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

Jennifer M. Coller1, Fei Fei Gong1,2,3, Michele McGrady4, Michael V. Jelinek1,3, Julian M. Castro1, Umberto Boffa5, Louise Shiel5, Danny Liew5, Simon Stewart6, Henry Krum5†, Christopher M. Reid5,6,7, David L. Prior1,3 and Duncan J. Campbell1,2,3*

1Department of Cardiology, St. Vincent’s Hospital, Melbourne, Australia; 2Molecular Cardiology, St. Vincent’s Institute of Medical Research, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia; 3Department of Medicine, University of Melbourne, Parkville, Australia; 4Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, Australia; 5School of Public Health and Preventive Medicine, Monash University, Prahran, Australia; 6Department of Cardiology, The Queen Elizabeth Hospital, Adelaide, Australia; 7School 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 risk factors. Addition of LS to ASE/EACVI or ARIC SBHF criteria did not improve prediction of symptomatic HF.

Keywords Heart failure; Stage B; Echocardiography; Diastolic dysfunction; Longitudinal strain

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.3 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. 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 (WMA), and moderate or greater aortic or mitral stenosis or regurgitation. SBHF predicts symptomatic HF 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.

Age-related changes in cardiac structure and function are well recognized, including smaller LV size, greater LVEF, and lower early diastolic mitral annulus tissue Doppler velocities (TDI e’). 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, 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 and TDI septal e’, and similar for the peak early diastolic mitral flow E/e’ ratio and left atrial volume (LAV) indexed to BSA. 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, 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 S2). 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. 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. 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. LVM was calculated.
using the two-dimensional area–length method when endo-
cardial 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
height2,7.9 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 vi-
sually estimated, and LV volumes were not calculated. LV re-
gional 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.2 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 e0 were measured from pulsed
TDI and E/e0 obtained. Mitral and aortic valve function was
assessed and graded according to American College of Cardi-
ology 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 inter-
est was automatically defined and the integrity of the speckle
tracking was visually assessed and manually corrected if re-
quired. 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/m2
(men) and >61 mL/m2 (women); LVM/BSA >115 g/m2
(men) or >95 g/m2 (women), linear method, or
>102 g/m2 (men) or >88 g/m2 (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 e0 <7 cm/s; lateral e0 <10 cm/s; septal E/e0
ratio >15; lateral E/e0 ratio >13; average E/e0 ratio >14;
and LAV/BSA >34 mL/m2.10

ARIC SBHF criteria were at least one of LVEF <59% (men)
or <57.4% (women); WMA; LVEDV/BSA >60.2 mL/m2
(men) or >51.9 mL/m2 (women); LVM/height2,7 >45 g/m2
(men) or >41.5 g/m2, (women), linear method; and moder-
ate 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 e0 <4.3 cm/s (men)
or <4.1 cm/s (women); septal E/e0 ratio >14.8 (men) or >17.4
(women); and LAV/BSA >34.2 mL/m2 (men) or >32.4 mL/
m2 (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 (interquar-
tile range). Categorical variables are presented as percentages.
Differences between groups were tested with Mann–
Whitney U test for continuous variables and χ2 tests for cat-
ergorical 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 propor-
tional 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 echocardiog-
raphy, 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/m2), 49% of men and 39% of women were overweight
(25 < body mass index < 30 kg/m2), 19% of men and 20% of
women had an estimated glomerular filtration rate
<60 mL/min/1.73 m2, 14% of men and 10% of women had
atrial fibrillation (AF), 15% of men and 5% of women had pre-
vious 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\(^7\) 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 2). 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

| Parameter                      | Men (n = 1762) |   |   | Women (n = 1428) |   |   |
|-------------------------------|---------------|---|---|----------------|---|---|
|                               | Number of measurements (%) | Value | Number of measurements (%) | Value |
| LVEDD/BSA (mm/m²)             | 1446 (82%)    | 26 (24, 28) | 1223 (86%)    | 27 (25, 29) |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 30 mm/m²                    | 165 (11%)     |             | 179 (15%)     |             |
| LVEDV/BSA (mL/m²)             | 1333 (76%)    | 48 (42, 56) | 1036 (73%)    | 41 (35, 47) |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 74 mL/m²                    | 43 (3.2%)     |             | 25 (2.4%)     |             |
| LVM\(\text{a}\)/BSA (g/m²)   | 927 (62%)     | 88 (80, 97) | 856 (68%)     | 77 (70, 86) |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 102 g/m²                    | 147 (16%)     |             | 173 (20%)     |             |
| LVM\(\text{a}\)/height\(2,7\) (g/m²\(2,7\)) | 1439 (82%) | 95 (80, 110) | 1213 (85%)    | 83 (71, 99) |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 115 g/m²                    | 291 (20%)     |             | 354 (29%)     |             |
| LVM\(\text{a}\)/height\(2,7\) (g/m²\(2,7\)) | 1439 (82%) | 43 (36, 51) | 1213 (85%)    | 42 (35, 51) |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 48 g/m²\(2,7\)             | 485 (34%)     |             | 520 (43%)     |             |
| LAV/BSA (mL/m²)               | 1682 (95%)    | 34 (28, 41) | 1362 (95%)    | 32 (26, 39) |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 34.0 mL/m²                  | 848 (50%)     |             | 574 (42%)     |             |
| > Normal\(\text{a}\)          |               |             |               |             |
| > 34.2 mL/m²                  | 833 (50%)     |             | 657 (48%)     |             |

BSA, body surface area; LAV, left atrial volume; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVM\(\text{a}\), LVM determined by area–length method; LVM\(\text{a}\)/BSA, LVM determined by the linear method.

Summary statistics are median (interquartile range) or n (%).

\(\text{a}\)American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.\(^7\)

\(\text{b}\)Atherosclerosis Risk in Communities study 95th percentile limit.\(^3\)

\(\text{c}\)American Society of Echocardiography and European Association of Echocardiography guidelines.\(^9\)
Diastolic function (mitral valve Doppler and TDI measurements).

Summary statistics are median (interquartile range) or LS, longitudinal strain; LVEF, left ventricular ejection fraction; WMA, wall motion abnormality.

Aortic or mitral valve disease

Pulmonary regurgitation

Tricuspid regurgitation

Mitral regurgitation

Mitral stenosis

Aortic regurgitation

Aortic stenosis

Systolic function

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

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 (%) | 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, 9.9) | 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 b | >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 (%).

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, 9.9) | 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 b | >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%) |

Summary statistics are median (interquartile range) or n (%).

A/AE/EACVI 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 (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...
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 $\geq 60$ 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, a or a composite of new onset HF and cardiovascular death, b we examined the prediction of incident symptomatic HF using models adjusted for the competing risk of death, c,d and most cases of incident HF were
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), whereas the ASE/EACVI guideline cut points were determined in younger populations. 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\(^2\), 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. In addition, ARIC criteria

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**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.\(^2\) 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.
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 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 $>-18%$. Wang et al. used a similar definition except that the LS cut point was $>-16%$. Neither definition included LVEF. 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, 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 $\sim 100$ per 1000 person years, which was $\sim$nine-fold higher than we observed in the SCREEN-HF cohort.

In contrast to the studies of Yang et al. and Wang et al., 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.

**Strengths and limitations of the study**

The strengths of our study include the diagnosis of HF in a predominantly ambulatory 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. 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, 17% have diabetes, 38.2% of men and 32.7% of women are obese, 5% have AF, and 53% have CVD, 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**

We thank all SCREEN-HF study participants and the study nurses, echocardiographers, and administrative staff for their invaluable contribution.

**Conflict of interest**

Bupa Australia was involved in study design, recruitment of participants, and funding but was not involved in data collection, analysis or interpretation, or writing of the article. Bupa Australia had no control or influence over the decision to submit the final manuscript for publication.

J.M.Ca. has received payments from Pfizer, Servier, Bayer, and Alphapharm for lectures. U.B. was an employee of Bupa Australia. D.L. has received honoraria from Pfizer, Sanofi, Astra-Zeneca, Abbott, Bayer, MSD, GSK, Novartis, and Nycomed. S.S. has received unrestricted educational grants from Schering Plough and Boehringer Ingelheim and was...
Principal Investigator of the Novartis sponsored Valsartan Intensified Primary Care Reduction of Blood Pressure (VIPER-BP) study. H.K. received support from Novartis, Bristol-Myers Squibb, and Adrain/Medtronic. D.L.P. has received payment from Servier for sitting on their advisory board and from Boehringer Ingelheim, CSL, Merck Sharp & Dohme, and Sanofi Aventis for lectures. D.J.C. has received payments from the Australasian Renin Academy for lectures.

Funding

This work was supported by Bupa Australia, with subsequent support from the National Health and Medical Research Council of Australia (GTN0559010, GTN1044619, GTN1092642, GTN0395508 to D.J.C., GTN1045862, GTN1136372 to C.M.R., GTN1041796 to S.S., GTN0620241 to J.M.Co., GTN0519456 to M.M.), the National Heart Foundation of Australia (G 07M 3198), the Diabetes Australia Research Trust (Y15G-CAMD), The University of Melbourne, St. Vincent’s Hospital Melbourne, St. Vincent’s Institute of Medical Research, and the Victorian Government’s Operational Infrastructure Support Program.

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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Author/s:
Coller, JM; Gong, FF; McGrady, M; Jelinek, M; Castro, JM; Boffa, U; Shiel, L; Liew, D; Stewart, S; Krum, H; Reid, CM; Prior, DL; Campbell, DJ

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

Date:
2019-08-01

Citation:
Coller, J. M., Gong, F. F., McGrady, M., Jelinek, M., Castro, J. M., Boffa, U., Shiel, L., Liew, D., Stewart, S., Krum, H., Reid, C. M., Prior, D. L. & Campbell, D. J. (2019). Age-specific diastolic dysfunction improves prediction of symptomatic heart failure by Stage B heart failure. ESC HEART FAILURE, 6 (4), pp.747-757. https://doi.org/10.1002/ehf2.12449.

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