact be treated with more cardioprotective medications. In theory, this could then have potential downstream consequences of delaying or slowing progression of heart failure. While this was out of the scope of the present article, this would certainly be of interest in future studies.

Screening Strategies and Prevention of Progression in Preclinical HF

Previous studies have evaluated various heart failure screening strategies. In STOP-HF (St Vincent's Screening

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Table 3. Characteristics of Individuals With Stage B Heart Failure Who Progressed vs Did Not Progress by Visit 2 (2001–2004)

	Did not progress (n=390)	Progressed (n=23)	*P* value, age and sex adjusted
Age, y, mean (SD)	63.5 (10.0)	72.2 (10.4)	<0.001
Female, n (%)	225 (58)	10 (43)	0.15
BMI, mean (SD), kg/m^2	28.8 (5.4)	30.3 (5.3)	0.06
Comorbidities			
Hypertension, n (%)	149 (38)	9 (39)	0.43
Diabetes, n (%)	30 (8)	5 (22)	0.15
Prior myocardial infarction, n (%)	26 (7)	2 (9)	0.64
Obesity,* n (%)	147 (38)	10 (43)	0.30
Coronary artery disease, n (%)	66 (17)	8 (35)	0.57
Hyperlipidemia, n (%) (n=388)	94 (26)	12 (52)	0.11
Medication use (n=388)			
Aspirin, n (%)	144 (39)	7 (30)	0.14
Beta blocker, n (%)	96 (26)	3 (13)	0.09
Calcium channel blocker, n (%)	36 (10)	4 (17)	0.90
Angiotensin receptor blocker, n (%)	11 (3)	1 (4)	0.71
ACE inhibitor, n (%)	31 (8)	7 (30)	0.007
Diuretic,† n (%)	67 (18)	6 (26)	0.86
Statin, n (%)	94 (26)	12 (52)	0.11
Echocardiogram			
EF, %, mean (SD)	62.7 (6.8)	57.2 (12.3)	<0.001
EF <50%, n (%)	20 (5)	6 (26)	0.002
Left atrial volume index, mL/m^2, mean (SD) (n=398)	29.3 (8.2)	36.9 (13.2)	0.003
E/e', mean (SD) (n=345)	9.8 (3.32)	10.6 (3.31)	0.97
e', mean (SD) (n=348)	0.08 (0.02)	0.07 (0.01)	0.30
Left ventricular mass index, g/m^2, mean (SD) (n=364)	106.2 (21.8)	122.3 (34.0)	0.03
Diastolic dysfunction, mild, n (%) (n=377)	54 (15)	5 (28)	0.87
Diastolic dysfunction, moderate or severe, n (%) (n=377)	108 (30)	7 (39)	
Significant valve disease, n (%)	28 (7)	6 (26)	0.08
Regional wall motion abnormality, n (%)	29 (7)	6 (26)	0.03
Biomarkers‡			
Creatinine, mg/dL (n=405)	0.8 (0.7–0.9)	0.9 (0.8–1.2)	0.05
NT-proBNP,§ pg/mL (n=402)	95.8 (41.0–190.0)	461.1 (247.8–1024.0)	<0.001
HS-troponin,‖ pg/mL (n=370)	3.50 (2.2–5.8)	10.35 (4.6–16.2)	<0.001
NT-atrial natriuretic peptide,¶ pg/mL (n=386)	2519 (1624–3684)	3172 (2188–6013)	0.10

ACE indicates angiotensin-converting enzyme; BMI, body mass index; EF, ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Defined as BMI ≥30 kg/m^2.

†Loop, thiazide-based, and potassium sparing diuretics included.

‡Numbers shown are median (25th–75th percentile).

§Normal reference range 10–138 pg/mL for males and 10–263 pg/mL for females.[31–33]

‖Normal reference range ≤40 pg/mL.[34,35]

¶Normal reference range 365±104 pg/mL for ages 20–30 y and 438±72 pg/mL for ages 55–70 y.[36]

to Prevent Heart Failure Study), the authors utilized a BNP (brain natriuretic peptide)-guided screening strategy in individuals with heart failure risk factors, similar to the current study's definition of Stage A. With implementation of their screening strategy, they found a reduction in combined clinical outcomes, including incidence of

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clinical heart failure in the intervention group.[25,43] To be noted, individuals who had an elevated BNP level received more cardiac testing including cardiac imaging. The overall effect of the difference seen in the intervention group is thought to be multifactorial. Similarly, the PONTIAC (NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients) trial utilized a BNP screening strategy in individuals with no cardiovascular disease and type 2 diabetes. Those individuals with an elevated BNP level underwent progressive medication titrations with renin-angiotensin-aldosterone system inhibitors and beta-blockers.[43,44] At 2 years, their primary end point of hospitalization/death because of cardiac disease was reduced in the intervention group.[44]

Not surprisingly, in the current study, higher levels of NT-ProBNP were seen in those who progressed from Stage A and B. However, further ROC curve analysis revealed that NT-ProBNP did not add any further value over age and sex for Stage A. In contrast, for Stage B, the addition of NT-proBNP identified individuals at higher risk for progression to clinical heart failure. Therefore, use of NT-proBNP for screening of HF in the asymptomatic patient seems best reserved for those with known structural/functional cardiac abnormalities.

Cardiac imaging, predominantly echocardiography, has been explored as an approach to screening for heart failure and heart failure progression.[38] Diastolic parameters have shown higher sensitivity compared with systolic parameters in prediction of clinical HF; however, the highest sensitivity is seen by utilizing a composite of echocardiography parameters.[38] Recently, the STAAB consortium published their findings on the prevalence and characteristics of preclinical HF stages and identified that approximately one-third of Stage B individuals lacked Stage A defining risk factors.[4] These individuals with structural/functional cardiac abnormalities would have been missed by traditional, nonimaging based screening. There has been at least one trial, which utilized echocardiography as a screening tool for preclinical HF in community individuals with HF risk factors.[45] In this study, renin-angiotensin-aldosterone system inhibitors and beta-blockers were recommended to those with evidence of structural heart disease (Stage B) on screening echocardiography. No difference in primary outcome of event free survival was seen in those recommended to initiate therapy; however, the trial was stopped because of poor therapeutic adherence.[45]

The approach to prevention of progression from preclinical to clinical HF is likely multifaceted. While the purpose of the current study was not to develop a screening protocol for individuals with preclinical HF, the information obtained does have clinical implications important to help guide future strategies. First, the authors would emphasize the importance that patients with risk factors (Stage A) be identified as having preclinical HF, which carries risk of development to clinical heart failure. Additionally, there appears to be a role for cardiac imaging as progression of preclinical HF is marked by asymptomatic development of structural/functional cardiac abnormalities not easily detected by other means. Findings from the present study would suggest consideration for screening echocardiogram in those identified as Stage A HF, as has been previously purposed.[38] This would allow the opportunity to individualize prevention strategies, such as aggressive risk factor modification or use of targeted cardioprotective medications.

Limitations

This study has limitations that should be acknowledged to aid in the interpretation of the data. Our study population is from 1 community in Southeastern Minnesota and is largely White, which may limit the generalizability of the data. In our study, we described the progression of individuals over a 4-year period; however, the duration of time that individuals had been in preclinical HF stages before visit 1 is unknown. Therefore, our extended follow-up period of 8 years may be too short to fully describe the morbidity and mortality risk of those who progressed. Because we did not collect progression data after visit 2, we are unable to update progression status during extended follow-up, which may cause a misclassification issue for long-term outcomes comparison. Our study was analyzed conditional on individuals having visit 2; however, there remains the possibility of survival bias contributing to study results. Finally, as the cohort is divided into various stages, the number of subjects is reduced, which may limit reliability of the estimates of risk and raises concerns of lack of power. In particular, given the small size of Stage B progressors, we were unable to create a reliable multivariate model as done for Stage A. We acknowledge this as a limitation, but given the retrospective nature of this study, we are unable to correct this.

CONCLUSIONS

There is a significant rate of progression of preclinical HF in a community population, with higher rates of progression seen for individuals with Stage A HF. A range of echocardiographic features were seen in those who progressed from Stage A; however, the development of LV systolic dysfunction was uncommon overall. The addition of NT-ProBNP to subjects with Stage B could identify a subgroup that is at high risk for progression to clinical HF. These results may help guide further preclinical heart failure detection, screening, and prevention strategies.

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Disclosures

None.

Supplemental Materials

Table I

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147–e239. doi: 10.1016/j.jacc.2013.05.019
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509
3. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC Jr, Rodeheffer RJ. 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. *Circulation*. 2007;115:1563–1570. doi: 10.1161/CIRCULATIONAHA.106.666818
4. Morbach C, Gelbrich G, Tiffe T, Eichner FA, Christa M, Mattern R, Breunig M, Cejka V, Wagner M, Heuschmann PU, Stork S. Prevalence and determinants of the precursor stages of heart failure: results from the population-based STAAB cohort study [published online May 6, 2020]. *Eur J Prev Cardiol*. doi: 10.1177/2047487320922636
5. Shah AM, Claggett B, Loehr LR, Chang PP, Matsushita K, Kitzman D, Konety S, Kucharska-Newton A, Sueta CA, Mosley TH, et al. Heart failure stages among older adults in the community: the atherosclerosis risk in communities study. *Circulation*. 2017;135:224–240. doi: 10.1161/CIRCULATIONAHA.116.023361
6. Xanthakis V, Enserro DM, Larson MG, Wollert KC, Januzzi JL, Levy D, Aragam J, Benjamin EJ, Cheng S, Wang TJ, et al. Prevalence, neurohormonal correlates, and prognosis of heart failure stages in the community. *JACC Heart Fail*. 2016;4:808–815. doi: 10.1016/j.jchf.2016.05.001
7. Jorge AL, Rosa ML, Martins WA, Correia DM, Fernandes LC, Costa JA, Moscavitch SD, Jorge BA, Mesquita ET. The prevalence of stages of heart failure in primary care: a population-based study. *J Card Fail*. 2016;22:153–157. doi: 10.1016/j.cardfail.2015.10.017
8. 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. doi: 10.1161/01.CIR.0000085166.44904.79
9. Melton LJ 3rd. History of the Rochester epidemiology project. *Mayo Clin Proc*. 1996;71:266–274. doi: 10.4065/71.3.266
10. 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. doi: 10.1001/jama.289.2.194
11. 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. doi: 10.1016/s0735-1097(02)02059-4
12. Jacobsen SJ, Mahoney DW, Redfield MM, Bailey KR, Burnett JC Jr, Rodeheffer RJ. Participation bias in a population-based echocardiography study. *Ann Epidemiol*. 2004;14:579–584. doi: 10.1016/j.annepidem.2003.11.001
13. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: 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): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:e154–e235. doi: 10.1161/CIRCULATIONAHA.105.167586
14. Devereux RB, Lutas EM, Casale PN, Kligfield P, Eisenberg RR, Hammond IW, Miller DH, Reis G, Alderman MH, Laragh JH. Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol*. 1984;4:1222–1230. doi: 10.1016/s0735-1097(84)80141-2
15. 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. doi: 10.1016/0735-1097(95)00275-0
16. 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. doi: 10.1016/j.jacc.2004.09.054
17. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol*. 2003;41:1036–1043. doi: 10.1016/s0735-1097(02)02981-9
18. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. *Am J Cardiol*. 2007;99:1643–1647. doi: 10.1016/j.amjcard.2007.01.041
19. Correa de Sa DD, Hodge DO, Slusser JP, Redfield MM, Simari RD, Burnett JC, Chen HH. Progression of preclinical diastolic dysfunction to the development of symptoms. *Heart*. 2010;96:528–532.
20. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306:856–863. doi: 10.1001/jama.2011.1201
21. Vogel MW, Slusser JP, Hodge DO, Chen HH. The natural history of preclinical diastolic dysfunction: a population-based study. *Circ Heart Fail*. 2012;5:144–151. doi: 10.1161/CIRCHEARTFAILURE.110.959668
22. Echouffo-Tcheugui JB, Erqou S, Butler J, Yancy CW, Fonarow GC. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis. *JACC Heart Fail*. 2016;4:237–248. doi: 10.1016/j.jchf.2015.09.015
23. Zhang L, Liebelt JJ, Madan N, Shan J, Taub CC. Comparison of predictors of heart failure with preserved versus reduced ejection fraction in a multiracial cohort of preclinical left ventricular diastolic dysfunction. *Am J Cardiol*. 2017;119:1815–1820. doi: 10.1016/j.amjcard.2017.03.005
24. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol*. 2010;55:300–305. doi: 10.1016/j.jacc.2009.12.003
25. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Bermingham M, Patle A, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA*. 2013;310:66–74. doi: 10.1001/jama.2013.7588
26. 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. doi: 10.1056/NEJM197112232852601
27. 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. doi: 10.1016/S0894-7317(03)00516-9

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28. 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. doi: 10.1161/CIRCULATIONAHA.105.541078
29. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1997;157:2413–2446. doi: 10.1001/archinte.1997.00440420033005
30. 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. doi: 10.1016/0002-8703(84)90558-1
31. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *Am J Cardiol*. 2008;101(3A):82–88. doi: 10.1016/j.amjcard.2007.11.029
32. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J*. 2006;27:330–337. doi: 10.1093/eurheartj/ehi631
33. van Kimmenade RR, Pinto YM, Bayes-Genis A, Lainchbury JG, Richards AM, Januzzi JL Jr. Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. *Am J Cardiol*. 2006;98:386–390. doi: 10.1016/j.amjcard.2006.02.043
34. McKie PM, Heublein DM, Scott CG, Gantzer ML, Mehta RA, Rodeheffer RJ, Redfield MM, Burnett JC Jr, Jaffe AS. Defining high-sensitivity cardiac troponin concentrations in the community. *Clin Chem*. 2013;59:1099–1107. doi: 10.1373/clinchem.2012.198614
35. McKie PM, AbouEzzeddine OF, Scott CG, Mehta R, Rodeheffer RJ, Redfield MM, Burnett JC Jr, Jaffe AS. High-sensitivity troponin I and amino-terminal pro–B-type natriuretic peptide predict heart failure and mortality in the general population. *Clin Chem*. 2014;60:1225–1233. doi: 10.1373/clinchem.2014.222778
36. Lerman A, Gibbons RJ, Rodeheffer RJ, Bailey KR, McKinley LJ, Heublein DM, Burnett JC Jr. Circulating N-terminal atrial natriuretic peptide as a marker for symptomless left-ventricular dysfunction. *Lancet*. 1993;341:1105–1109. doi: 10.1016/0140-6736(93)93125-k
37. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479. doi: 10.1161/CIRCULATIONAHA.109.192065
38. Gong FF, Campbell DJ, Prior DL. Noninvasive cardiac imaging and the prediction of heart failure progression in preclinical stage A/B Subjects. *JACC Cardiovasc Imaging*. 2017;10:1504–1519. doi: 10.1016/j.jcmg.2017.11.001
39. Yang H, Negishi K, Wang Y, Nolan M, Saito M, Marwick TH. Echocardiographic screening for non-ischaemic stage B heart failure in the community. *Eur J Heart Fail*. 2016;18:1331–1339. doi: 10.1002/ejhf.643
40. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail*. 2017;5:565–574. doi: 10.1016/j.jchf.2017.05.001
41. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, Milani RV. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis*. 2018;61:142–150. doi: 10.1016/j.pcad.2018.07.003
42. Lavie CJ, Sharma A, Alpert MA, De Schutter A, Lopez-Jimenez F, Milani RV, Ventura HO. Update on obesity and obesity paradox in heart failure. *Prog Cardiovasc Dis*. 2016;58:393–400. doi: 10.1016/j.pcad.2015.12.003
43. Gallagher J, Watson C, Campbell P, Ledwidge M, McDonald K. Natriuretic peptide-based screening and prevention of heart failure. *Card Fail Rev*. 2017;3:83–85. doi: 10.15420/cfr.2017:20:1
44. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, Adlbrecht C, Prager R, Luger A, Pacher R, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;62:1365–1372. doi: 10.1016/j.jacc.2013.05.069
45. Yang H, Negishi K, Wang Y, Nolan M, Marwick TH. Imaging-guided cardioprotective treatment in a community elderly population of stage B heart failure. *JACC Cardiovasc Imaging*. 2017;10:217–226. doi: 10.1016/j.jcmg.2016.11.015

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