ORIGINAL RESEARCH ARTICLE

# Age-specific diastolic dysfunction improves prediction of symptomatic heart failure by Stage B heart failure

Jennifer M. Coller[1], Fei Fei Gong[1,2,3], Michele McGrady[4], Michael V. Jelinek[1,3], Julian M. Castro[1], Umberto Boffa[5], Louise Shiel[5], Danny Liew[5], Simon Stewart[6], Henry Krum[5†], Christopher M. Reid[5,7], David L. Prior[1,3] and Duncan J. Campbell[1,2,3]*

[1]Department of Cardiology, St. Vincent's Hospital, Melbourne, Australia; [2]Molecular Cardiology, St. Vincent's Institute of Medical Research, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia; [3]Department of Medicine, University of Melbourne, Parkville, Australia; [4]Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, Australia; [5]School of Public Health and Preventive Medicine, Monash University, Prahran, Australia; [6]Department of Cardiology, The Queen Elizabeth Hospital, Adelaide, Australia; [7]School of Public Health, Curtin University, Bentley, Australia

## Abstract

**Aims**  We investigated whether addition of diastolic dysfunction (DD) and longitudinal strain (LS) to Stage B heart failure (SBHF) criteria (structural or systolic abnormality) improves prediction of symptomatic HF in participants of the SCReening Evaluation of the Evolution of New Heart Failure study, a self-selected population at increased cardiovascular disease risk recruited from members of a health insurance fund in Melbourne and Shepparton, Australia. Both American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) criteria and age-specific Atherosclerosis Risk in Communities (ARIC) study criteria, for SBHF and DD, and ARIC criteria for abnormal LS, were examined.
**Methods and results**  Inclusion criteria were age ≥60 years with one or more of self-reported ischaemic or other heart disease, irregular or rapid heart rhythm, cerebrovascular disease, renal impairment, or treatment for hypertension or diabetes for ≥2 years. Exclusion criteria were known HF, or ejection fraction <50% or >mild valve abnormality detected on previous echocardiography or other imaging. Echocardiography was performed in 3190 participants who were followed for a median of 3.9 (interquartile range: 3.4, 4.5) years after echocardiography. Symptomatic HF was diagnosed in 139 participants at a median of 3.1 (interquartile range: 2.1, 3.9) years after echocardiography. ARIC structural, systolic, and diastolic abnormalities predicted HF in univariate and multivariable proportional hazards analyses, whereas ASE/EACVI structural and systolic, but not diastolic, abnormalities predicted HF. ARIC and ASE/EACVI SBHF criteria predicted HF with sensitivities of 81% and 55%, specificities of 39% and 76%, and C statistics of 0.60 (95% confidence interval: 0.57, 0.64) and 0.66 (0.61, 0.71), respectively. Adding ARIC DD to SBHF increased sensitivity to 94% with specificity of 24% and C statistic of 0.59 (0.57, 0.61), whereas addition of ASE/EACVI DD to SBHF increased sensitivity to 97% but reduced specificity to 9% and the C statistic to 0.52 (0.50, 0.54, $P < 0.0001$). Addition of LS to ARIC or ASE/EACVI SBHF criteria had minimal impact on prediction of HF.
**Conclusions**  Age-specific ARIC DD criteria, but not ASE/EACVI DD criteria, predicted symptomatic HF, and addition of age-specific ARIC DD criteria to ARIC SBHF criteria improved prediction of symptomatic HF in asymptomatic individuals with cardiovascular disease risk factors. Addition of LS to ASE/EACVI or ARIC SBHF criteria did not improve prediction of symptomatic HF.

## Introduction

Heart failure (HF) is a complex and progressive clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood,[1] with a lifetime risk of 20% to 46%.[2] HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels, or metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) structure or function.[1] The American College of

Cardiology Foundation and American Heart Association guideline describes four stages of HF, Stages A and B that are asymptomatic and Stages C and D that are symptomatic.[1] Stage A HF refers to asymptomatic individuals with cardiovascular disease (CVD) risk factors but without structural heart disease, whereas Stage B HF (SBHF) refers to asymptomatic individuals with structural heart disease, which may include any of LV dilatation, LV hypertrophy (LVH), reduced LV ejection fraction (LVEF), wall motion abnormalities (WMAs), and moderate or greater aortic or mitral stenosis or regurgitation.[3,4] SBHF predicts symptomatic HF,[3,4] and its recognition offers an opportunity to use cardioprotective medication and/or lifestyle modification to prevent or retard its progression to symptomatic HF. There has been discussion about how best to define SBHF with respect to cut-offs for LV dimensions, LVH, and LVEF, and whether inclusion of diastolic dysfunction (DD) and longitudinal strain (LS) as part of SBHF criteria improves the prediction of symptomatic HF.[3–6]

Age-related changes in cardiac structure and function are well recognized, including smaller LV size, greater LVEF, and lower early diastolic mitral annular tissue Doppler velocities (TDI e′).[7,8] The American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) guideline describes normal ranges based on populations with mean ages ranging from 37 to 50 years,[7] whereas the Atherosclerosis Risk in Communities (ARIC) study defined 95th percentile limits derived from the ARIC study healthy subgroup aged 67–91 years. In comparison with the ASE/EACVI guidelines, ARIC cut points are higher for LVEF, lower for LV end diastolic volume indexed to body surface area (LVEDV/BSA), LV mass (LVM) indexed to height$^{2.7}$ and TDI septal e′, and similar for the peak early diastolic mitral flow E/e′ ratio and left atrial volume (LAV) indexed to BSA.[3,7,9,10] In the present study, we compared the prevalence of SBHF in a community-based cohort of individuals aged ≥60 years with CVD risk factors using ASE/EACVI and ARIC criteria and investigated whether addition of DD and LS to SBHF criteria improved the prediction of symptomatic HF. We hypothesized that addition of DD and LS to SBHF criteria improves the prediction of symptomatic HF.

## Methods

### Study population

The SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) study was a community-based evaluation of the use of serum amino-terminal pro-B-type natriuretic peptide to identify individuals with cardiac dysfunction (as assessed by echocardiography) and increased risk of HF and other CVD events. The study has been described elsewhere,[11–13] and participant recruitment and baseline

assessment are described in the Supporting Information. A flow chart for participant recruitment and follow-up is shown in Supporting Information, *Figure S1*. The SCREEN-HF study was approved by the Alfred Human Research Ethics Committee, conformed to the ethical standards of the Declaration of Helsinki, and written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov NCT00400257, NCT00604006, and NCT01581827.

### Follow-up

Participants were examined for signs of HF during Visits 2 and 3. Details of symptoms, interim clinical events, and medication were collected at each visit and also by telephone interview (Supporting Information, *Figure S1*). In order to capture all incident cases of HF, a participant was referred to their cardiologist or to a SCREEN-HF study cardiologist if he or she reported symptoms consistent with HF or if signs consistent with HF were detected during a study visit, and information was requested from the participant's primary care provider, physician, and cardiologist. All participant files were reviewed by a cardiovascular physician, and documentation of all deaths and other events was requested from hospitals and the participant's primary care provider, physician, and cardiologist. All diagnoses of HF and suspicion of HF were submitted to adjudication by two HF specialists according to European Society of Cardiology criteria of 2012.[14] When one adjudicator made a diagnosis of HF and the other did not, a third HF specialist adjudicated on the presence or absence of HF. We excluded 23 participants who developed HF before the echocardiography visit.

### Echocardiographic assessment

Cardiac structure and function were assessed using transthoracic echocardiography with either a Vivid 7 (*n* = 2929) or Vivid i (*n* = 261) instrument (GE Healthcare, Chicago, Illinois, USA). Echocardiography was performed according to ASE/EACVI guidelines.[7,9,10,15] Data were stored in raw data format and analysed offline by two experienced cardiologists. Interobserver intraclass correlation coefficients (ICCs) for M-mode measurements were >0.78 for wall thickness, >0.88 for LA diameter, and >0.9 for other M-mode measurements, ≥0.87 for two-dimensional measurements, >0.85 for standard Doppler measurements except pulmonary vein A wave velocity, and >0.92 for tissue Doppler measurements. Intraobserver ICCs were generally higher than for interobserver ICCs. Pulmonary vein A wave velocity and duration are not reported because interobserver and intraobserver ICCs were <0.6.

Left ventricular dimensions were estimated using the two-dimensional-guided M-mode approach.[7] LVM was calculated

using the two-dimensional area–length method when endocardial definition and alignment in the parasternal short-axis view were satisfactory and also with the linear method.[7] LVM from either method was indexed to BSA and, for LVM estimated by the linear method, was also indexed to height.[2,7,9] LVEF was calculated using the modified Simpson's biplane method. Where endocardial definition was poor in both four-chamber and two-chamber views, the LVEF was visually estimated, and LV volumes were not calculated. LV regional WMA was identified based on the presence of hypokinesis, akinesis, or dyskinesis of two or more contiguous segments of the LV.

Measures of diastolic function were estimated according to the 2016 ASE/EACVI guideline.[10] LAV was calculated using the biplane method of disks from LA areas measured in the apical four-chamber and two-chamber views in the frame prior to mitral valve opening.[7] LV inflow was obtained using pulsed wave Doppler in the apical four-chamber view; peak early (E) and late (A) diastolic velocities, deceleration time, and E/A ratio were obtained. Peak early diastolic medial and lateral mitral annular e' were measured from pulsed TDI and E/e' obtained. Mitral and aortic valve function was assessed and graded according to American College of Cardiology Foundation guidelines.[16] The right ventricle was assessed according to ASE guidelines.[9,17]

Longitudinal strain was assessed using speckle-tracking and EchoPac software (GE Healthcare) when the frame rate was ≥30 frames per cardiac cycle.[18] The endocardial border of the left ventricle was traced in the apical four-chamber and two-chamber views at end-systole where the region of interest was automatically defined and the integrity of the speckle tracking was visually assessed and manually corrected if required. Peak systolic strain in the two views was averaged to obtain LS. LS was not measured if more than two segments in either the four-chamber or two-chamber view could not be tracked. In the setting of a rhythm other than sinus rhythm, LS measurement was performed using 5 cycles and averaged. LS is not reported for participants with left bundle branch block or paced rhythm.

## Definitions of Stage B heart failure

ASE/EACVI SBHF criteria were at least one of LVEF <52% (men) or <54% (women); WMA; LVEDV/BSA >74 mL/m$^2$ (men) and >61 mL/m$^2$ (women); LVM/BSA >115 g/m$^2$ (men) or >95 g/m$^2$ (women), linear method, or >102 g/m$^2$ (men) or >88 g/m$^2$ (women), area–length method; and moderate or greater stenosis or regurgitation of the aortic or mitral valve.[7] We examined the effect of addition of ASE/EACVI DD criteria to this definition: at least one of septal e' <7 cm/s; lateral e' <10 cm/s; septal E/e' ratio >15; lateral E/e' ratio >13; average E/e' ratio >14; and LAV/BSA >34 mL/m$^2$.[10]

ARIC SBHF criteria were at least one of LVEF <59% (men) or <57.4% (women); WMA; LVEDV/BSA >60.2 mL/m$^2$ (men) or >51.9 mL/m$^2$ (women); LVM/height$^{2.7}$ >45 g/m$^{2.7}$ (men) or >41.5 g/m$^{2.7}$ (women), linear method; and moderate or greater stenosis or regurgitation of the aortic or mitral valve.[3] We examined the effect of addition of ARIC DD criteria to this definition: at least one of septal e' <4.3 cm/s (men) or <4.1 cm/s (women); septal E/e' ratio >14.8 (men) or >17.4 (women); and LAV/BSA >34.2 mL/m$^2$ (men) or >32.4 mL/m$^2$ (women).[3]

We also examined the effect of addition of LS to ASE/EACVI and ARIC SBHF criteria, using ARIC cut points (>−14.7% in men and >−15.2% in women) and a cut point of >−18%.[5]

## Statistical analysis

Continuous variables are presented as median (interquartile range). Categorical variables are presented as percentages. Differences between groups were tested with Mann–Whitney $U$ test for continuous variables and $\chi^2$ tests for categorical variables, and statistical significance was interpreted as a two-tailed $P$ value <0.05. Hazard ratios were calculated using a semiparametric proportional hazards model for the subdistribution of the competing risk of death,[19] and follow-up was restricted to 4 years (106 cases) to ensure proportional hazards assumptions were met. Receiver operating characteristic (ROC) C statistics were estimated from time-dependent ROC curves for censored event times with the competing risk of death.[20] Analyses were conducted using Statview 5.0.1 (SAS Institute, Cary, NC, USA) and R.

# Results

## Baseline clinical characteristics

The baseline characteristics of participants who attended and those who did not attend for echocardiography are shown in Supporting Information, *Table S1*. At the time of echocardiography, participants who attended for echocardiography had a median age of 71 (interquartile range: 67, 77) years, 55% were male, 89% of men and 94% of women had hypertension, 20% of men and 15% of women had diabetes, 34% of men and 37% of women were obese (body mass index ≥30 kg/m$^2$), 49% of men and 39% of women were overweight (25 < body mass index < 30 kg/m$^2$), 19% of men and 20% of women had an estimated glomerular filtration rate <60 mL/min/1.73 m$^2$, 14% of men and 10% of women had atrial fibrillation (AF), 15% of men and 5% of women had previous myocardial infarction, and 31% of men and 14% of women had a history of ischaemic heart disease.

## Echocardiography

Measures of LV and LA structure are shown in *Table 1*. Approximately 3% of participants had increased LVEDV/BSA according to ASE/EACVI criteria, whereas 16% of men and 11% of women had increased LVEDV/BSA according to ARIC criteria. LVM/BSA was elevated in 16% to 29% of participants when LVM was estimated by either the area–length or linear method, according to ASE/EACVI criteria. However, the proportion with LVH was approximately two-fold higher when LVM was indexed to height[2.7], using either ASE and European Association of Echocardiography[9] or ARIC criteria.[3] Approximately half of participants had elevated LAV/BSA, with similar proportions according to ASE/EACVI and ARIC criteria.

Measures of systolic function and valve abnormality are shown in *Table 2*. LVEF was reduced in 10.2% of men and 6.3% of women, according to ASE/EACVI criteria, and in 46% of men and 24% of women (36% of men and women), according to ARIC criteria. LS was measured in only 1401 participants (*Table 2*), who resembled the whole cohort in that 492 (35%) had reduced LVEF according to ARIC criteria. Among those with LS measurement, abnormal LS was present in 6% of men and 3% of women according to the ARIC criteria. LS was abnormal in only 1.8% of men and 1.3% of women with normal LVEF according to ASE/EACVI criteria who had LS measurement. These proportions were reduced to 0.5% of men and women when ARIC criteria were used to define normal LVEF.

Measures of diastolic LV function, and right ventricular function, are shown in *Table 3*. The higher e′ cut point of

the ASE/EACVI criteria caused more than half of participants to have reduced septal or lateral e′, whereas only 6% of men and 5.9% of women had reduced septal e′ according to ARIC criteria. However, similar proportions of participants had elevated septal E/e′ ratio (6% to 15%) according to ASE/EACVI and ARIC criteria.

## Structural, systolic, and diastolic abnormalities and incident symptomatic heart failure

The 3190 participants were followed for a median of 3.9 (interquartile range: 3.4, 4.5) years, and symptomatic HF was diagnosed in 139 participants at a median of 3.1 (interquartile range: 2.1, 3.9) years after echocardiography, representing an incidence rate of 11.2 per 1000 person years. Symptomatic HF was diagnosed in 83 participants in the ambulant setting and in 56 participants on hospitalization; 35 diagnosed in the ambulant setting were subsequently hospitalized with HF.

The distributions of structural, systolic, and diastolic abnormalities according to ASE/EACVI and ARIC criteria are shown in *Figure 1*. Higher numbers of participants had structural abnormality according to ARIC (*n* = 1390) than ASE/EACVI criteria (*n* = 584), reflecting the higher prevalence of LVH when LVM was indexed to height[2.7] (*Table 1*). Moreover, higher numbers of participants had systolic abnormality according to ARIC (*n* = 1167) than ASE/EACVI criteria (*n* = 329), reflecting the higher LVEF cut points for ARIC than ASE/EACVI criteria (*Table 2*). By contrast, more participants had diastolic abnormality according to

**Table 1** Measures of left ventricular and left atrial structure in men and women

| Parameter | Men (*n* = 1762) | | Women (*n* = 1428) | |
|---|---|---|---|---|
| | Number of measurements (%) | Value | Number of measurements (%) | Value |
| LVEDD/BSA (mm/m$^2$) | 1446 (82%) | 26 (24, 28) | 1223 (86%) | 27 (25, 29) |
| >Normal[a] | >30 mm/m$^2$ | 165 (11%) | >31 mm/m$^2$ | 179 (15%) |
| LVEDV/BSA (mL/m$^2$) | 1333 (76%) | 48 (42, 56) | 1036 (73%) | 41 (35, 47) |
| >Normal[a] | >74 mL/m$^2$ | 43 (3.2%) | >61 mL/m$^2$ | 25 (2.4%) |
| >Normal[b] | >60.2 mL/m$^2$ | 216 (16%) | >51.9 mL/m$^2$ | 114 (11%) |
| LVM$^{AL}$/BSA (g/m$^2$) | 927 (62%) | 88 (80, 97) | 856 (68%) | 77 (70, 86) |
| >Normal[a] | >102 g/m$^2$ | 147 (16%) | >88 g/m$^2$ | 173 (20%) |
| LVM$^{LIN}$/BSA (g/m$^2$) | 1439 (82%) | 95 (80, 110) | 1213 (85%) | 83 (71, 99) |
| >Normal[a] | >115 g/m$^2$ | 291 (20%) | >95 g/m$^2$ | 354 (29%) |
| LVM$^{LIN}$/height$^{2.7}$ (g/m$^{2.7}$) | 1439 (82%) | 43 (36, 51) | 1213 (85%) | 42 (35, 51) |
| >Normal[c] | >48 (g/m$^{2.7}$) | 485 (34%) | >44 (g/m$^{2.7}$) | 520 (43%) |
| >Normal[b] | >45 (g/m$^{2.7}$) | 613 (43%) | >41.5 (g/m$^{2.7}$) | 628 (52%) |
| LAV/BSA (mL/m$^2$) | 1682 (95%) | 34 (28, 41) | 1362 (95%) | 32 (26, 39) |
| >Normal[a] | >34.0 mL/m$^2$ | 848 (50%) | >34.0 mL/m$^2$ | 574 (42%) |
| >Normal[b] | >34.2 mL/m$^2$ | 833 (50%) | >32.4 mL/m$^2$ | 657 (48%) |

BSA, body surface area; LAV, left atrial volume; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVM$^{AL}$, LVM determined by area–length method; LVM$^{LIN}$, LVM determined by the linear method.
Summary statistics are median (interquartile range) or *n* (%).
[a]American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[7]
[b]Atherosclerosis Risk in Communities study 95th percentile limit.[3]
[c]American Society of Echocardiography and European Association of Echocardiography guidelines.[9]

**Table 2** Measures of left ventricular systolic function and valve abnormality in men and women

| Parameter | Men (n = 1762) | | Women (n = 1428) | |
|---|---|---|---|---|
| | Number of measurements (%) | Value | Number of measurements (%) | Value |
| Systolic function | | | | |
| LVEF (%) | 1760 (99.9%) | 60 (55, 62) | 1427 (99.9%) | 60 (58, 63) |
| <Normal[a] | <52% | 180 (10.2%) | <54% | 90 (6.3%) |
| <Normal[b] | <59% | 805 (46%) | <57.4% | 338 (24%) |
| LVEF <40% | | 25 (1.4%) | | 2 (0.1%) |
| WMA | | 145 (8.2%) | | 32 (2.2%) |
| LS (%) | 792 (45%) | −19.3 (−17.9, −20.8) | 609 (43%) | −20.1 (−18.8, −21.7) |
| Abnormal LS[b] | >−14.7% | 48 (6%) | >−15.2% | 17 (3%) |
| Aortic stenosis | >mild | 8 (0.5%) | >mild | 3 (0.2%) |
| Aortic regurgitation | >mild | 6 (0.3%) | >mild | 7 (0.5%) |
| Mitral stenosis | >mild | 0 (0%) | >mild | 0 (0%) |
| Mitral regurgitation | >mild | 19 (1.1%) | >mild | 12 (0.8%) |
| Tricuspid regurgitation | >mild | 23 (1.3%) | >mild | 29 (2.0%) |
| Pulmonary regurgitation | >mild | 7 (0.4%) | >mild | 10 (0.7%) |
| Aortic or mitral valve disease | >mild | 33 (1.9%) | >mild | 22 (1.5%) |

LS, longitudinal strain; LVEF, left ventricular ejection fraction; WMA, wall motion abnormality.
Summary statistics are median (interquartile range) or n (%).
[a]American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[7]
[b]Atherosclerosis Risk in Communities study 95th percentile limit.[3]

**Table 3** Measures of left ventricular diastolic function, and right ventricular function, in men and women

| Parameter | Men (n = 1762) | | Women (n = 1428) | |
|---|---|---|---|---|
| | Number of measurements (%) | Value | Number of measurements (%) | Value |
| Diastolic function (mitral valve Doppler and TDI measurements) | | | | |
| E/A ratio | 1599 (91%) | 0.89 (0.74, 1.08) | 1343 (94%) | 0.87 (0.73, 1.05) |
| Reduced E/A ratio[a] | ≤0.8 | 550 (34%) | ≤0.8 | 491 (37%) |
| Increased E/A ratio[a] | ≥2 | 11 (0.7%) | ≥2 | 13 (1.0%) |
| Septal e′ (cm/s) | 1598 (91%) | 6.5 (5.5, 7.6) | 1331 (93%) | 6.3 (5.2, 7.4) |
| Reduced septal e′[a] | <7 cm/s | 972 (61%) | <7 cm/s | 875 (66%) |
| Reduced septal e′[b] | <4.3 cm/s | 96 (6.0%) | <4.1 cm/s | 78 (5.9%) |
| Lateral e′ (cm/s) | 1590 (90%) | 8.5 (7.0, 10.0) | 1332 (93%) | 7.9 (6.6, 9.3) |
| Reduced lateral e′[a] | <10 cm/s | 1184 (74%) | <10 cm/s | 1119 (85%) |
| Septal E/e′ ratio | 1565 (89%) | 9.5 (7.9, 11.8) | 1310 (92%) | 10.9 (9.0, 13.3) |
| >Normal septal E/e′ ratio[a] | >15 | 119 (7.6%) | >15 | 192 (15%) |
| >Normal septal E/e′ ratio[b] | >14.8 | 130 (8.3%) | >17.4 | 84 (6.4%) |
| Lateral E/e′ ratio | 1556 (88%) | 7.4 (5.9, 9.2) | 1301 (91%) | 8.6 (7.1, 10.8) |
| >Normal septal E/e′ ratio[a] | >13 | 87 (5.6%) | >13 | 140 (11%) |
| Average E/e′ ratio | 1548 (88%) | 8.6 (7.1, 10.4) | 1294 (91%) | 9.8 (8.3, 12.0) |
| Increased average E/e′ ratio[a] | >14 | 85 (5.5%) | >14 | 147 (11.3%) |
| PV S/D ratio | 1496 (85%) | 1.4 (1.2, 1.7) | 1211 (85%) | 1.5 (1.3, 1.7) |
| Reduced S/D ratio[a] | <1 | 151 (10%) | <1 | 95 (8%) |
| Right ventricle | | | | |
| RV dilatation | | 42 (2.4%) | | 20 (1.4%) |
| RV dysfunction | | 39 (2.2%) | | 6 (0.4%) |
| RVSP (mmHg) | 691 (39%) | 27 (24, 31) | 670 (47%) | 26 (23, 31) |
| Increased RVSP[c] | >36 mmHg | 73 (10.6%) | >36 mmHg | 61 (9.1%) |
| TR max velocity (m/s) | 725 (41%) | 2.4 (2.3, 2.6) | 708 (50%) | 2.4 (2.2, 2.6) |
| Increased TR velocity[a] | >2.8 m/s | 74 (10%) | >2.8 m/s | 72 (10%) |

A velocity, peak mitral inflow during atrial contraction; E velocity, peak mitral inflow in early diastole; e′, peak mitral annular velocity in early diastole; PV S/D ratio, ratio of systolic and diastolic velocities in the pulmonary vein; RV, right ventricle; RVSP, RV systolic pressure; TDI, tissue Doppler imaging; TR, tricuspid regurgitation.
Summary statistics are median (interquartile range) or n (%).
[a]American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines for the evaluation of diastolic function.[10]
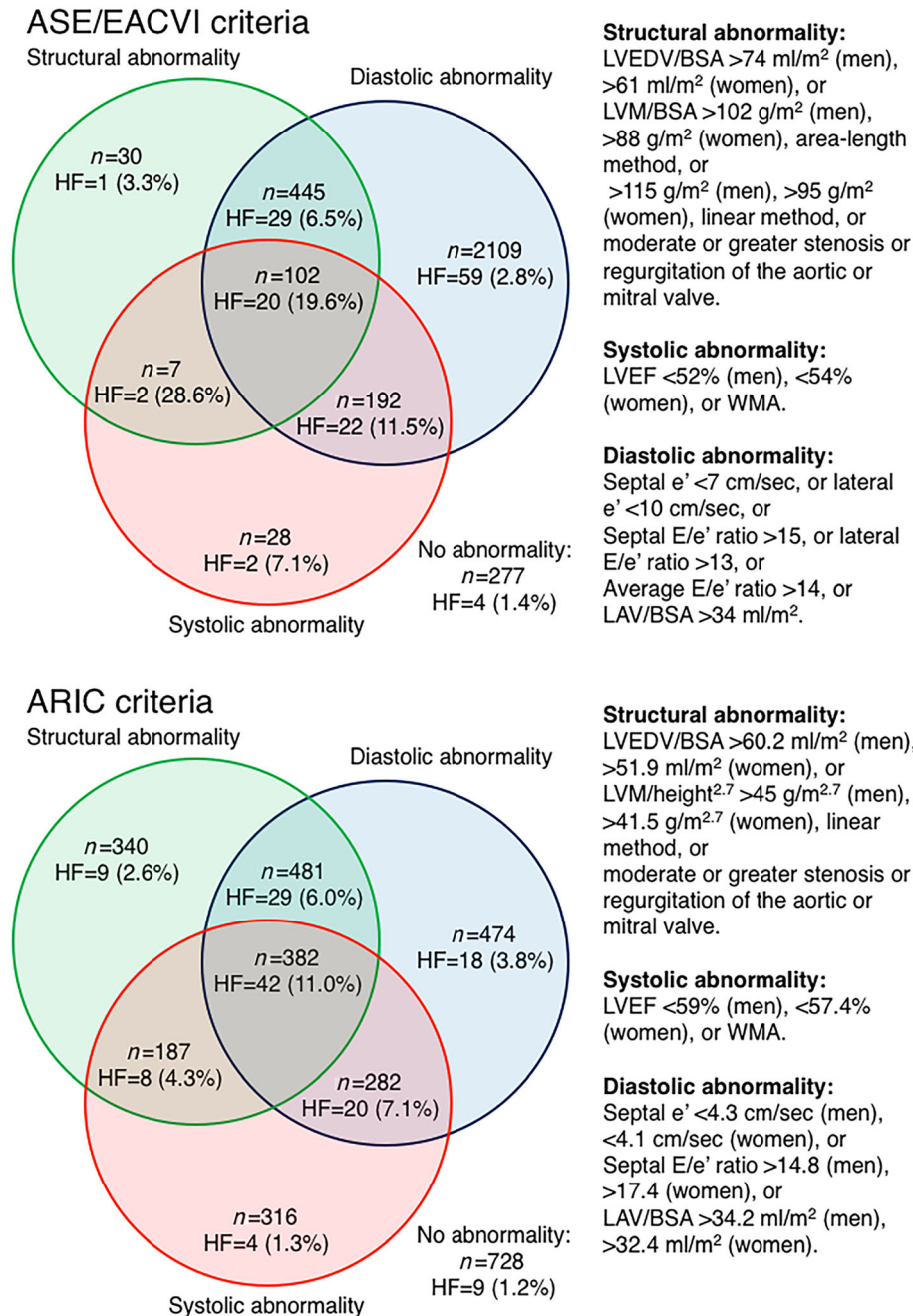[b]Atherosclerosis Risk in Communities study 95th percentile limit.[3]
[c]American Society of Echocardiography guidelines for assessment of the right heart.[17] RV dysfunction defined as ≥mild dysfunction, and RV dilatation defined as ≥mild dilatation.[9]

ASE/EACVI (n = 2848) than ARIC criteria (n = 1619), largely reflecting the higher e′ cut points for ASE/EACVI than ARIC criteria (Table 3).

ARIC structural, systolic, and diastolic abnormalities predicted HF in univariate and multivariable proportional hazards analyses, whereas ASE/EACVI structural and systolic, but not

**Figure 1** Venn diagram demonstrating the numbers of SCREEN-HF participants (men and women) with structural, systolic, and diastolic abnormalities, according to the ASE/EACVI and ARIC guidelines, and the number (%) in each category who subsequently developed heart failure (HF). BSA, body surface area; LAV, left atrial volume; LVEDV, LV end diastolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; WMA, wall motion abnormality.

## ASE/EACVI criteria

Structural abnormality

$n=30$
HF=1 (3.3%)

Diastolic abnormality

$n=445$
HF=29 (6.5%)

$n=2109$
HF=59 (2.8%)

$n=102$
HF=20 (19.6%)

$n=7$
HF=2 (28.6%)

$n=192$
HF=22 (11.5%)

$n=28$
HF=2 (7.1%)

No abnormality:
$n=277$
HF=4 (1.4%)

Systolic abnormality

**Structural abnormality:**
LVEDV/BSA >74 ml/m$^2$ (men), >61 ml/m$^2$ (women), or LVM/BSA >102 g/m$^2$ (men), >88 g/m$^2$ (women), area-length method, or >115 g/m$^2$ (men), >95 g/m$^2$ (women), linear method, or moderate or greater stenosis or regurgitation of the aortic or mitral valve.

**Systolic abnormality:**
LVEF <52% (men), <54% (women), or WMA.

**Diastolic abnormality:**
Septal e' <7 cm/sec, or lateral e' <10 cm/sec, or Septal E/e' ratio >15, or lateral E/e' ratio >13, or Average E/e' ratio >14, or LAV/BSA >34 ml/m$^2$.

## ARIC criteria

Structural abnormality

$n=340$
HF=9 (2.6%)

Diastolic abnormality

$n=481$
HF=29 (6.0%)

$n=474$
HF=18 (3.8%)

$n=382$
HF=42 (11.0%)

$n=187$
HF=8 (4.3%)

$n=282$
HF=20 (7.1%)

$n=316$
HF=4 (1.3%)

No abnormality:
$n=728$
HF=9 (1.2%)

Systolic abnormality

**Structural abnormality:**
LVEDV/BSA >60.2 ml/m$^2$ (men), >51.9 ml/m$^2$ (women), or LVM/height$^{2.7}$ >45 g/m$^{2.7}$ (men), >41.5 g/m$^{2.7}$ (women), linear method, or moderate or greater stenosis or regurgitation of the aortic or mitral valve.

**Systolic abnormality:**
LVEF <59% (men), <57.4% (women), or WMA.

**Diastolic abnormality:**
Septal e' <4.3 cm/sec (men), <4.1 cm/sec (women), or Septal E/e' ratio >14.8 (men), >17.4 (women), or LAV/BSA >34.2 ml/m$^2$ (men), >32.4 ml/m$^2$ (women).

diastolic, abnormalities predicted HF (*Table 4*). ROC curve analysis confirmed the results of Cox regression analysis, with statistically significant C statistics for ARIC criteria for structural, systolic, and diastolic abnormalities, but only for ASE/EACVI structural and systolic, and not diastolic, abnormalities (*Figure 2*).

## Stage B heart failure and incident symptomatic heart failure

Given the higher prevalence of structural and systolic abnormalities for ARIC criteria, 2.5-fold more participants had ARIC SBHF ($n = 1988$) than ASE/EACVI SBHF ($n = 804$). The C statistics

**Table 4** Cox regression: univariate and multivariable subdistribution hazard ratios

| Parameter | Univariate hazard ratios | | Multivariable hazard ratios | |
|---|---|---|---|---|
| | (95% CI) | P values | (95% CI) | P values |
| ASE/EACVI criteria | | | | |
| Age (per decade) | 2.68 (2.03, 3.54) | <0.0001 | 2.33 (1.68, 3.24) | <0.0001 |
| Male gender | 1.37 (0.96, 1.95) | 0.085 | | |
| Structural abnormality | 3.27 (2.17, 4.93) | <0.0001 | 2.19 (1.42, 3.27) | 0.0004 |
| Systolic abnormality | 5.58 (3.77, 8.27) | <0.0001 | 3.82 (2.43, 6.01) | <0.0001 |
| Diastolic abnormality | 1.48 (0.69, 3.19) | 0.31 | | |
| ARIC criteria | | | | |
| Age (per decade) | 2.68 (2.03, 3.54) | <0.0001 | 2.23 (1.62, 3.05) | <0.0001 |
| Male gender | 1.37 (0.96, 1.95) | 0.085 | | |
| Structural abnormality | 3.16 (2.00, 4.99) | <0.0001 | 2.40 (1.50, 3.83) | 0.0003 |
| Systolic abnormality | 2.48 (1.68, 3.64) | <0.0001 | 1.81 (1.19, 2.74) | 0.0056 |
| Diastolic abnormality | 5.35 (3.14, 9.12) | <0.0001 | 3.47 (1.94, 6.21) | <0.0001 |

ARIC, Atherosclerosis Risk in Communities; ASE/EACVI, American Society of Echocardiography and European Association of Cardiovascular Imaging; CI, confidence interval.
Hazard ratios were calculated using a semiparametric proportional hazards model for the subdistribution of the competing risk of death.[19] The ASE/EACVI and ARIC criteria for structural, systolic, and diastolic abnormality are described in *Figure 1*.

for ARIC SBHF [0.60, 95% confidence interval (CI): 0.57, 0.64] and ASE/EACVI SBHF (0.66, 95% CI: 0.61, 0.71) were not significantly different (P = 0.07 at 4 years), although ARIC SBHF criteria achieved 81% sensitivity for prediction of incident symptomatic HF, in comparison with 55% for ASE/EACVI SBHF criteria, at the expense of lower specificity (*Figure 2*).

## Addition of diastolic dysfunction to Stage B heart failure criteria

Nearly twice as many participants had DD according to the ASE/EACVI (n = 2848) than the ARIC criteria (n = 1619), and addition of DD to SBHF criteria increased the total number with any structural, systolic, or diastolic abnormality to 2913 (91% of participants) according to ASE/EACVI criteria and 2462 (77% of participants) according to ARIC criteria (*Figure 1*). Addition of ASE/EACVI DD to ASE/EACVI SBHF criteria increased the sensitivity of prediction of symptomatic HF to 97%, at the expense of reduced specificity (9%), and reduction in the C statistic to 0.52 (95% CI: 0.50, 0.54, P < 0.0001 in comparison with ASE/EACVI SBHF criteria), whereas addition of ARIC DD to ARIC SBHF criteria increased sensitivity to 94%, without change in the C statistic (0.59, 95% CI: 0.57, 0.61), which was higher than for combined ASE/EACVI SBHF and DD criteria (P < 0.0001, *Figure 2*).

## Addition of longitudinal strain to Stage B heart failure criteria

Of the 1401 participants with LS measurement, 45 developed symptomatic HF and 373 were classified as SBHF by ASE/EACVI criteria, which included 26 (58%) of the 45 participants who developed HF. This sensitivity of 58% was similar to the sensitivity of 55% for ASE/EACVI SBHF criteria applied
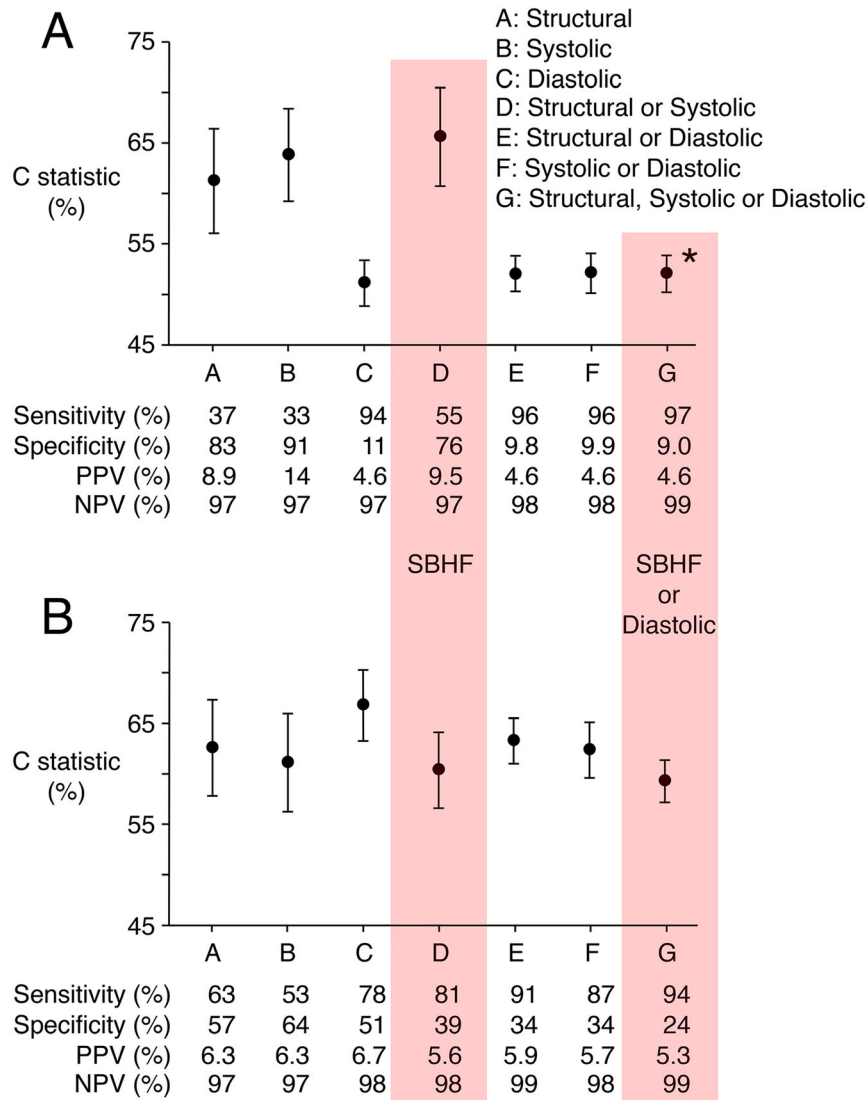
to the whole cohort (*Figure 2*). Addition of ARIC LS criteria (>−14.7% for men, >−15.2% for women) to ASE/EACVI SBHF criteria increased the number with abnormality to 386 but did not identify additional participants who developed symptomatic HF. Addition of LS >−18% to ASE/EACVI SBHF criteria increased the number with abnormality to 522 and identified an additional six participants who developed symptomatic HF, bringing the number to 32 (sensitivity 71%).

ARIC criteria classified 723 of the 1401 participants with LS measurement as SBHF. Participants with ARIC SBHF included 35 of the 45 with LS measurement who developed symptomatic HF (sensitivity 78%), similar to the sensitivity of 81% for ARIC SBHF criteria applied to the whole cohort (*Figure 2*). Addition of ARIC LS criteria (>−14.7% for men, >−15.2% for women) to ARIC SBHF criteria increased the number with abnormality to 897 but did not identify additional participants who developed symptomatic HF. Addition of LS >−18% to ARIC SBHF criteria increased the number with abnormality to 938 and identified one additional participant who developed HF, bringing the number to 36 (sensitivity 80%).

## Discussion

Both the ASE/EACVI and ARIC criteria identified a high prevalence of echocardiographic abnormalities in this community-based Australian cohort ≥60 years of age with CVD risk factors, and both ASE/EACVI and ARIC SBHF criteria (cardiac structural or systolic abnormalities) predicted symptomatic HF. In contrast to previous studies that examined the prediction of a composite of HF hospitalization or death,[3] or a composite of new onset HF and cardiovascular death,[5] we examined the prediction of incident symptomatic HF using models adjusted for the competing risk of death,[19,20] and most cases of incident HF were

**Figure 2** C statistics, sensitivities, specificities, positive (PPV) and negative (NPV) predictive values for the prediction of symptomatic HF by structural, systolic, and diastolic abnormalities, and their combination, according to ASE/EACVI (Panel A) and ARIC criteria (Panel B). C statistics were calculated from the receiver operating characteristic curve for 4 years follow-up after echocardiography, adjusted for competing risk of death.[20] Sensitivity, specificity, PPV, and NPV were calculated for complete follow-up. *P < 0.0001 in comparison with ASE/EACVI SBHF criteria (Panel A) and in comparison with combined SBHF and DD according to ARIC criteria (Panel B). The C statistic for combined ARIC SBHF and DD criteria was not statistically significantly different from that for ARIC SBHF alone.



Panel legend:
A: Structural
B: Systolic
C: Diastolic
D: Structural or Systolic
E: Structural or Diastolic
F: Systolic or Diastolic
G: Structural, Systolic or Diastolic

Panel A:

|                 | A   | B   | C   | D   | E   | F   | G   |
|-----------------|-----|-----|-----|-----|-----|-----|-----|
| Sensitivity (%) | 37  | 33  | 94  | 55  | 96  | 96  | 97  |
| Specificity (%) | 83  | 91  | 11  | 76  | 9.8 | 9.9 | 9.0 |
| PPV (%)         | 8.9 | 14  | 4.6 | 9.5 | 4.6 | 4.6 | 4.6 |
| NPV (%)         | 97  | 97  | 97  | 97  | 98  | 98  | 99  |

Panel B:

|                 | A   | B   | C   | D   | E   | F   | G   |
|-----------------|-----|-----|-----|-----|-----|-----|-----|
| Sensitivity (%) | 63  | 53  | 78  | 81  | 91  | 87  | 94  |
| Specificity (%) | 57  | 64  | 51  | 39  | 34  | 34  | 24  |
| PPV (%)         | 6.3 | 6.3 | 6.7 | 5.6 | 5.9 | 5.7 | 5.3 |
| NPV (%)         | 97  | 97  | 98  | 98  | 99  | 98  | 99  |

diagnosed in the ambulant setting. We also showed that the addition of DD, but not LS, to SBHF criteria improved the prediction of symptomatic HF according to ARIC criteria, but not according to ASE/EACVI criteria.

The different performance of ASE/EACVI and ARIC SBHF criteria in predicting symptomatic HF in SCREEN-HF participants may have been due in part to the different ages of the populations from which these criteria were derived. The age of our cohort (median 71 years) more closely resembled that of the ARIC study (median 75 years),[3] whereas the ASE/EACVI guideline cut points were

determined in younger populations.[7] We were unable to define cut points for the SCREEN-HF cohort because none were free of CVD risk factors.

Our finding that ARIC criteria for LVH, based on LVM/height$^{2.7}$, identified more than twice as many SCREEN-HF participants with structural abnormality than ASE/EACVI criteria for LVH based on LVM/BSA was in agreement with previous studies demonstrating that normalization of LVM to BSA underestimates LVH prevalence in obese and overweight hypertensive subjects, who comprised the majority of SCREEN-HF participants.[21–24] In addition, ARIC criteria

identified 3.5-fold more SCREEN-HF participants with systolic dysfunction than ASE/EACVI criteria, due to the higher LVEF cut points for ARIC criteria. Consequently, ARIC criteria classified 2.5-fold more SCREEN-HF participants as SBHF than ASE/EACVI criteria, thereby achieving higher sensitivity for the prediction of symptomatic HF while maintaining similar C indices.

The identification of nearly twice as many SCREEN-HF participants with DD according to ASE/EACVI than ARIC criteria was largely due to the lower $e'$ cut points of the ARIC criteria. Our findings support the conclusion of Shah et al. that $e'$ values below the ASE/EACVI cut points, but above the ARIC cut points, are largely prognostically benign[25] and support the use of the age-specific ARIC cut points for $e'$.

Some authors have used alternative definitions of SBHF. For example, Yang et al. defined SBHF as at least one of LVM/BSA $>115$ g/m$^2$ for men or $>95$ g/m$^2$ for women, LAV/BSA $>34$ mL/m$^2$, average E/$e'$ $>13$, and LS $>-18\%$.[5] Wang et al. used a similar definition except that the LS cut point was $>-16\%$.[6] Neither definition included LVEF.[5,6] Yang et al. reported a sensitivity of 82% and specificity of 41% for the prediction of symptomatic HF by their SBHF algorithm in asymptomatic patients $\geq 65$ years of age with at least one HF risk factor,[5] which is comparable with the 81% sensitivity and 39% specificity we obtained in the SCREEN-HF cohort for ARIC SBHF criteria alone. There were, however, differences in study design and event rates between the study of Yang et al. and the SCREEN-HF study. Unlike Yang et al., we did not exclude any participant because of poor images, AF, or known coronary artery disease. Moreover, despite these exclusions, Yang et al. reported an HF incidence rate of ~100 per 1000 person years, which was ~nine-fold higher than we observed in the SCREEN-HF cohort.[5]

In contrast to the studies of Yang et al. and Wang et al.,[5,6] we found that LS made little contribution to the prediction of symptomatic HF when added to either ASE/EACVI or ARIC SBHF criteria. The importance of this observation is that LVEF is an established echocardiographic parameter that can be measured in almost all patients, whereas reliable LS measurement may not be possible in the same high proportion of echocardiographic examinations. Moreover, use of an LS cut point is problematic because echocardiographic equipment from different manufacturers has different normal values and there is no consensus about the cut points that define abnormal LS.[7]

### Strengths and limitations of the study

The strengths of our study include the diagnosis of HF in a predominantly ambulant setting and the long duration of observation before HF diagnosis. Our outcome data were for HF, and not a composite of HF and death, as used in previous studies.[3,25] We enrolled a cohort $\geq 60$ years of age with CVD risk factors in order to achieve sufficient events during follow-up. However, we excluded individuals known at baseline to have LVEF $<50\%$ or significant valve abnormality because such individuals have well-recognized HF risk, and our aim was to identify otherwise unrecognized HF risk in a community cohort. The inclusion criteria with respect to age and CVD risk factors, and the SCREEN-HF cohort comprising volunteers who were predominantly members of a health fund, may be cause for caution in the generalization of our findings to the general community. However, the SCREEN-HF cohort was not that dissimilar to the general Australian population aged $\geq 60$ years; of Australians aged 65–74 years, 70% have hypertension,[26] 17% have diabetes,[27] 38.2% of men and 32.7% of women are obese,[28] 5% have AF,[29] and 53% have CVD,[30] and our findings are therefore likely to be applicable to the general community.

## Conclusions and implications

Both the ASE/EACVI and ARIC criteria demonstrated a high prevalence of echocardiographic abnormalities in an Australian cohort $\geq 60$ years of age with CVD risk factors, and SBHF criteria (cardiac structural or systolic abnormalities) predicted symptomatic HF. Age-specific ARIC DD criteria, but not ASE/EACVI DD criteria, predicted symptomatic HF, and addition of age-specific ARIC DD criteria to ARIC SBHF criteria improved prediction of symptomatic HF in asymptomatic individuals with CVD risk factors. Addition of LS to ASE/EACVI or ARIC SBHF criteria did not improve prediction of symptomatic HF.

## Acknowledgements

## Conflict of interest

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Characteristics on enrolment (Visit 1) of SCREEN-HF participants who subsequently attended for echocardiography and those who did not

**Figure S1.** Flow chart of numbers of individuals invited to participate in the SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) study who were subsequently enrolled and attended Visit 1 and subsequent echocardiography (Visit 2).

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