Echocardiographic Screening for Non-ischemic Stage B Heart Failure in the Community

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Running title: Community Detection of Stage B Heart Failure

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Abbreviations and Acronyms

2D: two-dimensional
6MW: six minute walk test
ACEi: angiotensin-Converting Enzyme
AF: atrial fibrillation
AIC: Akaike's Information Criterion
BB: beta-blocker
BMI: body mass index
CAD: coronary artery disease
CV: cardio-vascular walk
CART: classification and regression tree
DecT: deceleration time
E/e' mitral inflow peak early diastolic velocity/tissue Doppler early diastolic velocity
ESC: European Society of cardiology
GLS: global longitudinal strain
GCS: global circumferential strain
HF: heart failure
HTN: hypertension
LA: left atrium
LAVi: left atrium volume index
LAE: left atrium enlargement
LV: left ventricle
LVEF: left ventricular ejection fraction
LVH: left ventricular hypertrophy
LVM: left ventricular mass
LVMi: left ventricular mass index
NRI: net reclassification improvement
SAHF: stage A heart failure
SBHF: stage B heart failure
T2DM: type 2 diabetes

Abstract

Background. Incident heart failure (HF) continues to pose a common and serious problem. We sought to examine the value of echocardiographic predictors of new HF in a community-based elderly population at risk for HF, independent of and incremental to clinical evaluation.

Method. Asymptomatic patientse 65 years, withe 1 HF risk (hypertension, type 2 diabetes, obesity) were recruited from the community; patients with valve disease, reduced EF and atrial fibrillation were excluded. Patients underwent standard clinical evaluation including calculation of Charlson comorbidity score and a comprehensive echocardiography including global longitudinal strain (GLS). Functional capacity was assessed by 6 minute-walk test (6MW). New HF and cardiovascular (CV) death were assessed after a mean follow-up of 14±4 months by 3 independent cardiologists using Framingham criteria.

Results. Of 410 subjects (age 70±5 years; 48% men), the prevalence of Stage B HF was 13% (by LVH), 12% (by abnormal E/e'), 33% (by impaired GLS) and 31% (by enlarged LA, LAE). New HF symptoms developed in 49 and 2 died of CV causes, giving an event-rate of 104/1000 person-years. These patients were older ($p=0.012$), had higher Charlson score ($p<0.001$), larger LV mass and LA, higher E/e' and lower GLS ($p<0.05$). LAE, LVH, abnormal GLS and E/e' were independent predictors of new HF. In sequential models, LV mass and GLS added incremental information to clinical parameters. GLS significantly reclassified individuals ($p=0.002$), but no reclassification improvement was identified using LVMi, E/e' and LAVi.

Conclusion – Echocardiographic assessment (especially GLS and LV mass) provides incremental value in predicting incident HF.

The prevalence and cost of congestive heart failure (HF) remain a common and serious problem in the community(1). Treatment of known risk HF risk factors (stage A HF, SAHF), with more intensive targeting of its preclinical stages of asymptomatic left ventricular (LV) damage (stage B HF, SBHF) may be an effective strategy to prevent or delay the onset of HF(2). Previous studies in ischemic SBHF patients with reduced LV ejection fraction (LVEF) have shown that early intervention can delay or prevent the onset of overt HF(3). However, the recognition of these asymptomatic stage B patients requires imaging guidance, so choosing the right test for community screening is an important step. An ideal screening marker needs to be safe, accurate and cost-effective. Previous evidence did not support LVEF-based community-wide screening as it was insufficiently sensitive for detecting early myocardial disease to justify its cost(4). However, recent technological developments have led to the availability of new imaging markers that are sensitive to mild LV impairment.

Among the increasing numbers of patients with non-ischemic SBHF and normal LVEF, increased LV mass(5), increased left atrial (LA) size(6), LV diastolic dysfunction and impaired global longitudinal systolic strain (GLS) (7, 8)have been reported to predict new onset HF. While the extension of echocardiographic features of SBHF from reduced LVEF and/or LV hypertrophy (LVH) to impaired GLS and abnormal diastolic function has been investigated with reference to functional capacity(9), no previous comparison of these imaging markers in relation to subsequent incident HF has been reported in the literature. Accordingly, we sought to compare the prediction of incident HF with common echocardiographic markers of SBHF including LV mass index (LVMi), GLS, LA volume index (LAVi) and diastolic function in a community elderly cohort with non-ischemic SAHF. We hypothesized that GLS would be the optimal screening marker for community detection of non-ischemic SBHF.

Methods

Patient selection. Participants were voluntarily enrolled through local media advertising. Data were prospectively collected from subjects ≥65 years old and living in the community. Inclusion was based on the presence of one or more of HF risk factors: 1) hypertension (HTN, based on SBP >140 mmHg and self-report of HTN including anti-hypertensive medication); 2) type 2 diabetes mellitus (T2DM, based on self-report of diagnosis including medication); 3) obesity (body mass index [BMI] ≥30); 4) previous potentially cardiotoxic chemotherapy; 5) family history of heart failure; 6) previous history of heart disease (but not existing heart failure). We excluded subjects with: 1) symptoms or a known history of HF; 2) known coronary artery disease (CAD) including history of myocardial infarction, coronary artery by-pass graft and coronary stenting; 3) more than moderate valvular heart disease; 4) reduced LVEF (<40%) on baseline echo; 5) atrial fibrillation (AF); 6) inability to acquire interpretable images at baseline. This study was performed in accordance with a research protocol approved by the Human Research Ethics Committee of participating centres in Australia and New Zealand (ACTRN12614000080628). Individual written informed consent was obtained from participants after explanation of the nature and purpose, complexity and level of risk of the study.

Data collection. Data were prospectively collected at facilities in the community, from all participants enrolled in the study. All underwent a physical examination and symptom questionnaire. They also underwent a comprehensive transthoracic echocardiogram and 6MW test. Anthropometric measurements were obtained and body mass index (BMI) was calculated (body weight [kg]/height^2 [m^2]). Blood pressure was measured twice after 10-minutes of rest. Data were also collected on socioeconomic indicators, complete medical history, and family history. The Charlson comorbidity score was used for comorbidity assessment(10).

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens ACUSON SC2000, Siemens Healthcare, Mountain

View, CA) and transducer (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz) in accordance with the American Society of Echocardiography (ASE) guidelines(11, 12). LV dimensions during diastole and systole and wall thicknesses were measured according to the recommended criteria, and LVMi was calculated accordingly (11). LV hypertrophy (LVH) was defined as LVMi>115 g/m^2 in men and >95 g/m^2 in women. LV and LA volumes were calculated by the Simpson biplane method (11), and LA volume was indexed to body surface area, with LA enlargement (LAE) defined as LAVi≥34 ml/m^2.

Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT) were measured for diastolic function assessment(12). Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral and averaged for calculation of E/e'; an averaged E/e'≥13 was defined as abnormal(12).

LV peak longitudinal strain measurements were obtained from gray scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analyzed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS and GLS rate (GLSR) were measured on-line in the community setting by averaging strain from the regional of interest in the apical 4-chamber, 2-chamber and long-axis views. Complete analysis (in all views) was possible due to our baseline exclusion of patients with poor apical images. Impaired GLS was defined using cut-off of <18 %(13). Global circumferential strain (GCS) and GCS rate (GCSR)

Definition of stage B heart failure. Evidence of SBHF required the presence of at least one of the following: 1) LVH; 2) LAE; 3) Abnormal E/e'; 4) Impaired GLS.

Functional capacity. Functional capacity was assessed using a 6-minute walk test (6MW) distance following a standardized protocol(14). Mean peak VO2 was estimated using an established equation(15) for calculation of age and gender adjusted functional capacity.

Follow-up. Potential HF symptoms were assessed through regular follow-up phone calls, followed by symptom surveillance questionnaires and clinical visits. During the process, information on

all-cause hospitalization was monitored and collected. Possible heart failure signs and symptoms were reviewed by 3 independent cardiologists, and heart failure diagnosis was confirmed using the Framingham criteria for HF(16). The primary composite end-point was defined as new-onset of HF and CV death.

Statistical analysis. Data are presented as mean (±standard deviation [SD]) after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. For differences among groups, Mann-Whitney U test was used for continuous variables and X^2 tests for categorical variables. Associations between variables were assessed with Pearson or Spearman correlation coefficients. The primary outcome of time to event was examined with univariable and multivariable Cox proportional hazards models. The independent predictive value of continuous echo variables was assessed by adding each of LVMi, LAVi, and E/e' and GLS to an initial model based on clinical variables. The incremental value of categorical SBHF features was assessed in nested Cox models by sequential addition of LVH, LAE, abnormal E/e' and abnormal GLS. The performance of each model was compared using the Akaike's Information Criterion (AIC), and C statistic. Net Reclassification Improvement (NRI) was based on quartile boundaries of each model probability calculated from the multivariable logistic regression for incremental value of SBHF features over clinical measures(17). Receiver operator characteristic analysis was used to examine the discriminative ability of variables for outcome. Comparisons of AUCs was performed with the method suggested by Hanley and McNeil(18).

A decision–tree model based on the four categorical SBHF markers for the prediction of events was built using classification and regression tree (CART) analysis. In each level of the tree, the variable with strongest relationship to the events was selected. The CART model was built using commercial available software (DTREG 10.8.0, Brentwood TN, USA). Other statistical analyses

were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Statistical significance was defined by $p< 0.05$.

Results

Patient selection. Of 822 individuals from the community who were potentially eligible and volunteered for assessment, 352 were excluded due to failure to meet the baseline clinical inclusion criteria and 42 were excluded after baseline echo screening, leaving 428 patients (median age 70 years [IQR:67-74], 48% men) who underwent baseline testing (patient selection shown in **Appendix F1**). HF risk factors were present in all – most commonly HTN (81%), T2DM (56%) and obesity (46%), which were present in isolation or in combination in 414 out of 428 (97%) of the entire cohort. More than one of the listed risk factors was present in 81%.

Follow-up. After a median interval of 14±4 months (492 person-years) of follow-up, 18 of 428 participants (4%) were lost to follow-up or alive but unable to attend follow-up. This group was no different from the remaining 410 individuals who completed follow-up (**Appendix T1**). New HF symptoms developed in 49 patients, (2 were admitted to hospital with HF) and 4 died (2 of CV causes). The primary composite end-point of new-onset of HF and CV death occurred in 51 (12.4%) of the entire cohort - an event-rate of 104 per 1000 person-years.

Characteristics of individuals with and without events. Table 1 shows the baseline demographic, clinical characteristics of individuals with and without composite endpoint (events). Participants with events were older, had higher BMI, and greater prevalence of T2DM and higher Charlson comorbidity score. There is no difference in medication history and age and gender adjusted functional capacity.

Echocardiographic characteristics. Conventional systolic and diastolic echocardiographic characteristics are also summarized in **Table 1**. Baseline LVEF were preserved in all subjects (e40%) and showed no differences in those with events (p=0.22). Indexed LV sizes were similar

(p=0.19-0.61). Diastolic function grading according to ASE recommendation did not show difference but individuals who had events had higher prevalence of increased E/e' and LAE. Comparisons of the median of LVMi, E/e', GLS and LAVi between individuals with and without events are displayed in **Appendix F1**. According to conventional cut-offs of the 4 markers, the prevalence of SBHF was 13% (by LVH), 12% (by abnormal E/e'), 33% (by impaired GLS) and 31% (by LAE) in the entire population. Of the 51 individuals having events, 25 (49%) had impaired GLS, 26 (51%) had LAE, 12 (24%) had abnormal E/e' and only 10 (20%) had LVH. The annualized incident rate was 16% in LVH, 20% in abnormal E/e', 16% in impaired GLS and 17% in LAE.

Of the entire cohort, 62% had ≥1 of any SBHF features. 41% had one, 15% had two, 5% had three and 1% had all four. The odds ratio of events was 3.24 (95% CI: 1.5-6.8, p=0.002) in those ≥1 of any SBHF features. **Figures 1A and 1B** illustrate the distribution of events according to features of SBHF**.** This level of risk increased in proportion to increasing number of SBHF features **(Figure 2).**

Independent and incremental value of SBHF features to predict outcome. The independent and incremental predictive value of 4 SBHF markers for outcome was examined using both continuous and categorical measures using series of Cox regression models. Based on univariable analysis **(Table 1**), age, gender and Charlson comorbidity score were selected as the variables comprising the initial clinical model for subsequent analysis. In this model, age and Charlson score (but not male gender) were independent predictors. In subsequent models by adding each of the 4 SBHF markers (as continuous variables), LVMi, GLS and LAVi were predictive of outcome, independent of clinical evaluation. However, only LVMi and GLS (not LAVi and E/e') were independent predictors when all measures were combined **(Appendix T2).** Nested models were also used to assess the measures as categorical variables; LAE and impaired GLS (p<0.038) but not LVH and E/e' (p>0.09) were independent and incremental to clinical parameters **(Figure 3).**

Using receiver operating characteristic (ROC) analysis, the discriminatory ability of clinical variables (age, gender, Charlson score) with addition of GLS (AUC: 0.72, p<0.01) exceeded that with LVMi, LAVi and E/e' **(Appendix F3A).** Comparison of AUC showed improvement with the addition of GLS to clinical model (p=0.05), but no improvement with the addition of LVMi, LAVi and E/e' (p>0.14). The discriminatory ability of LVMi, LAVi, E/e' and GLS without clinical variables showed AUC of LVMi, GLS and LAVi were superior to E/e' **(Appendix F3B)**. The incremental value of each SBHF feature over clinical parameters was further examined as net reclassification improvement (NRI). GLS significantly reclassified individuals into a higher risk over clinical risks (NRI: 26%, p=0.001) **(Table 2),** while no NRI improvement was observed using LVMi, E/e' and LAVi (p=0.08-0.09).

In a decision tree based on the four SBHF markers, LAE was the strongest predictor followed by impaired GLS and abnormal E/e', defining three risk groups – low, intermediate and high- risk. This model proposed that LAE should be evaluated first, with GLS applied to patients with normal LA size, and E/e' to those with normal LA and GLS **(Figure 4)**.

Discussion

The results of this study of SBHF, outcome events (mainly new HF) were associated with structural (LVH, LAE) as well as functional (GLS, E/e') changes. Of the 4 common SBHF markers, the presence of any one is associated with a 3-folder higher risk for events. GLS and LVMi were independent predictors, but only GLS was associated with significant incremental value.

Definition of new HF. Heart failure is a clinical diagnosis. Patients in SBHF may minimize or deny their symptoms in the early phases, and clinical recognition can be difficult. The prevalence estimates may vary broadly depending on the diagnostic criteria. A recent meta-analysis reported that incident HF diagnosis in 8 out of 15 included studies was based on a non-standardized clinical description(19). Differences in the diagnostic criteria for HF may have impact on the outcome

assessment in these studies. Among four commonly used HF diagnostic criteria (Framingham, Boston, Gothenburg, and European Society of Cardiology (ESC) criteria) (20), there were significant differences in predicting clinically relevant outcomes including incident hospital admission. The absolute 3-year risk of hospital admission following a Framingham HF diagnosis was 6.1% (odds ratio 2.4, 95% CI 0.8-6.8, p=0.022) (20), and disturbances of cardiac structural and functional characteristics at baseline were best predicted using the Framingham HF criteria (20). Accordingly, we selected the Framingham HF criteria to adjudicate events in our study. It needs to be noted, although we excluded any known and possible HF at baseline, the annualized rate of incident HF was 11%. This may partially be explained by a higher proportion of stage C1 at baseline – it is known that Framingham criteria may not capture mild or early HF (stage C1) in individuals with atypical symptoms(21), and the diagnosis of this subgroup may be helped by the addition of functional assessment and echocardiographic findings. Individuals in stage C1 had a significantly worse outcome than SBHF. A high incidence rate was observed in another community study of a cohort with combined diabetes and hypertension(8), in whom E/e' > 15 (detected in 23%) was used to categorized stage B HF. In our cohort, the prevalence of increased E/e' was lower in entire cohort (12%) but was similar in those with both HTN and T2DM (20%).

Markers of SBHF. The progression of HF is a continuum from hemodynamic disturbance to functional and structural remodeling that precede the onset of symptoms. The conventional non-valvular markers of SBHF are reduced LVEF and LVH(2), which have been found to be insensitive for early disease changes(22); in this study, LVMi was unrelated to events **(Figure 1).** Thus, not only structural markers but also systolic and diastolic dysfunction might be considered components of SBHF(9). However, little is known about which marker(s) may symbolize the earliest changes. Ernande showed both diastolic and strain imaging are early markers(23), but these measurements are often discordant. It is unclear whether these differences reflect different disease entities of SBHF; in our study, of the 51 individuals who had events, 21 had one of four markers; 9

had impaired GLS, 3 had abnormal E/e', 9 had LAE, and none had LVH **(Figure 1).** Markers of SBHF result from underlying causes which often co-exist, including hypertension, diabetes(24, 25), obesity(26) and aging(27); different combinations may explain some differences in their structural responses. In our analysis, GLS was consistently associated with outcome, but the CART model supports consideration of simpler measures (LAE and GLS) as the primary steps for screening, with E/e' adding most when these parameters are normal. This has improved screening efficacy by capturing majority of those with events (82%) (28).

In community screening, the balance between the prevalence of a disease and that of abnormal screening markers to be used are important determinants for screening efficacy. In a community screening study for SBHF, Mureddu used NT-proBNP and ECG screening comparing against echocardiogram as gold standard (29). NT-proBNP screening was only sensitive in detecting those with reduced LVEF (prevalence: 1.5%), which may partially explain authors' conclusion about the inadequacy of this test in the community. The prevalence of LVEFd50% in the local community trials was 5-6%(30), compared to 16-19% for LVH(31); 6-7% for increased E/e'(32) and 46% for LAE (e32 ml/m^2)(6). The prevalence of impaired GLS in our study was 33% using a GLS cutoff of 18% and 17% with a GLS cutoff of 16%. In contrast to previous reported prevalence of 43% SBHF(21), in our study group of >65 year old subjects with HF risk factors, 62% had SBHF if any of the four markers was present, and this captured 42 out of 51 events (82%).

Clinical implications. The identification of SBHF in non-ischemic individuals is difficult, because echocardiography is not currently indicated for routine management. Clearly, an echo screening strategy is most efficient if it is restricted to a high-risk population. A previous echo screening study by Mureddu et al included 19% with known CAD and 7.4% with known valve disease; our approach to these patient has been to exclude them from screening on the basis that their disease warrants therapy. In contrast to our work, follow-up for incident HF was not defined in this study. Our findings provide evidence to justify the use of echocardiography for the prediction of adverse

outcomes. Using LAE and impaired GLS, markers reflecting the burden of diastolic dysfunction and early myocardial alteration, 31% were classified as high (>20%) and intermediate risk (10-20%). In those with normal LAVi and GLS, abnormal E/e' further identified 10% of subjects who belonged to the intermediate risk group, which accounted for 46% of subjects otherwise deemed to be of low risk.

Given the recognized adverse outcome of SBHF, further effort should be made not only to identify this problem but also to monitor and potentially stop disease progression by preventive treatment. Previous trials of SBHF management were largely based on ischemic etiology with reduced LVEF(3), but effective management of non-ischemic SBHF awaits further evidence.

Study limitation. The present analysis was based on a community-based clinical trial and has several limitations. First, a relatively high rate of incident HF in this cohort may suggest the presence of unrecognized HF at baseline. As previously reported, the possibility of high prevalence of stage C1 in this cohort may explain their rapid progress to new HF(21). Second, the concomitant presence of coronary artery disease (CAD) was not investigated. Diabetic cardiomyopathy and hypertensive heart disease may co-exist with atherosclerosis, which may cause LV dysfunction due to CAD. We sought to exclude patients with a history consistent with CAD, but we cannot exclude an ischemic contribution to the reported cardiac functional changes. Third, inclusion of individuals with T2DM based on self-report rather than blood results (due to feasibility and cost constraints, and may thereby underestimate the true prevalence of this disease in the community. Fourth, the lack of protection of clinical outcome by treatment may indicate confounding by indication (i.e. the most at risk patients were treated in primary care, but were more likely to have events. Fifth, we used strain rather than tissue Doppler imaging systolic component (S') for the detection of subclinical systolic dysfunction because of a desire to avoid systolic translational movement. However, it might be considered that tissue velocity is more widely available than speckle tracking. Sixth, recruitment from the community through self-selection inherently carries a risk of population

selection bias. On the other hand, we were interested in patients >65 years (15% of the Tasmanian population), with HF risk factors (probably half of this number). To gather a dataset of 400 patients with an extremely optimistic expectation of 50% engagement would therefore have required screening >10,000 patients. Finally, the relatively short follow-up period is an important limitation of the current study.

Conclusion. Echocardiographic assessment provides incremental value in predicting incident HF. Impaired GLS and LVH were independent predictors; however, impaired GLS was a more sensitive marker with significant incremental value for prediction of HF. The presence of any SBHF feature is associated with more than 3-folder higher risk.

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Figure Legends

Figure 1. Distribution of event cases among patients with LVH, abnormal GLS, and LAE (1A) or abnormal E/e' (1B). Most patients with events have abnormal strain.
(GLS=global longitudinal strain, cutoff [18%]; LAE= left atrial enlargement, cutoff [34 ml/m2]; abnormal E/e', cutoff [13]; LVH= left ventricular hypertrophy, cutoff [>115 g/m^2 for male, >95 g/m2 for female])

Figure 2. Comparison of outcomes between patients with one (left) or multiple markers of stage B heart failure (SBHF, right). There is increasing risk with increasing numbers of echocardiographic abnormalities.
(SAHF=stage A heart failure)

Figure 3. Incremental value of SBHF (categorical) over clinical parameters for composite outcome. LAE and abnormal GLS showed incremental value.
(SBHF=stage B heart failure; Charlson= Charlson comorbidity score; GLS=global longitudinal strain, cutoff [18%]; LAE= left atrial enlargement, cutoff [34 ml/m2]; abnormal E/e', cutoff [13]; LVH= left ventricular hypertrophy, cutoff [>115 g/m^2 for male, >95 g/m2 for female]; Clinical model= age, gender and Charlson comorbidity score)

Figure 4. Echo screening for stage B heart failure and risk stratification.
(GLS= global longitudinal strain)

Table 1. Baseline clinical and echocardiographic characteristics of individuals who developed new HF or cardiovascular (CV) death.

	No Event (n=359)	Event¶ (n=51)	HR (95% CI)	p value
Demographic and clinical characteristics				
Age (years)	70 (67-74)	72 (68-76)	1.070 (1.02, 1.13)	0.012
Gender male (%)	167 (47)	30 (59)	1.567 (0.89, 2.74)	0.115
Body Mass Index (g/m^2)	29 (26-32)	30 (27-35)	1.080 (1.03, 1.13)	0.001
Heart rate (BPM)	67 (60-75)	65 (57-75)	0.977 (0.95, 1.01)	0.119
Systolic blood pressure (mmHg)	139 (128-149)	138 (128-147)	0.995 (0.98, 1.01)	0.526
Diastolic blood pressure (mmHg)	82 (75-87)	81 (73-87)	0.983 (0.96, 1.01)	0.202
Current smoker, n (%)	6 (2)	2 (4)	1.608 (0.39, 6.64)	0.511
Ever Smoker, n (%)	181 (50)	26 (51)	0.791 (0.45, 1.38)	0.410
Type 2 diabetes, n (%)	194 (54)	34 (67)	3.001 (1.65, 5.48)	<0.001
Obese, n (%)	156 (44)	30 (59)	2.353 (1.30, 4.25)	0.004
Hypertension, n (%)	289 (81)	46 (90)	1.450 (0.57, 3.67)	0.433
Previous Chemotherapy, n (%)	35 (10)	3 (6)	0.594 (0.18, 1.91)	0.383
Family History of cardiac disease, n (%)	137 (38)	13 (26)	0.534 (0.28, 1.00)	0.051
Past cardiac History (not HF/CAD), n (%)	18 (5)	6 (11)	1.903 (0.81, 4.49)	0.143
Total # risk factors	3 (3-4)	4 (3-4)	1.466 (1.12, 1.91)	0.005
Charlson comorbidity score	1.0 (0-2)	2.0 (1-4)	1.213 (1.11, 1.33)	<0.001
Medications, n (%)				
Beta blocker	21 (6)	4 (8)	1.911 (0.68, 5.34)	0.217
ACEi/ARB	242 (67)	40 (78)	1.345 (0.69, 2.63)	0.385
Diuretics	45 (14)	6 (13)	0.792 (0.33, 1.88)	0.596
Calcium Ant	72 (23)	15 (33)	1.338 (0.72, 2.49)	0.358
Lipid Lowering Meds	190 (59)	32 (69)	1.887 (1.00, 3.55)	0.049
Antiplatelet	129 (40)	19 (41)	1.159 (0.64, 2.09)	0.623
Functional Capacity				
6MW test distance	485 (427-535)	454 (387-493)	0.996 (0.99, 0.999)	0.006
Functional Capacity (adjusted)	0.72 (0.63-0.82)	0.65 (0.59-0.75)	0.980 (0.96, 1.00)	0.061
Echocardiographic continuous variables, median(IQR)				
LVEDV index (ml/m^2)	44 (38-51)	46 (38-57)	1.013 (0.99, 1.04)	0.317
LVESV index (ml/m^2)	16 (13-19)	17 (14-23)	1.034 (0.98, 1.09)	0.185
Relative Wall Thickness	0.47 (0.42-0.52)	0.47 (0.40-0.52)	2.448 (0.08, 79.4)	0.614
LV mass index (g/m2)	81 (70-95)	90 (76-105)	1.028 (1.01, 1.04)	<0.001
LVEF (%)	64 (61-68)	63 (57-67)	0.972 (0.93, 1.02)	0.220
GLS (%)	18.7 (17.1-20.4)	17.8 (15.7-19.3)	0.841 (0.76, 0.93)	0.001
GLSR (1/s)	1.3 (1.2-1.5)	1.4 (1.2-1.5)	0.746 (0.17, 3.29)	0.699
GCS (%)	28.9 (25.5-32.9)	29.1 (24.6-31.7)	0.991 (0.94, 1.05)	0.741
GCSR (1/s)	2.5 (2.1-2.9)	2.5 (2.2-2.7)	1.228 (0.83, 1.82)	0.304
Mitral E/A	0.77 (0.66-0.91)	0.75 (0.66-0.92)	0.609 (0.16, 2.39)	0.477
DecT (ms)	244 (219-276)	258 (227-306)	1.002 (0.99, 1.01)	0.464
e' (cm/s) (averaged)	7.6 (6.5-8.9)	7.1 (6.1-8.4)	0.885 (0.74, 1.06)	0.186
E/e' (averaged)	8.4 (7.0-10.3)	8.9 (6.9-11.6)	1.099 (1.00, 1.21)	0.050
Diastolic Strain (%)	0.42 (0.32-0.51)	0.42 (0.30-0.54)	0.871 (0.12, 6.16)	0.890
Diastolic Strain rate (1/s)	0.94 (0.79-1.11)	0.89 (0.71-1.02)	0.581 (0.19, 1.75)	0.335
Left atrial volume (ml/m2)	29 (24-35)	34 (26-40)	1.038 (1.01, 1.06)	0.003
Echo categorical variables, n (%)				
LV Hypertrophy (yes)	45 (13)	10 (20)	1.017 (1.01, 1.03)	0.003
Diastolic dysfunction >=grade I (yes) *	229 (64)	37 (73)	1.339 (0.72, 2.49)	0.356
Diastolic dysfunction >=grade II	36 (10)	6 (12)	1.047 (0.45, 2.46)	0.916
Abnormal E/e' (cutoff, 13) (yes)	39 (11)	12 (24)	2.236 (1.16, 4.29)	0.016
Abnormal GLS (cutoff 18) (yes)	109 (30)	25 (49)	2.204 (1.27, 3.83)	0.005
LA Enlargement (cutoff 34) (yes)	103 (29)	26 (51)	2.351 (1.35, 4.10)	0.003
Presence of any SBHF features (yes)¥	212 (59)	42 (82)	3.169 (1.54, 6.53)	0.002

¶Event=primary composite end-point (new HF and death of cardiovascular causes); *Diastolic function grading according ASE recommendation; ¥The presence of at least one of the following: LVH, GLS<18, E/e'>13, LAE
Abbreviation: ACEi: angiotensin converting enzyme; ARB: angiotensin receptor blockers; DecT: mitral inflow deceleration time; EDV: end diastolic volume; ESV: end systolic volume; GLS: global longitudinal strain; GLSR: global longitudinal strain rate; GCS: global circumferential strain; GCSR: global circumferential strain rate; LV: left ventricle; LA: left atrium; LVEF: LV ejection fraction; 6MW: 6-minute walk test.

Table 2. Net Reclassification (Clinical characteristics +GLS)

		(Clinical + GLS)				Increased Risk	Decreased Risk	Net correctly reclassified %
	Composite endpoints (n=51)	Quartile 1 (<6.29%)	Quartile 2 (6.29-9.55%)	Quartile 3 (9.55-15.8%)	Quartile 4 (≥15.8%)	n	n	%
(Clinical)	Quartile 1 (<6.29%)	4	2	0	0	12	3	17.6
	Quartile 2 (6.29-9.55%)	2	1	1	1			
	Quartile 3 (9.55-15.8%)	0	0	7	8			
	Quartile 4 (≥15.8%)	0	0	1	24			
						Reclassified		
						Increased Risk	Decreased Risk	Net correctly reclassified %
	No event (n=359)	Quartile 1 (<6.29%)	Quartile 2 (6.29-9.55%)	Quartile 3 (9.55-15.8%)	Quartile 4 (≥15.8%)	n	n	%
	Quartile 1 (<6.29%)	85	11	1	0	51	82	8.64
	Quartile 2 (6.29-9.55%)	34	42	19	2			
	Quartile 3 (9.55-15.8%)	4	24	42	18			
	Quartile 4 (≥15.8%)	0	2	18	57			
	Net reclassification improvement (NRI) **p=0.002**							26.24

Clinical characteristics include: age, gender, body mass index, Charlson comorbidity score.
GLS: global longitudinal strain