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Predicting Heart Failure Hospitalization and Mortality by Quantitative Echocardiography: Is Body Surface Area the Indexing Method of Choice? The Heart and Soul Study

Bryan Ristow, MD, **Sadia Ali, MD, MPH**, **Beeya Na, MPH**, **Mintu P. Turakhia, MD**, **Mary A. Whooley, MD**, and **Nelson B. Schiller, MD, FACC**
California Pacific Medical Center, San Francisco, California (B.R.); Veterans Affairs Medical Center, San Francisco, California (S.A., B.N., M.A.W.); Veterans Affairs Palo Alto Health Care System, Stanford University, Palo Alto, California (M.P.T.); and University of California, San Francisco, California (N.B.S.)

Abstract

Background—Echocardiographic measurements of left ventricular (LV) mass, left atrial (LA) volume, and LV end-systolic volume (ESV) predict heart failure (HF) hospitalization and mortality. Indexing measurements by body size is thought to establish limits of normality among individuals varying in body habitus. The American Society of Echocardiography recommends dividing measurements by body surface area (BSA), but others have advocated alternative indexing methods.

Methods—Echocardiographic measurements were collected in 1024 ambulatory adults with coronary artery disease. LV mass, LA volume, and LV ESV were calculated using truncated ellipse method and biplane method of disk formulae. Comparison between raw measurements and measurements divided by indexing parameters was made by hazard ratios per standard deviation increase in variable and c-statistics for BSA, $BSA^{0.43}$, $BSA^{1.5}$, height, $height^{0.25}$, $height^2$, $height^{2.7}$, body weight (BW), $BW^{0.26}$, body mass index (BMI), and $BMI^{0.27}$.

Results—Mean LV mass was 192 ± 57 g, mean LA volume was 65 ± 24 mL, and mean LV ESV was 41 ± 26 mL. Average height was 171 ± 9 cm, average BSA was 1.94 ± 0.22 m^2, and average BMI was 28.4 ± 5.3 kg/m^2. At an average follow-up of 5.6 ± 1.8 years, there were 148 HF hospitalizations, 71 cardiovascular (CV) deaths, and 269 all-cause deaths. There was excellent correlation between raw measurements and those indexed by height (r = 0.98–0.99), and moderate correlation between raw measurements and those indexed by BW (r = 0.73–0.94). C-statistics and hazard ratios per standard deviation increase in indexed variables were similar for HF hospitalization, CV mortality, and all-cause mortality. There were no significant differences among indexing methods in ability to predict outcomes.

Conclusion—The choice of indexing method by parameters of BSA, height, BW, and BMI does not affect the clinical usefulness of LV mass, LA volume, and LV ESV in predicting HF hospitalization, CV mortality, or all-cause mortality among ambulatory adults with coronary artery disease. Continued use of BSA to index measurements of LV mass, LA volume, and LV ESV is acceptable.

Reprint requests: Bryan Ristow, MD, California Pacific Medical Center, Kanbar Cardiology Center, 2333 Buchanan St, San Francisco, CA 94115 (ristowb@sutterhealth.org).

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Keywords

Body surface area; Echocardiography; Heart failure; Mortality; Quantitative

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Echocardiographic measurements of left ventricular (LV) hypertrophy, LV dilatation, and left atrial (LA) dilatation are predictive of adverse events. Specifically, LV wall thickness,[1] LV mass,[2,3] LA diameter,[4,5] LA volume,[6] and LVend-systolic volume (ESV)[7] are predictive of heart failure (HF) hospitalization and mortality. Indexing measurements to body size may provide additional useful and prognostic information, because larger individuals normally have larger heart size. The ideal indexing method should identify abnormal increases in chamber dimensions through diverse body types. The American Society of Echocardiography recognizes debate about the best indexing method but recommends reporting normal measurements indexed, or divided by, body surface area (BSA).[8]

Indexing measurements to BSA has limitations, because the BSA calculation is complex,[9] has different formulae,[10–13] and may falsely normalize obese individuals, obscuring pathologic remodeling. In other words, indexing to BSA may underestimate the prevalence of dilated or hypertrophied chambers in overweight individuals.[8] The use of BSA has been questioned,[14] and alternative indexes have been proposed, including powers of height, $BSA^{1.5}$, body weight $(BW)^{0.26}$, and body mass index $(BMI)^{0.27}$.[15–19] Determination of the best indexing method has application in echocardiography and in any imaging modality where limits of normal size are reported. Standardization of indexing method would allow comparison among reference values and echocardiographic laboratories.[20] We hypothesized that chamber volumes and LV mass predict HF hospitalization and mortality, and that BSA is as useful as other indexing methods to adjust measurements for body size.

MATERIALS AND METHODS

Study Participants

The Heart and Soul Study is a prospective cohort study with the objective of evaluating psychosocial factors and health outcomes in patients with coronary disease. Methods and objectives have been described.[21] We used administrative databases to identify outpatients with documented coronary artery disease (CAD) at 2 Department of Veterans Affairs Medical Centers (San Francisco Veterans Affairs Medical Center and the Veterans Affairs Palo Alto Health Care System, California), 1 university medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had at least 1 of the following: a history of myocardial infarction, angiographic evidence of at least 50% stenosis in 1 or more coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of CAD by an internist or cardiologist.

A total of 15,438 eligible patients were mailed an invitation to participate, and 2,495 responded that they would be interested. Of the 2,495 patients whom we attempted to contact by telephone to schedule a study appointment, 505 could not be reached and 596 declined to participate. An additional 370 patients were excluded because they had a history of myocardial infarction in the prior 6 months, deemed themselves unable to walk 1 block, or were planning to move out of the local area within 3 years.

Between September 2000 and December 2002, a total of 1024 participants enrolled, including 549 (54%) with a history of myocardial infarction, 237 (23%) with a history of revascularization but not myocardial infarction, and 238 (23%) with a diagnosis of CAD that was documented by their physician (based on a positive angiogram or treadmill test in > 98% of cases).

This protocol was approved by the following institutional review boards: the Committee on Human Research at the University of California, San Francisco; the Research and Development Committee at the San Francisco Veterans Affairs Medical Center; the Medical Human Subjects Committee at Stanford University; the Human Subjects Committee at the Veterans Affairs Palo Alto Health Care System; and the Data Governance Board of the Community Health Network of San Francisco. All participants provided written informed consent.

Data Collection

Each participant completed a detailed interview and questionnaire regarding age, gender, race, medical history, current smoking, and level of alcohol consumption. Echocardiographic studies were performed in the standard left lateral recumbent and supine positions with a commercially available ultrasound system with harmonic imaging (Acuson Sequoia, Siemens Corporation, Mountain View, CA). A single cardiologist (NBS), blinded to clinical and laboratory information, evaluated each comprehensive resting echocardiogram. ESV and LA volume were calculated using the biplane method of discs in the apical 4- and 2-chamber views at end systole, as recommended by the American Society of Echocardiography. LV mass was calculated from 2-dimensional wall thickness using the truncated ellipse method, using the semi-major and minor axis radius of the left ventricle.[8]

Cardiovascular Outcomes

We conducted telephone follow-up interviews and questioned participants or their proxies regarding hospitalizations and mortality. Medical records, death certificates, and coroner's reports were retrieved. Two blinded adjudicators reviewed each event, and if there was agreement the outcome classification was binding. If there was disagreement, a third blinded adjudicator reviewed the event and determined the outcome classification. All-cause mortality results were complete for at least 1 year of follow-up for 1,018 of 1,024 individuals. Five individuals were completely lost to follow-up, and 1 individual declined to participate further in the study.

Hospitalization for HF was defined as a clinical syndrome requiring a minimum one-night hospital stay and involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, a third heart sound, cardiomegaly on chest radiography, or pulmonary edema on chest radiography. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and must have been accompanied by either failing cardiac output as determined by peripheral hypoperfusion (in the absence of other causes, eg, sepsis or dehydration) or peripheral or pulmonary edema treated with intravenous diuretics, inotropes, or vasodilators.

Mortality adjudications were based on hospital records, death certificates, and autopsy results. Death was considered due to cardiovascular (CV) causes if the death certificate listed acute myocardial infarction, congestive HF, or arrhythmia as the primary cause of death. Sudden death also was considered CV if it was unexpected, otherwise unexplained, and occurred within 1 hour of the onset of terminal symptoms.

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Statistical Analysis

Baseline characteristics are reported as the mean plus or minus standard deviation for continuous variables and as percentages for categoric variables. Given the limitation of differentiating among risk factors by comparisons of hazard ratios (HRs) or c-statistic alone,[22–24] we made calculations for both HR and c-statistic for each variable indexed to different parameters of body size. We used Cox proportional hazards (survival) models to calculate HR. To further explore our hypothesis that BSA is as useful as other methods of indexing for body size, we directly compared parameters indexed to basic values (BSA, height, BW, and BMI) with raw measurements using Pearson correlation coefficients. If excellent correlation was identified, less variation in predictive ability of indexing methods would be expected.

The c-statistics and HR are reported in radial plots, where the further distance from the center indicates higher c-statistics or HR. Figure 1 shows a sample radial plot for various echocardiographic variables measured among our population for the outcome of HF hospitalization. A symmetric circle would indicate equivalence among the different indexing parameters. Asymmetry of the image identifies variables with higher predictive ability as being further from the center. Analyses were performed using software (Statistical Analysis, Version 9.2, SAS Institute Inc, Cary, NC). Outcome events were counted once for each individual (eg, recurrent HF hospitalizations in the same participant were not counted). Predefined end points were HF hospitalization and all-cause mortality.

RESULTS

At an average 5.6 ± 1.8 year follow-up, there were 148 HF hospitalizations, 71 CV deaths, and 269 all-cause deaths. Baseline characteristics of study participants are shown in Table 1. The range of BW was 43 to 214 kg. The raw echocardiography measurements correlated most closely with measurements indexed height ($r \geq 0.98$) followed by BSA ($r \geq 0.92$), BMI ($r \geq 0.81$), and BW ($r \geq 0.73$), as shown in Table 2. The close correlation of raw measurements to those indexed to BSA and height suggested that these indexing parameters would not significantly reclassify individuals in our study population. However, we explored the predictive ability of all the indexing measurements further by HR, c-statistic, and direct comparison of BSA to height$^{2.7}$. The standard deviations of each of the calculated variables are shown in Table 3.

A radial plot of the c-statistics and HRs per standard deviation increase in variables is shown in Figures 2 and 3. The symmetric circular shapes indicate equivalence of the predictive ability for the tested indexing parameters. There were no significant differences among indexing methods in predictive ability by either c-statistic or HRs.

Percentages of events correctly identified by the highest quartile of LV mass indexed to BSA or height$^{2.7}$ are shown in Figure 4. The green (bottom) bar indicates the percentage of individuals for whom there was agreement in classification. The yellow (top) bar indicates the percentage of individuals identified only by the one indexing method. There was no significant difference among indexing methods in ability to correctly classify individuals who developed HF hospitalization, CV mortality, or all-cause mortality.

DISCUSSION

We found that indexing parameters including BSA, height, BW, and BMI do not significantly alter the predictive ability of quantitative echocardiographic measurements for HF and mortality among ambulatory adults with CAD. There is at least moderate correlation among indexing parameters, and the c-statistics and HRs do not differ significantly in predictive ability among the sample size of 1024 individuals.

Several indexing parameters have been proposed for LV mass and LA volume among different patient populations. Theoretically, an indexing method that detects increases in chamber size or mass without regard to adiposity is desirable. Height-based parameters would satisfy this criterion. de Simone et al[25] showed that LV hypertrophy indexed to height$^{2.7}$ predicted mortality when inappropriately increased among 294 hypertensive individuals. However, Liao et al[26] showed that a minority of individuals are reclassified from a "normal" to an "abnormal" group on the basis of height-based indices, and the predictive value for mortality in this group was not significantly different among height or BSA indexing methods. Our findings extend the results of similarity in indexing method to LV mass, LA volume, and LV ESV with regard to outcomes of both HF hospitalization and mortality.

The predictive value of various indexing methods for HF hospitalization and mortality is complicated by the "U"-shaped relationship between BW and mortality. Although obesity confers a significant risk for development of myocardial infarction,[27] HF,[28] and mortality,[29] improvement in cardiac function after bariatric surgery in morbidly obese individuals has been described.[28] Overweight individuals have been shown to have better prognosis when diagnosed with HF or CAD than normal weight or underweight individuals.[30–32]

Sever al limitations need to be considered in the study findings. Our study population was predominantly men aged more than 50 years, and previous studies have shown at least minor variations in body size relation to cardiac chamber dimensions by age and gender.[33–35] We have no data on whether our results apply in childhood or adolescence, where allometric variables may have more impact.[36,37] Second, we suspect that the principle of adjusting anatomic measurements to body size should not apply to exclusively individuals with underlying CAD, but we limit our conclusions to individuals enrolled in our study. Others have reported no difference in mortality risk by body size adjusted LV mass among those with or without CAD,[26] but our population consists entirely of individuals with CAD. Third, our population consists primarily of overweight and mildly to moderately obese individuals, and our results may not apply to those with morbid obesity or severely underweight individuals.

The scope of this report applies primarily to differences in indexing methods as continuous variables; the possibility of diagnostic advantages using different cutpoints within 1 indexing parameter was addressed only for the highest quartile of LV mass comparing BSA to height$^{2.7}$. It is possible that separate cutpoints among individual indexing parameters may have better discriminative ability compared with other indexing parameters. Also, the sample size of 1,024 individuals may not have had adequate power to differentiate among advantages in 1 indexing method that may be apparent in a larger population. Finally, we report the prognostic value of echocardiographic measurements divided by body size parameters, and the possibility of a risk score that combines body size parameters, such as waist circumference or BMI, was not addressed.

CONCLUSIONS

Although we considered a theoretic advantage of using different indexing parameters other than BSA to adjust for body size, we found a correlation among indexed variables and similarity of predictive value among ambulatory adults with CAD. Increases in echocardiographic measurements predict outcome when indexed to various powers of height, BW, BMI, and BSA. Given the advantage of standardization among reporting techniques among echocardiography laboratories, it is reasonable to continue using BSA to adjust for LA size, LV mass, and LV ESV in predicting HF hospitalization and mortality among ambulatory adults with CAD.

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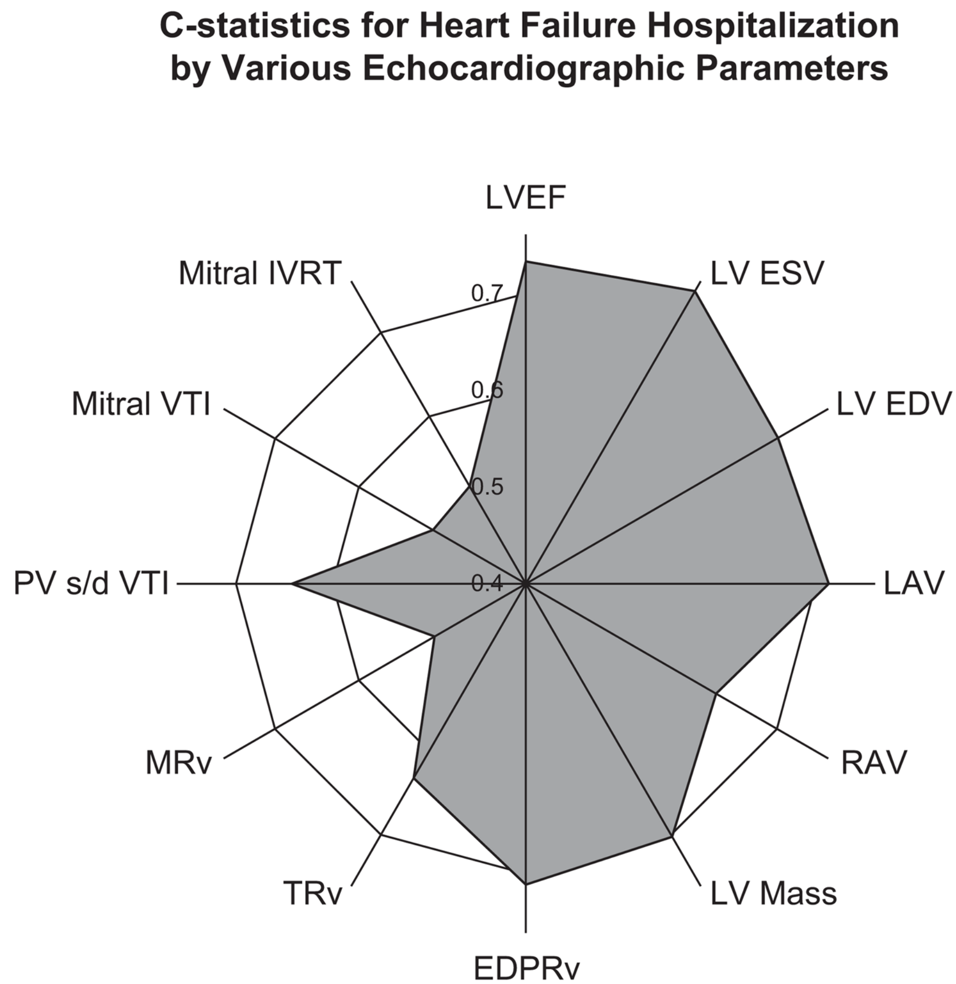

Figure 1.

Radial plot of c-statistics, or area under the receiver operating characteristic curve, for standard echocardiographic variables in predicting HF hospitalization. Further distance from the center of the plot indicates higher predictive ability. *LVEF*, Left ventricular ejection fraction (%); *LV ESV*, left ventricular end-systolic volume (mL); *EDV*, end-diastolic volume (mL); *LAV*, left atrial volume (mL); *RAV*, right atrial volume (mL); *EDPRv*, end-diastolic pulmonary regurgitation velocity (m/s); *TRv*, TR velocity (m/s); *MRv*, mitral regurgitation velocity (m/s); *PV s/d VTI*, pulmonary vein systolic to diastolic flow ratio by velocity time integral (dimensionless ratio); *IVRT*, isovolumic relaxation time (ms).

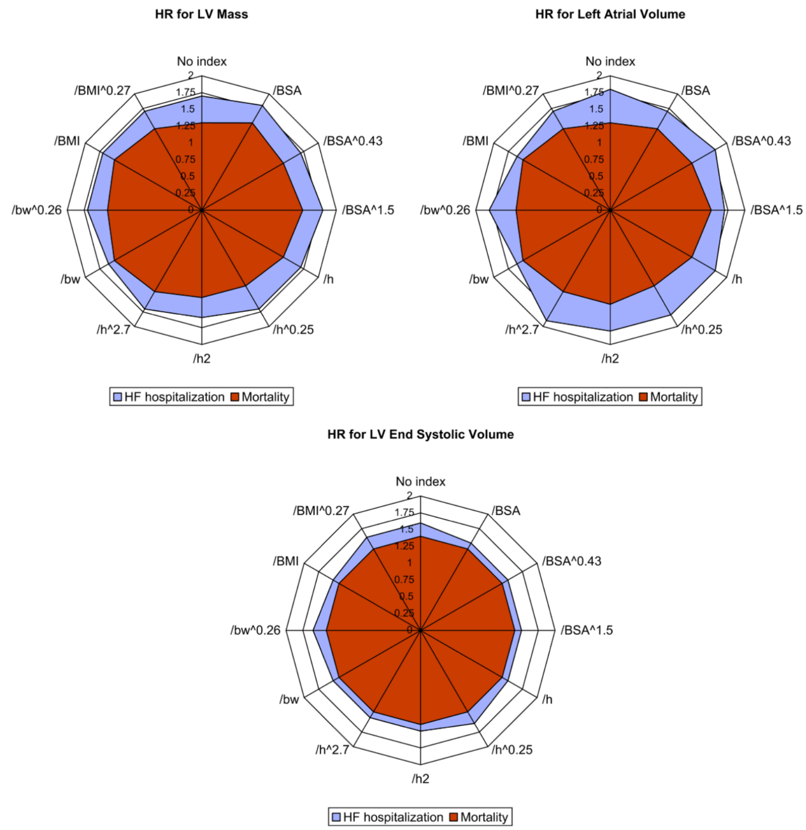

Figure 2.

HRs per standard deviation (as shown in Table 3) increase in variables indexed to different parameters of body size in the entire sample (n = 1,024). A circular configuration of the radial plot indicates equivalence among indexing methods. *LV*, Left ventricular; *BSA*, body surface area; *h*, height; *bw*, body weight; *BMI*, body mass index. The numeric values used to create these plots are listed in Table 4.

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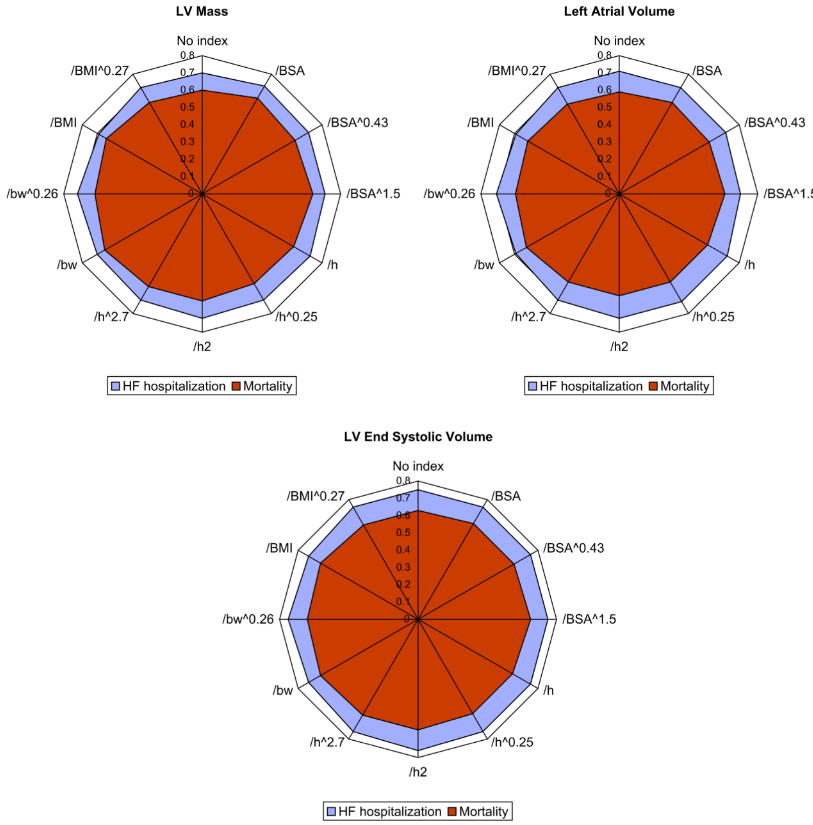

Figure 3.

C-statistics, or area under the receiver operating characteristic curve, for HF hospitalization and mortality by different methods of indexing for LV mass LA volume, and LV ESV in the entire sample (n = 1024). A circular configuration of the radial plot indicates equivalence among indexing methods. *LV*, Left ventricular; *BSA*, body surface area; *h*, height; *bw*, body weight; *BMI*, body mass index. The numeric values used to create these plots are listed in Table 4.

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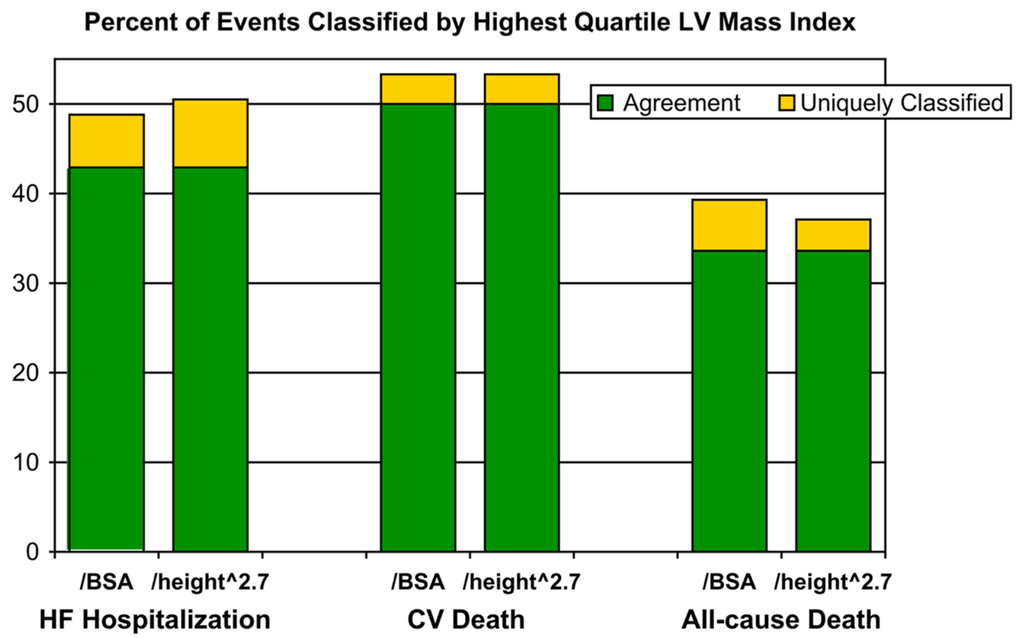

Figure 4.
Percentage of HF hospitalizations, CV deaths, or all-cause deaths correctly classified by the highest quartile of LV mass indexed to BSA or height$^{2.7}$ with results limited to men. The cutoff at the highest quartile indexing was 114 g/m^2 for BSA and 52 g/m$^{2.7}$ for height$^{2.7}$.

Table 1

Baseline characteristics

Characteristic	Baseline measurement
Age	67 ± 11 y
Weight	83 ± 18 kg
Height	171 ± 9 cm
BSA	1.94 ± 0.22 m^2
BMI	28.4 ± 5.3 kg/m^2
Waist circumference	101 ± 15 cm
Hip circumference	105 ± 13 cm
Systolic blood pressure	133 ± 21 mm Hg
Diastolic blood pressure	75 ± 11 mm Hg
Heart rate	68 ± 12 beats/min
Male	82%
Race	
White	60%
Black	16%
Asian	12%
Other race	12%
Diabetes mellitus	26%
History of hypertension	71%
History of MI	54%
History of revascularization	59%
History of stroke	15%
LV end-systolic volume	41 ± 26 mL
LV end-diastolic volume	101 ± 37 mL
LV mass	192 ± 57 g
Left atrial volume	65 ± 24 mL
LV ejection fraction	62 ± 10 %

BSA, Body surface area; *BMI*, body mass index; *MI*, myocardial infarction; *LV*, left ventricular. This table summarizes the baseline data of 1024 study participants.

Table 2

Correlation coefficients

	LV ESV (mL)	LA volume (mL)	LV mass (g)
No index	1.0	1.0	1.0
/BSA, m^2	.98	.95	.92
/Height, m	.99	.99	.98
/BW, kg	.94	.83	.73
/BMI, kg/m^2	.96	.88	.81

LV ESV, Left ventricular end-systolic volume; *LA*, left atrial; *BSA*, body surface area; *BW*, body weight; *BMI*, body mass index. The correlation among indexing methods for LV mass, LA volume, and LV ESV using Pearson correlation coefficients is shown. A value near 1 indicates excellent correlation among the different variables.

Table 3

Standard deviations

	LV ESV (mL)	LA volume (mL)	LV mass (g)
No index	32	24	57
/BSA, m^2	16	12	26
/$BSA^{0.43}$	24	18	40
/$BSA^{1.5}$	12	8.9	19
/h, m	0.47	0.35	0.80
/$h^{0.25}$	11	8.2	20
/h^2	0.006	0.005	0.01
/$h^{2.7}$	0.0004	0.0003	0.0006
/BW, kg	0.18	0.14	0.32
/$BW^{0.26}$	8.2	6.0	14
/BMI, kg/m^2	1.2	.91	2.1
/$BMI^{0.27}$	13	9.6	23

LV ESV, Left ventricular end-systolic volume; *LA*, left atrial; *h*, height; *BW*, body weight; *BMI*, body mass index. These standard deviation measurements were used for calculation of HRs for each indexing method for LV ESV, LA volume, and LV mass.

Table 4

Data used for construction of radial plots

	LV ESV (mL)			LA volume (mL)			LV mass (g)		
C-stats	**HF**	**CVD**	**Death**	**HF**	**CVD**	**Death**	**HF**	**CVD**	**Death**
No index	0.75	0.66	0.63	0.71	0.59	0.59	0.7	0.65	0.6
/BSA, m^2	0.75	0.68	0.64	0.71	0.62	0.61	0.72	0.69	0.64
/BSA^$^{0.43}$	0.75	0.67	0.64	0.71	0.61	0.6	0.71	0.67	0.62
/BSA^$^{1.5}$	0.75	0.68	0.65	0.7	0.63	0.61	0.71	0.70	0.64
/h, m	0.75	0.67	0.63	0.72	0.60	0.59	0.72	0.67	0.61
/h^$^{0.25}$	0.75	0.66	0.63	0.72	0.60	0.59	0.71	0.65	0.6
/h^2	0.76	0.68	0.64	0.72	0.61	0.59	0.72	0.68	0.62
/h^$^{2.7}$	0.75	0.68	0.64	0.71	0.62	0.59	0.71	0.69	0.62
/BW, kg	0.73	0.68	0.65	0.69	0.63	0.62	0.7	0.70	0.65
/BW^$^{0.26}$	0.75	0.67	0.64	0.71	0.61	0.6	0.72	0.67	0.62
/BMI, kg/m^2	0.73	0.68	0.65	0.69	0.62	0.61	0.69	0.68	0.64
/BMI^$^{0.27}$	0.75	0.67	0.63	0.71	0.60	0.6	0.71	0.66	0.61

	LV ESV (mL)			LA volume (mL)			LV mass (g)		
HR	HF	CVD	Death	HF	CVD	Death	HF	CVD	Death
No index	1.6	1.2	1.4	1.8	1.5	1.3	1.7	1.5	1.3
/BSA, m^2	1.5	1.2	1.4	1.7	1.6	1.4	1.8	1.7	1.5
/BSA^$^{0.43}$	1.5	1.3	1.4	1.8	1.6	1.4	1.7	1.6	1.4
/BSA^$^{1.5}$	1.5	1.3	1.4	1.7	1.6	1.5	1.8	1.8	1.5
/h, m	1.5	1.3	1.4	1.8	1.6	1.4	1.7	1.8	1.4
/h^$^{0.25}$	1.6	1.2	1.4	1.8	1.5	1.3	1.7	1.5	1.3
/h^2	1.5	1.2	1.4	1.8	1.6	1.4	1.6	1.5	1.3
/h^$^{2.7}$	1.5	1.2	1.4	1.9	1.7	1.4	1.7	1.6	1.4
/BW	1.5	1.3	1.4	1.6	1.6	1.5	1.6	1.6	1.5
/BW^$^{0.26}$	1.6	1.3	1.4	1.8	1.6	1.4	1.7	1.6	1.4
/BMI, kg/m^2	1.5	1.3	1.4	1.6	1.6	1.5	1.7	1.6	1.5

	LV ESV (mL)			LA volume (mL)			LV mass (g)		
C-stats	**HF**	**CVD**	**Death**	**HF**	**CVD**	**Death**	**HF**	**CVD**	**Death**
/BMI^0.27	1.6	1.2	1.4	1.7	1.6	1.4	1.7	1.5	1.4

C-statistics and HRs for events by echocardiographic indexing parameters are shown, with additional results listed for the outcome of CV death. *LV*, Left ventricular; *ESV*, end-systolic volume; *LA*, left atrial; *HF*, heart failure hospitalization; *CVD*, cardiovascular death; *h*, height; *BW*, body weight; *BSA*, body surface area; *BMI*, body mass index.