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ORIGINAL RESEARCH

Incidence of Preclinical Heart Failure in a Community Population

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BACKGROUND: A high prevalence of preclinical heart failure (HF) (Stages A and B) has previously been shown. The aim of this study was to explore factors associated with the incidence of preclinical HF in a community population.

METHODS AND RESULTS: Retrospective review of 393 healthy community individuals aged ≥45 years from the Olmsted County Heart Function Study that returned for 2 visits, 4 years apart. At visit 2, individuals that remained normal were compared with those that developed preclinical HF. By the second visit, 191 (49%) developed preclinical HF (12.1 cases per 100 person-years of follow-up); 65 (34%) Stage A and 126 (66%) Stage B. Those that developed preclinical HF (n=191) were older (P=0.004), had a higher body mass index (P<0.001), and increased left ventricular mass index (P=0.006). When evaluated separately, increased body mass index was seen with development of Stage A (P<0.001) or Stage B (P=0.009). Echocardiographic markers of diastolic function were statistically different in those that developed Stage A [higher E/e' (P<0.001), lower e' (P<0.001)] and Stage B [higher left atrial volume index (P<0.001), higher E/e' (P<0.001), lower e' (P<0.001)]. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was higher at visit 2 in those that developed Stage A or B (P<0.001 for both). Hypertension (57%), obesity (34%), and hyperlipidemia (25%) were common in the development of Stage A. Of patients who developed Stage B, 71% (n=84) had moderate or severe diastolic dysfunction.

CONCLUSIONS: There is a high incidence of preclinical HF in a community population. Development of Stage A was driven by hypertension and obesity, while preclinical diastolic dysfunction was seen commonly in those that developed Stage B.

Key Words: incidence ■ natural history ■ preclinical heart failure

The prevalence of heart failure (HF) is increasing, with a projection of >8 million people in the United States aged >18 years living with HF by 2030.[1] Preclinical HF (Stages A and B) represents the early, asymptomatic stages of HF as described by the American College of Cardiology/American Heart Association/Heart Failure Society of America 4-stage HF classification system.[2] Stage A includes individuals at-risk for HF, and Stage B includes people with asymptomatic cardiac structural or functional abnormalities.[2] With increasing prevalence, strategies targeted at HF prevention are paramount.[2,3]

Prior studies have demonstrated a high prevalence of preclinical HF, and that these individuals carry an increased risk of progression to clinical HF, as well as increased mortality risk.[4–8] Many studies have evaluated screening and management strategies for individuals with preclinical HF, with the thought that identification and intervention at these early stages may help prevent or delay progression to symptomatic, clinical HF.[9–17] In addition, prior studies have emphasized the importance that providers recognize individuals with HF risk factors (Stage A), and work to optimize treatment of their cardiovascular risk factors to prevent progression.[18–20]

Despite the advancements in knowledge about preclinical HF, the incidence of preclinical HF from a healthy patient population has not previously been described. The objectives of the current study were to evaluate the incidence of preclinical HF (Stages A and B) in a community population, and identify clinical,

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CLINICAL PERSPECTIVE

What Is New?

- The incidence of preclinical heart failure in 393 healthy community individuals was 49% over a 4-year period, corresponding to 12.1 cases per 100 person-years of follow-up.
- Development of Stage A was driven by incident hypertension and obesity, while asymptomatic moderate/severe diastolic dysfunction was seen in the majority of those that developed Stage B.

What Are the Clinical Implications?

- Recognition of a patient's American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure stage is needed to facilitate implementation of appropriate heart failure prevention strategies.
- Screening echocardiography in those with heart failure risk factors may help alert clinician to development of pre-heart failure, or Stage B heart failure, sooner.

echocardiographic, or biomarker characteristics associated with the development of preclinical HF. Defining the incidence of preclinical HF and the associated features has important implications for enhancing HF screening and prevention strategies.

METHODS

This is 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. The authors declare that all supporting data are available within the article (and its online supplementary files).

Study Design

The Olmsted County Heart Function Study is a population-based random sample of 2042 Olmsted County, Minnesota residents aged ≥45 years who underwent medical record abstraction and serial clinical evaluation and comprehensive Doppler echocardiography.[21–24] The present study identified a subgroup of 393 healthy community individuals that returned for both visit 1 (1997–2000) and visit 2 (2001–2004). These individuals had no HF risk factors and normal cardiac structure and function at baseline. Normal, healthy individuals that did not return for visit 2 were excluded (n=132). Comparison of normal, healthy subjects that were included (n=393) versus excluded (n=132) demonstrated the 2 groups to be similar with no clinically significant differences in baseline characteristics. At visit 2, we compared individuals that remained normal to those that developed preclinical HF (Stage A or B).

Definition of HF Stages

Stage A was defined as no prior diagnosis of HF and normal echocardiogram with ≥1 of the following: coronary artery disease, hypertension, diabetes, or obesity (defined as body mass index (BMI) ≥30 kg/m2). A normal echocardiogram was defined as left ventricular ejection fraction (LVEF) ≥50%, no significant valve disease on echocardiogram (defined by less than or equal to moderate in severity), normal left ventricular mass index, normal left atrial volume index, and normal left ventricular size. As a marker of coronary artery disease, individuals with previous myocardial infarction were included in Stage A if they had no history of HF and no structural or functional abnormality, as evidenced by a normal echocardiogram.[25]

Stage B was defined as no previous diagnosis of HF and evidence of a structural or functional abnormality including: LVEF <50%,[2,8,21,25] diastolic dysfunction at least moderate in severity, left ventricular hypertrophy (left ventricular mass index >134 g/m^2 for men and >110 g/m^2 for women),[25,26] significant valve disease per echocardiogram (defined as greater than moderate in severity), presence of regional wall motion abnormalities on echocardiogram, enlarged left ventricle (indexed left ventricular 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),[8,25,27] or abnormal left atrial volume index (>33 mL/m^2 for men and >30 mL/m^2 for women).[25,28,29]

Echocardiography

At visits 1 and 2, comprehensive echocardiographic assessment was performed by 1 of 3 registered diagnostic cardiac sonographers using standardized instruments and techniques and reviewed by 2 cardiologists, as previously reported.[22,30] Clinicians performing studies at visit 2 were masked to both visit 1 clinical and echocardiography 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 based on criteria validated at the time of database completion.[22,25] Mild diastolic dysfunction was defined as impaired relaxation (E/A ≤0.75) without evidence of increased filling pressure (E/e' <10), moderate diastolic dysfunction was defined as abnormal relaxation (E/A 0.75–1.5 and deceleration time >140 ms) with elevation of filling pressures (E/e' >10), and severe diastolic dysfunction was defined as restrictive

filling pattern (E/A >1.5 and deceleration time <140 ms) with elevation of filling pressures (E/e' >10).[22] To be classified as moderate or severe diastolic dysfunction, 2 Doppler criteria consistent with such diagnosis were required.[22]

Additional Data

Demographics, comorbidities, and medication use data were obtained by trained nurse abstractors. 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.[25,31,32]

Statistical Analysis

Individual characteristics are presented as number (%) for categorical variables, mean (SD) for normally distributed continuous variables, and median (interquartile range) for non-normally distributed variables. Development of preclinical HF 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, sex, and BMI as covariates to control for differences between groups. Paired t-tests or non-parametric signed-rank tests were used to evaluate changes in continuous characteristics of patient subgroups between visits 1 and 2. Changes in categorical characteristics between visits was evaluated using McNemar test. For continuous characteristics, percentage change from visit 1 was defined and summarized. The percentage changes for patients who progressed to Stage A and separately Stage B were compared with patients who remained normal using Wilcoxon rank-sum tests.

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

Incidence of Preclinical HF

At visit 1, 393 healthy individuals with no HF risk factors and normal cardiac structure and function were identified. On average, visit 2 was completed 4 years (range, 2.7–5.2) after visit 1 for all individuals. At visit 2, 191 (49%) individuals developed preclinical HF, corresponding to 12.1 cases per 100 person-years of follow-up. Of those that developed preclinical HF, 65 individuals (34%) developed Stage A HF and 126 individuals (66%) developed Stage B HF (Figure 1).

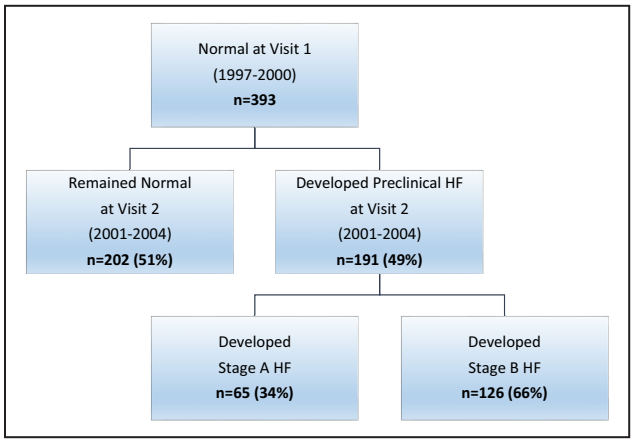

Figure 1. Incidence of preclinical heart failure (Stages A and B) between visit 1 (1997–2000) and visit 2 (2001–2004). The number (percentage) of those that developed preclinical heart failure (either Stage A or B) at visit 2. Incidence rate of preclinical heart failure was 12.1 cases per 100 person-years of follow-up. HF indicates heart failure.

When baseline characteristics at visit 1 were compared for individuals that developed preclinical HF (Stage A or B) versus those that remained normal at visit 2, individuals that developed preclinical HF were older ($P=0.004$) and had a higher baseline BMI ($P<0.001$, Table 1), thus we adjusted the remainder of comparisons for age, sex, and BMI. On baseline echocardiogram, a higher left ventricular mass index ($P=0.006$) was seen in those that developed preclinical HF. No differences were seen between groups for baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) values ($P=0.18$, Table 1). Baseline high-sensitivity troponin was not statistically different between groups ($P=0.05$, Table 1).[33–39]

Baseline characteristics were also compared between those that developed Stage A and Stage B HF at visit 2 (Table S1). Those that developed Stage A were noted to have higher baseline BMI (27 versus 26, $P=0.007$), systolic blood pressure (133 versus 122 mm Hg, $P<0.001$), and diastolic blood pressure (75 versus 71 mm Hg, $P=0.004$). Those that developed Stage B had higher baseline high-density lipoprotein cholesterol (48 versus 42 mg/dL, $P=0.010$). No statistically significant differences were seen in echocardiographic parameters or other biomarkers (Table S1).

Development of Stage A HF

Among the 192 individuals who developed preclinical HF at visit 2, a total of 65 (34%) individuals were classified as Stage A (Figure 1). When visit 2 characteristics were compared with baseline visit for individuals that developed Stage A HF, significant differences included: higher BMI ($P<0.001$), lower diastolic blood

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

	Overall (N=393)	Remained normal (n=202)	Developed preclinical HF (n=191)	*P* value* age, sex, BMI adjusted
Age, y, mean (SD)	58.1 (8.3)	56.8 (7.8)	59.4 (8.7)	0.004
Women, n (%)	210 (53)	115 (57)	95 (50)	0.93
BMI, mean (SD), kg/m^2	25.5 (2.6)	24.9 (2.6)	26.2 (2.6)	<0.001
Systolic blood pressure, mean (SD), mm Hg	122.5 (17.3)	119.7 (15.2)	125.6 (18.8)	0.06
Diastolic blood pressure, mean (SD), mm Hg	71.6 (9.3)	70.6 (8.8)	72.6 (9.7)	0.10
Heart rate, mean (SD), bpm	65.0 (10.1)	65.0 (9.9)	65.1 (10.4)	0.82
Aspirin use, n (%)	87 (25)	51 (27)	36 (23)	0.17
Echocardiogram				
EF, mean (SD), %	63.7 (4.3)	63.6 (3.9)	63.8 (4.7)	0.45
Left atrial volume index, mean (SD), mL/m^2	21.2 (4.5)	20.9 (4.7)	21.5 (4.4)	0.67
E/e', mean (SD)	7.5 (2.2)	7.2 (2.2)	7.8 (2.2)	0.17
e', mean (SD)	0.10 (0.04)	0.10 (0.03)	0.09 (0.04)	0.81
Left ventricular mass index, mean (SD), g/m^2	87.0 (14.4)	84.3 (12.7)	89.8 (15.6)	0.006
Left ventricular end-diastolic volume, mean (SD)	92.2 (24.2)	89.9 (22.6)	94.9 (25.7)	0.09
Left ventricular end-systolic volume, mean (SD)	33.4 (11.4)	32.4 (10.6)	34.7 (12.1)	0.05
Diastolic dysfunction, mild, n (%)	41 (11)	19 (10)	22 (12)	0.30
Laboratory data†				
Total cholesterol, mg/dL	207 (186, 226)	203 (182, 224)	209 (190, 228)	0.20
HDL cholesterol, mg/dL	47 (39, 58)	47 (39, 61)	46 (38, 55)	0.62
LDL cholesterol, mg/dL	131 (111, 150)	128 (108, 147)	134 (116, 155)	0.08
Triglycerides, mg/dL	113 (83, 156)	109 (83, 152)	117 (84, 163)	0.65
Creatinine, mg/dL	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.78
NT-proBNP‡, pg/mL	45.8 (21.3, 90.8)	44.1 (19.6, 84.8)	49.1 (23.9, 95.6)	0.18
Aldosterone§, ng/dL	4.2 (2.5, 6.5)	3.9 (2.5, 6.2)	4.4 (2.5, 6.6)	0.28
Atrial natriuretic peptide‖, pg/mL	10.5 (7.0, 15.5)	10.8 (7.0, 15.7)	10.2 (6.7, 15.4)	0.51
Hs-troponin#, pg/mL	2.0 (1.2, 3.3)	1.7 (1.1, 2.9)	2.2 (1.5, 3.7)	0.05

BMI indicates body mass index; EF, ejection fraction; HDL, high-density lipoprotein; HF, heart failure; Hs, high-sensitivity; LDL, low-density lipoprotein; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Remained normal versus developed preclinical heart failure.

†Numbers shown are median (25th, 75th percentile).

‡Normal reference range 10–138 pg/mL for males and 10–263 pg/mL for women.[33–35]

§Normal reference range 9.6 ± 1.3 ng/dL.[36]

‖Normal reference range 25 ± 11 pg/mL.[37]

#Normal reference range ≤40 pg/mL.[38,39]

pressure (*P*<0.001), and higher heart rate (*P*=0.007) at visit 2 (Table 2). On comparison of serial echocardiography data, higher EF (66% versus 64%, *P*=0.005), higher E/e' (*P*<0.001), and lower e' (*P*<0.001) were seen at visit 2 (Table 2). There were more individuals with mild diastolic dysfunction (24% versus 13%, *P*=0.03) at visit 2. NT-proBNP (59.7 versus 34.3 pg/mL, *P*<0.001) and aldosterone (*P*<0.001) values were higher at visit 2 (Table 2). Comparing the percentage change in continuous clinical and echocardiographic variables for those that remained normal to those that developed Stage A HF demonstrated a statistically significant higher increase in BMI in those that developed Stage A (Table S2).

In those that developed Stage A HF, the most common comorbidities resulting in individuals being classified were hypertension (n=37) and obesity (n=22, Figure 2A). While hyperlipidemia is not included in the definition for Stage A HF, 25% (n=15) were noted to develop hyperlipidemia by visit 2 (Table 2).

Development of Stage B HF

More individuals developed Stage B HF by visit 2, accounting for 66% (n=126) of those that developed preclinical HF (n=192) (Figure 1). When comparing individual characteristics between visit 1 and visit 2 for those that developed Stage B HF, notable differences included: higher BMI (*P*=0.009), lower diastolic blood pressure (*P*=0.002), and lower heart rate (*P*=0.02) at visit 2 (Table 3). These individuals also developed comorbidities, most commonly hypertension (n=23) and

Table 2. Comparison of Visit 1 and Visit 2 Characteristics for Individuals that Developed Stage A Heart Failure at Visit 2

	Visit 1 (1997–2000), n=65	Visit 2 (2001–2004), n=65	*P* value
Age, y, mean (SD)	60.1 (9.5)	64.0 (9.6)	…
Women, n (%)	28 (43)	28 (43)	…
BMI, mean (SD), kg/m^2	26.8 (2.4)	27.7 (3.1)	<0.001
Systolic blood pressure, mean (SD), mm Hg	133.0 (20.8)	128.6 (21.0)	0.08
Diastolic blood pressure, mean (SD), mm Hg	75.5 (10.1)	71.5 (11.1)	<0.001
Heart rate, mean (SD), bpm	65.5 (8.6)	69.2 (10.8)	0.007
Aspirin use, n (%)	14 (26)	16 (27)	0.82
Comorbidities			
Myocardial infarction, n (%)		1 (2)	
Diabetes, n (%)		5 (9)	
Hypertension, n (%)		37 (57)	
Obesity, n (%)		22 (34)	
Coronary artery disease, n (%)		8 (12)	
Hyperlipidemia, n (%)		15 (25)	
Echocardiogram			
EF, mean (SD), %	64.0 (4.5)	66.2 (4.8)	0.005
Left atrial volume index, mean (SD), mL/m2	21.6 (3.9)	21.1 (4.5)	0.50
E/e prime, mean (SD)	7.8 (2.5)	9.2 (2.7)	<0.001
e', mean (SD)	0.09 (0.05)	0.07 (0.02)	<0.001
Left ventricular mass index, mean (SD), g/m^2	89.0 (16.0)	87.0 (15.2)	0.07
Left ventricular end-diastolic volume, mean (SD)	93.5 (24.7)	85.5 (25.5)	0.06
Left ventricular end-systolic volume, mean (SD)	33.8 (11.4)	29.3 (11.4)	0.06
Diastolic dysfunction, mild, n (%)	8 (13)	14 (24)	0.03
Laboratory data*			
Creatinine, mg/dL	0.9 (0.7, 0.9)	0.9 (0.8, 1.0)	<0.001
NT-proBNP†, pg/mL	34.3 (20.6, 83.1)	59.7 (40.1, 105.0)	<0.001
Aldosterone‡, ng/dL	4.8 (2.5, 7.8)	7.4 (5.0, 11.6)	<0.001

BMI indicates body mass index; EF, ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Numbers shown are median (25th, 75th percentile).
†Normal reference range 10–138 pg/mL for men and 10–263 pg/mL for women.[33–35]
‡Normal reference range 9.6 ± 1.3 ng/dL.[36]

hyperlipidemia (n=16, Table 3). On echocardiography, those that developed Stage B HF had higher left atrial volume index (*P*<0.001), higher E/e' (*P*<0.001), lower e' (*P*<0.001), lower left ventricular end-diastolic volume (*P*<0.001), and lower left ventricular end-systolic volume (*P*=0.001) at visit 2 (Table 3). NT-proBNP was higher at visit 2 (70.6 versus 54.3 pg/mL, *P*<0.001, Table 3). Comparing the percentage change in continuous clinical and echocardiographic variables for those that remained normal to those that developed Stage B HF demonstrated a statistically significant higher increase in left atrial volume index and E/e' ratio in those that developed Stage B (Table S3).

Individuals qualified as Stage B largely based on the development of preclinical moderate or severe diastolic dysfunction (n=84, Figure 2B). Additional echocardiography features seen more commonly in those classified as Stage B included: abnormal left atrial volume index (n=20), left ventricular enlargement (n=17), and left ventricular hypertrophy (n=13, Figure 2B). Asymptomatic left ventricular systolic dysfunction (LVEF <50%) was not common (n=7).

DISCUSSION

To our knowledge, the current study is the first to determine the incidence of preclinical HF (Stages A and B). In the described community population, the incidence was 49% over a 4-year period, corresponding to 12.1 cases per 100 person-years of follow-up. Individuals that developed preclinical HF (Stage A or B) at visit 2 were older and had a higher BMI at visit 1 compared with those that remained normal. Of those that developed preclinical HF at visit 2, 34% developed Stage A and 66% developed Stage B. Development of Stage A was driven by the development of hypertension and obesity, while preclinical moderate/severe

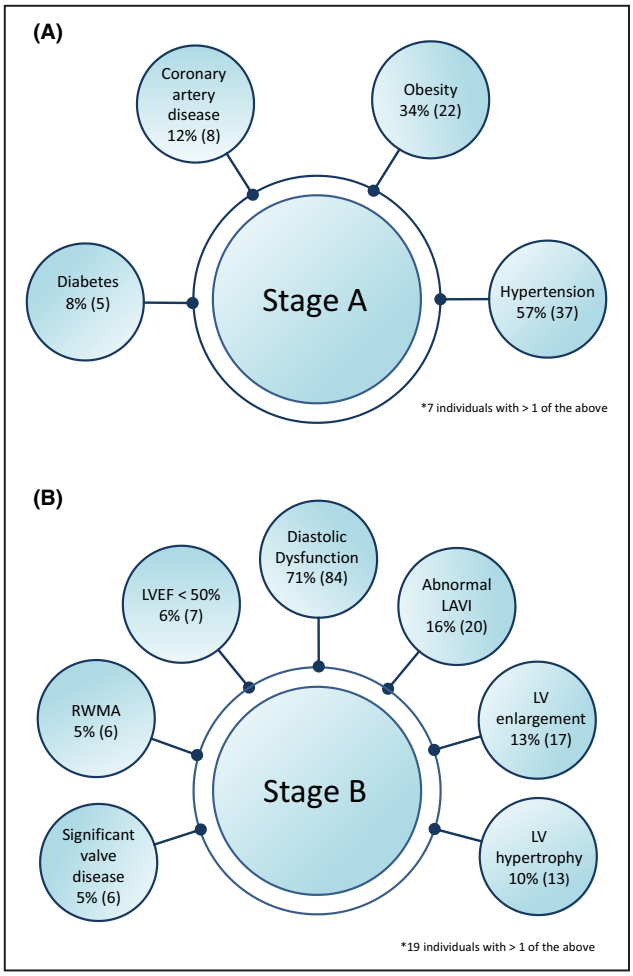

Figure 2. Individuals with Stage A and Stage B heart failure at visit 2 (2001–2004) by classification criteria.
This figure highlights the clinical and echocardiographic features that established development of Stage A (**A**) and Stage B (**B**) heart failure, and the percentage (number) of individuals which met those criteria. LAVI indicates left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; and RWMA, regional wall motion abnormalities.

diastolic dysfunction was seen in the majority of those that developed Stage B. NT-proBNP values were similar at visit 1, but were higher at visit 2 in those that developed preclinical HF.

Prior evaluations on the incidence of HF have focused on the development of symptomatic, clinical HF (Stages C and D).[13,40,41] However, with the rise in prevalence of HF there is increasing interest in HF primary prevention, with a focus on the preclinical HF stages (Stages A and B). Previous studies have shown that there is a high prevalence of preclinical HF and that these individuals have both an increased risk of developing clinical HF as well as increased mortality risk.[4–8] We have previously evaluated the progression of preclinical HF and found that 20% of those classified as Stage A or B progressed in HF stage over a 4-year period.[25] The objective of the current study was to explore the natural history of preclinical HF development from a cohort of healthy community-based individuals.

In the current study, nearly half of healthy individuals were able to be categorized as either Stage A or B HF by visit 2. Stage A HF is hallmarked by the presence of cardiovascular risk factors known to be associated with the development of clinical HF and has been reported to be under-recognized.[19] Of those that were classified as Stage A by visit 2 (n=65), the most common comorbidities which influenced their categorization were hypertension and obesity (Figure 2A). Hypertension is a known powerful risk factor in the development of HF, often manifested by the development of diastolic dysfunction.[42–45] Corresponding with this, the current study found that on serial transthoracic echocardiography those that developed Stage A were noted to have higher E/e' and lower e'. There was also a higher prevalence of mild diastolic dysfunction in those that developed Stage A HF. Obesity was also seen commonly in those that developed Stage A HF and has previously been associated with an increased risk of development of HF with preserved ejection fraction.[46,47]

A greater portion of individuals that developed preclinical HF had evidence of asymptomatic functional and structural changes on serial echocardiography. This led to more individuals being categorized as Stage B by visit 2 (n=126). By far, the most frequent characteristic that determined classification as Stage B was the development of preclinical diastolic dysfunction (moderate or greater, Figure 2B). The presence of preclinical systolic dysfunction (LVEF <50%) was uncommon. Individuals that developed Stage B HF had higher E/e', lower e', and higher left atrial volume index values at visit 2, all echocardiographic markers of diastolic dysfunction. Multiple prior studies have demonstrated that preclinical diastolic dysfunction is associated with both an increased risk of clinical HF and an increased mortality risk.[48–52] Within the most recent American College of Cardiology/American Heart Association/Heart Failure Society of America HF guidelines, criteria for Stage B or "pre-HF" now includes those with evidence of increased filling pressures (either invasively or non-invasively by Doppler echocardiography) which will capture those with preclinical diastolic dysfunction.[2] This study adds to the current literature by demonstrating that structural and functional changes related to diastolic function are among the earliest echocardiographic markers of change in patients who develop preclinical HF.

Clinical Implications

The relatively high incidence of preclinical HF over a short 4-year follow-up in the current study demonstrates the importance of recognizing and labeling

Table 3. Comparison of Visit 1 and Visit 2 Characteristics for Individuals that Developed Stage B Heart Failure at Visit 2

	Visit 1 (1997–2000), n=126	Visit 2 (2001–2004), n=126	*P* value
Age, y, mean (SD)	59.0 (8.3)	63.0 (8.3)	…
Women, n (%)	67 (53)	67 (53)	…
BMI, mean (SD), kg/m^2	25.8 (2.6)	26.1 (2.7)	0.009
Systolic blood pressure, mean (SD), mm Hg	121.8 (16.6)	120.5 (16.9)	0.44
Diastolic blood pressure, mean (SD), mm Hg	71.1 (9.2)	68.7 (9.8)	0.002
Heart rate, mean (SD), bpm	64.9 (11.3)	62.8 (10.8)	0.02
Aspirin use, n (%)	22 (21)	24 (21)	>0.99
Comorbidities			
Myocardial infarction, n (%)		2 (2)	
Diabetes, n (%)		1 (1)	
Hypertension, n (%)		23 (18)	
Obesity, n (%)		6 (5)	
Coronary artery disease, n (%)		4 (3)	
Hyperlipidemia, n (%)		16 (14)	
Echocardiogram			
EF, mean (SD), %	63.7 (4.8)	64.4 (7.0)	0.15
Left atrial volume index, mean (SD), mL/m2	21.4 (4.6)	23.6 (6.1)	<0.001
E/e prime, mean (SD)	7.8 (2.0)	11.1 (3.5)	<0.001
e', mean (SD)	0.09 (0.02)	0.07 (0.02)	<0.001
Left ventricular mass index, mean (SD), g/m^2	90.2 (15.5)	92.4 (21.0)	0.92
Left ventricular end-diastolic volume, mean (SD)	95.7 (26.3)	88.9 (27.6)	<0.001
Left ventricular end-systolic volume, mean (SD)	35.2 (12.5)	31.9 (13.1)	0.001
Diastolic dysfunction, mild, n (%)	12 (14)	11 (9)	…
Diastolic dysfunction, moderate or severe, n (%)	0 (0)	84 (71)	
Laboratory data*			
Creatinine, mg/dL	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	<0.001
NT-proBNP†, pg/mL	54.3 (26.2, 96.8)	70.6 (40.5, 117.0)	<0.001
Aldosterone‡, ng/dL	4.0 (2.6, 6.4)	5.0 (2.7, 7.8)	0.12

BMI indicates body mass index; EF, ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Numbers shown are median (25th, 75th percentile).
†Normal reference range 10–138 pg/mL for men and 10–263 pg/mL for women.[33–35]
‡Normal reference range 9.6 ± 1.3 ng/dL.[36]

patients within the appropriate stage on the American College of Cardiology/American Heart Association/Heart Failure Society of America HF continuum, so that appropriate HF prevention strategies can be implemented early. Prior evidence for those at risk for HF, or Stage A, has highlighted the imperative role of healthy lifestyle habits, aggressive risk factor modification, and treatment of cardiovascular comorbidities to reduce risk of HF development.[2,18–20,53,54] Newer to the area of HF prevention is the class of antidiabetic agents, sodium-glucose cotransporter-2 inhibitors. In patients with type 2 diabetes with established cardiovascular disease or at high-risk for cardiovascular disease, sodium-glucose cotransporter-2 inhibitors are now recommended to be used to help prevent hospitalizations for HF.[2,53]

The St Vincent's Screening to Prevent Heart Failure (STOP-HF) study previously evaluated a natriuretic peptide biomarker-based screening strategy in a population of patients with HF risk factors, essentially those who would be classified as Stage A.[16] Those with elevated NT-proBNP values on screening underwent more intensive evaluation and care which included screening echocardiography and initiation of appropriate medical therapy. The implementation of these efforts reduced the risk of incident HF.[16] The present study found that patients who developed Stage A or B HF had statistically significant higher NT-proBNP values at visit 2, and there was a high occurrence of asymptomatic structural and functional echocardiographic abnormalities which developed by visit 2. The current study's findings offer support for a role of natriuretic peptide biomarkers and echocardiography in preclinical HF screening and clinical HF prevention strategies.[9,11]

Recommendations for individuals with Stage B HF are primarily targeted for those with preclinical systolic dysfunction (LVEF <50%), which was uncommon in our study. For those individuals, the use of guideline-approved beta-blockers and angiotensin-converting enzyme inhibitors are recommended to prevent progression of HF.[2] In comparison, apart from continued aggressive lifestyle modifications and management of comorbidities there are currently no specific therapies for preclinical diastolic dysfunction, which was more commonly seen in the present study.[2] However, both improved blood pressure control[11,55,56] and weight loss[11,57] have been shown to improve left ventricular diastolic function parameters. For both Stage A and B HF, further studies are needed to determine if earlier recognition and aggressive treatment of comorbidities can deter progression to clinical HF.

Limitations

This study has limitations that need to be acknowledged to aid in the interpretation of the data. Our study population is from one community in Southeastern Minnesota with a large White population, which may limit the generalizability of the data. The association of cardiac troponin to the development of preclinical HF was unable to be assessed given this data was not available at visit 2. Our study was analyzed conditional on individuals having visit 2; however, there remains the possibility of survival bias contributing to study results.

CONCLUSIONS

This is the first study to describe the natural history of the development of preclinical HF among healthy adults aged ≥45 years in the community. Over a 4-year period, there was a high incidence of preclinical HF (Stages A and B). Hypertension and obesity were the most common comorbidities in those that developed Stage A HF and preclinical diastolic dysfunction was seen commonly in those that developed Stage B.

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Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of Baseline Characteristics for those that Developed Stage A versus Stage B Heart Failure.

	Developed Stage A N=65	Developed Stage B N=126	P value
Age, years, mean (SD)	60 (10)	59 (8)	0.43
Female, n (%)	28 (43)	67 (53)	0.19
BMI, mean (SD), kg/m^2	27 (2)	26 (3)	0.007
Systolic blood pressure, mean (SD), mmHg	133 (21)	122 (17)	<.001
Diastolic blood pressure, mean (SD), mmHg	75 (10)	71 (9)	0.004
Heart rate, mean (SD), bpm	65 (9)	65 (11)	0.74
Aspirin use, n (%)	14 (26)	22 (21)	0.48
Echocardiogram			
EF, mean (SD), %	64 (5)	64 (5)	0.67
Left atrial volume index, mean (SD), mL/m2	22 (4)	21 (5)	0.80
E/e prime, mean (SD)	8 (2)	8 (2)	0.80
e', mean (SD)	0.09 (0.05)	0.09 (0.02)	0.76
Left ventricular mass index, mean (SD), g/m^2	89 (16)	90 (16)	0.67
Left ventricular end-diastolic volume, mean (SD)	94 (25)	96 (26)	0.61
Left ventricular end-systolic volume, mean (SD)	34 (11)	35 (13)	0.47
Diastolic dysfunction, mild, n (%)	8 (13)	14 (12)	0.78
Biomarkers [*]			
Total cholesterol, mg/dL	211 (191, 224)	208 (190, 228)	0.96
HDL cholesterol, mg/dL	42 (36, 51)	48 (40, 57)	0.010
LDL cholesterol, mg/dL	137 (115, 155)	132 (117, 155)	0.76
Triglycerides, mg/dL	128 (78, 176)	113 (85, 149)	0.20
Creatinine, mg/dL	0.90 (0.7, 0.9)	0.80 (0.70, 0.90)	0.23
NT-proBNP [†], pg/mL	34.3 (20.6, 83.1)	54.3 (26.2, 97.8)	0.20
Aldosterone [‡], ng/dL	4.8 (2.5, 7.8)	4.0 (2.5, 6.4)	0.20
Atrial natriuretic peptide [§], pg/ml	11.1 (7.5, 17.1)	9.7 (6.3, 15.2)	0.21
HS-Troponin [ǁ], pg/mL	2.1 (1.5, 3.7)	2.3 (1.5, 3.7)	0.75

BMI= body mass index, EF= ejection fraction, SD= standard deviation

* Numbers shown are median (25^{th}, 75^{th} percentile)

† Normal reference range 10-138 pg/ml for males and 10-263 pg/mL for females [33-35]

‡ Normal reference range 9.6 ± 1.3 ng/dl [36]

§ Normal reference range 25 ± 11 pg/ml [37]

‖ Normal reference range ≤ 40 pg/ml [38, 39]

Table S2. Percent Change in Clinical and Echocardiographic Variables from Visit 1 to Visit 2 For Patients That Remained Normal Compared to Patients That Progressed to Stage A.

Variable Median (Q1, Q3)	Remained Normal (N=202)	Progression to Stage A (N=65)	P-value
Body mass index	0.4 (-0.5, 1.1)	0.8 (-0.3, 2.0)	0.02
Systolic blood pressure	-1.0 (-9.0, 6.0)	-1.0 (-14.0, 6.0)	0.37
Diastolic blood pressure	-2.0 (-8.0, 2.0)	-3.0 (-8.0, 1.0)	0.24
Heart Rate	3.0 (-3.0, 9.0)	4.0 (-3.0, 10.0)	0.77
Ejection fraction	1.0 (-2.0, 5.0)	2.0 (-2.0, 5.0)	0.41
Left atrial volume index	-0.5 (-3.3, 2.1)	-0.5 (-2.6, 2.4)	0.69
Medial E/e’	1.9 (0.8, 3.4)	1.5 (-0.8, 3.1)	0.16
Medial e’	-0.01 (-0.03, 0)	-0.01 (-0.03, 0)	0.27
Left ventricular mass index	-1.2 (-11.9, 9.3)	-2.0 (-9.9, 3.3)	0.51
Left ventricular end-diastolic volume	-4.8 (-21.5, 11.5)	-11.3 (-23.3, 10.5)	0.52
Left ventricular end-systolic volume	-2.0 (-10.5, 6.5)	-2.5 (-9.3, 4.8)	0.41
Creatinine	0 (0, 0.1)	0.1 (0, 0.1)	0.72
NT-proBNP	11.1 (-7.7, 33.3)	17.5 (-5.8, 44.1)	0.24
Aldosterone	1.1 (-0.6, 3.9)	2.5 (-0.2, 5.9)	0.15

Table S3. Percent Change in Clinical and Echocardiographic Variables from Visit 1 to Visit 2 For Patients That Remained Normal Compared to Patients That Progressed to Stage B.

Variable Median (Q1, Q3)	Remained Normal (N=202)	Progression to Stage B (N=126)	P-value
Body mass index	0.4 (-0.5, 1.1)	0.3 (-0.5, 1.1)	0.80
Systolic blood pressure	-1.0 (-9.0, 6.0)	-1.0 (-10.0, 9.0)	0.87
Diastolic blood pressure	-2.0 (-8.0, 2.0)	-2.5 (-8.0, 3.0)	0.99
Heart Rate	3.0 (-3.0, 9.0)	-1.5 (-7.0, 3.0)	<.001
Ejection fraction	1.0 (-2.0, 5.0)	2.0 (-4.0, 5.0)	0.77
Left atrial volume index	-0.5 (-3.3, 2.1)	1.9 (-1.0, 5.7)	<.001
Medial E/e’	1.9 (0.8, 3.4)	2.5 (1.1, 4.9)	0.006
Medial e’	-0.01 (-0.03, 0)	-0.02 (-0.03, 0)	0.31
Left ventricular mass index	-1.2 (-11.9, 9.3)	0.3 (-10.8, 9.9)	0.38
Left ventricular end-diastolic volume	-4.8 (-21.5, 11.5)	-7.0 (-25.3, 3.8)	0.18
Left ventricular end-systolic volume	-2.0 (-10.5, 6.5)	-3.0 (-10.5, 3.3)	0.19
Creatinine	0 (0, 0.1)	0 (0, 0.1)	0.29
NT-proBNP	11.1 (-7.7, 33.3)	16.5 (-7.3, 46.5)	0.15
Aldosterone	1.1 (-0.6, 3.9)	0.3 (-1.7, 2.8)	0.15