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Usefulness of Doppler Echocardiographic Left Ventricular Diastolic Function and Peak Exercise Oxygen Consumption to Predict Cardiovascular Outcomes in Patients with Systolic Heart Failure (From HF-ACTION)

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Abstract

HF-ACTION was a multicenter, randomized, controlled trial designed to examine the safety and efficacy of aerobic exercise training versus usual care in 2,331 patients with systolic heart failure (HF). In HF-ACTION patients with resting transthoracic echocardiographic (echo) measurements, we examined predictive value of 8 echo-Doppler measurements—left ventricular (LV) diastolic dimension, mass, systolic (ejection fraction) and diastolic function (mitral valve [MV] peak early diastolic-to-peak late diastolic [E/A], peak MV early diastolic velocity-to-tissue Doppler peak early diastolic myocardial velocity [E/E'] ratios, and deceleration time), left atrial (LA) dimension, and mitral regurgitation severity (MR)—for primary endpoint of all-cause death or hospitalization and secondary endpoint of cardiovascular disease (CVD) death or HF hospitalization. We also compared prognostic value of echo variables versus peak oxygen consumption (VO_2). MV E/A and E/E' ratios were more powerful independent predictors of clinical endpoints than was LV ejection fraction (LVEF), but less powerful than peak VO_2. In multivariate analyses for predicting primary endpoint, adding E/A ratio to a basic demographic/clinical model increased C-index from 0.61 to 0.62, compared with 0.64 after adding peak VO_2. For secondary endpoint, 6 echo variables, but not LVEF or LA dimension, provided independent predictive power over basic model. Addition of E/E' or E/A to the basic model increased C-index from 0.70 to 0.72 and 0.73,

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Disclosures
None

respectively (all p <0.0001). Simultaneously adding E/A and peak VO_2 to basic model increased C-index to 0.75 (p <0.0005). No echo variable was significantly related to 0-to-3 month change in exercise peak VO_2. In conclusion, addition of echo LV diastolic function variables improves prognostic value of a basic demographic/clinical model for CVD outcomes.

Keywords

Systolic heart failure; echocardiography; exercise training; clinical outcomes

The current analysis examines the prognostic power of baseline Doppler-echocardiography (echo) measures of left ventricular (LV) and left atrial (LA) anatomy, LV systolic and diastolic function, and mitral regurgitation (MR) for overall and cardiovascular disease (CVD)-related outcomes, and 3-month exercise training effect in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) patients. The major hypothesis was: Increased LV mass, LV internal dimension, LA dimension, and MR severity; decreased LV ejection fraction (LVEF); and decreased LV diastolic function, as measured at baseline by Doppler echo, will: (1) improve the prediction, over a basic model of demographic and clinical variables, of increased all-cause death or all-cause hospitalization (primary endpoint), as well as CVD death or heart failure (HF) hospitalization (secondary endpoints), over a 30-month median follow-up period; and (2) predict a poorer exercise training effect, as measured by baseline-to-3 month change in exercise peak oxygen consumption (VO_2), in the exercise training intervention group.

Methods

The design (1), primary outcome (2), and baseline Doppler-echo findings (3) of the HF-ACTION study have been previously reported. Enrollment criteria included an LVEF ≤35%, New York Heart Association (NYHA) clinical class II-IV HF, and sufficient ability to undergo exercise training. Patients were excluded if they were unable to exercise, already exercising regularly, or had experienced a CVD event in the prior 6 weeks. Patients were treated optimally according to current practice guidelines (2). Overall, 2,331 patients were randomly assigned to either participate in 36 sessions of facility-based, followed by home-based, exercise training for the remainder of the trial, in addition to usual care, or receive usual care alone; median follow-up was approximately 2.5 years.

Doppler-echocardiography was performed at baseline using standard methodology; echo recordings were forwarded to a core laboratory for analysis (3,4). Studies were read blinded as to demographic and clinical information by a primary reader and overread by an experienced Level III echocardiographer using a measurement workstation (Digisonics, Inc, Houston, TX). The following echo variables were measured or derived: LV mass, diastolic dimension (LVDD), volumes, and LVEF; LA dimension, peak MV early diastolic (E) velocity, average of septal and lateral myocardial annular tissue velocity (E'), E/E' ratio, peak early diastolic-to-peak late diastolic (E/A) velocity ratio, early diastolic deceleration time (Dec Time), and MR grade (4–6). MR was graded from apical-view color Doppler echo images, as follows: none, 0; trace, 1; mild, 2; mild-to-moderate, 3; moderate, 4; moderately severe, 5; and severe, 6. LV dimensions, wall thickness, and mass, and LA dimension, were measured from 2-dimensionally derived M-mode echocardiograms. If M-mode echocardiograms were judged suboptimal, linear dimensions were measured from 2-dimensional (2D) images (7). Peak E and A MV pulsed-Doppler velocities were measured at the mitral leaflet tip level during diastole in the apical 4-chamber view. Septal and lateral E' myocardial velocities were recorded with sample volumes positioned within 1 cm of septal and lateral insertion sites, respectively, of the anterior and posterior mitral leaflets (8).

Measures of decreased LV diastolic function included abnormal E/A ratio (<0.75 or >1.5), decreased early diastolic Dec Time, increased E/E' ratio, and increased LA dimension (8).

Symptom-limited exercise (CPX) testing with gas exchange measurement was completed using commercially-available metabolic carts and motor driven treadmills, employing a modified Naughton protocol in 91% and cycle ergometers in 9% of subjects (9). Exercise test supervisors encouraged patients to exercise to exhaustion. The respiratory exchange ratio was used to confirm satisfactory exercise effort. Peak VO_2 was determined in a core laboratory as the highest oxygen consumption normalized to body mass (VO_2, mL/kg/min) for a 15- or 20-second interval during last 90 seconds of exercise or first 30 seconds of recovery (9). The independent relationships of baseline demographic and clinical variables to clinical outcomes were assessed using bootstrapped, step-down variable selection. Based partially on this assessment, the following were included in models to determine the independent predictive ability of echo variables for primary or secondary CVD outcomes: age, gender, race, body surface area, geographic region, Kansas City Cardiomyopathy Questionnaire (KCCQ) symptom stability score, blood urea nitrogen (BUN), ventricular conduction, beta blocker dose, and loop diuretic dose.

Univariate and multivariate Cox regression were used to analyze relations of demographic/clinical, echo-Doppler and exercise training (peak VO_2) variables to the primary and secondary outcomes. The bootstrap-corrected C-index was used to evaluate predictive ability of multivariate models for both primary and secondary outcomes. In the exercise training group, univariate correlations between echo-Doppler variables and change in peak VO_2 between baseline and 3 months of training were examined using linear regression analysis. Kaplan-Meier curves were used to display event rates. Statistical analyses were performed using SAS (version 8.2, SAS Institute Inc, Cary, North Carolina) and R Design Library (version 2.9.2, The R Foundation for Statistical Computing). Statistical significance was set at the two-tailed alpha =.05 level, with no adjustment for multiple comparisons. Unless otherwise indicated, all *P* values are based on the likelihood ratio chi-square statistic.

Results

Table 1 presents selected demographic, clinical, and echo variables in the overall cohort (n=2,331) and in the subgroup (n=519) for whom complete data were available for the primary endpoint in multivariate models. Most patients in the cohort were men, white, and were in New York Heart Association clinical class II and class III HF. There were no qualitative differences in demographic (age, sex, BMI, and race), exercise, and LVEF variables between the overall cohort and the echo subgroup. The largest source of missing data was related to E' measurements being available in only 909 patients (see Table 2) because tissue velocity measurements were not routinely recorded at some centers.

Table 2 outlines univariate predictors of the primary endpoint (all-cause hospitalization or all-cause death). Among the 2,331 HF-ACTION patients, measurements for LVDD, LV mass, LA dimension, E/A, and Dec Time were available for 1,550–1,646 patients. Tissue Doppler-based parameters—including E' velocity and E/E' velocity—were present in only 909 and 796 patients, respectively. Except for E' velocity (barely significant), all echo variables were highly statistically significant univariate predictors of the primary endpoint; however, peak VO_2 was a better predictor than any echo variable.

Table 3 shows C-index and multivariate p-values for the primary endpoint when each echo variable was separately added to the basic multivariate model (which included only 519 patients who had non-missing data for all variables). Only E/A increased (slightly) the C-index of the basic model (from 0.61 to 0.62, p =0.003); nevertheless, E/A and E/E' had

highly significant chi-square p-values. (A significant chi-square p-value can indicate statistical improvement in model fit by inclusion of a variable in the absence of substantive improvement in model discrimination between higher and lower risk patients, denoted by C-index [**10**].) The other 7 echo variables added little to prediction beyond that achieved by the basic multivariate model plus E/A. Importantly, peak VO2 improved risk discrimination independently of the basic model and echo variables, increasing C-index from 0.62 to 0.64, while echo variables did not improve risk discrimination of the basic model plus peak VO_2 with C-index remaining unchanged at 0.64.

Table 4 displays the univariate predictors for the secondary combined endpoint (CVD mortality or HF hospitalization). All echo variables, except for E' velocity, were highly statistically significant predictors of the secondary endpoint. LA dimension, LVEF, MR grade, E/A, and E/E' were the most important echo predictors of the secondary endpoint, but peak VO_2 was even more important. Table 5 shows multivariate p-values and C-indices for the secondary endpoint when each of the 8 echo variables was separately added to the basic multivariate model. The multivariate models included only patients who had data for all variables. E/A and E/E' were the most statistically significant echo variables; their addition to the basic model resulted in the most substantial increases in C-index (from 0.70 for the basic model to 0.73 and 0.72, respectively). However, peak VO_2 was a stronger independent predictor for the secondary endpoint (C-index =0.74) than any echo variable. Moreover, peak VO_2 was an independent predictor of outcomes even when all 8 echo variables were included. There was no difference in predictive ability between the basic model plus all 8 echo variables and peak VO_2 versus the basic model plus E/A and peak VO_2. In the 972 individuals in the exercise training arm with serial measurements, no echo variable was significantly related to baseline-to-3 month change in peak VO_2.

Figures 1 and 2 present Kaplan-Meier curves demonstrating the relationship of the event-free probability for primary outcome versus time from randomization in patients with each echo variable above and below a defined clinically-relevant cutpoint. Note that (Figure 1) event-free probability for primary outcome was higher with an E/A < versus ≥1.0, E/E' < versus ≥15, Dec Time < versus ≥200 msec, and MR grades of < moderately severe (0–4) versus moderately severe or severe (5, 6). Figure 2 presents similar relationships in patients with LVDD < versus ≥6.5 cm, LV mass < versus ≥300 g, LA dimension < versus ≥4.5 cm, and LVEF < versus ≥25%. Event-free probabilities for the primary outcome were significantly higher in those with smaller LVDD, smaller LV mass, smaller LA dimension, and higher LVEF. Relations similar to those for the primary outcome were present between all 8 echo variables and the secondary outcome. Significant differences were present between the 2 curves for each echo variable, representing event-free probabilities for patients with echo measurements above and below the defined clinically-relevant cutpoint. Figure 3 presents relationships (all significant) between the secondary outcome and E/A, E/E', LV Dec Time and MR grade. Visual differences between the 2 event-free curves were greatest for MR grade.

Discussion

We examined predictive value for all-cause death or all-cause hospitalization (primary endpoint) and CVD death or HF hospitalization (secondary endpoint) of Doppler-echo measures of LV and LA anatomy, and LV systolic and diastolic function, in the HF-ACTION cohort. For the primary endpoint, peak VO_2 was a more powerful univariate and multivariate predictor than were echo variables when added to a basic demographic and clinical model. Moreover, peak VO_2 improved risk prediction independently of the basic model and the echo variables, while the echo variables did not improve the predictive ability of the basic model once peak VO_2 was included. Similarly, for the secondary endpoint, peak

VO_2 was a more important univariate predictor than the echo variables. Adding peak VO_2 was equivalent as an independent multivariate predictor of the secondary endpoint to adding all 8 echo variables to a basic model. E/A was the most important single echo predictor for both primary and secondary endpoints. For the secondary endpoint, including E/A in the basic model with peak VO_2 improved C-index modestly. However, LVEF was not an independent predictor beyond the basic multivariate model for primary or secondary endpoints.

We believe the HF-ACTION cohort is the largest to measure both echo variables and aerobic capacity using CPX testing in patients with systolic HF. Our study extends previous work by suggesting that in patients with systolic HF, a combination of commonly recorded resting echo variables may add modest prognostic value to peak VO_2; however, peak VO_2 is a stronger predictor of adverse outcomes than any individual echo variable. Kaplan-Meier event rate analysis showed significantly higher rates of overall and CVD/HF hospitalization and mortality in the groups with: (1) greater LVDD, LV mass, LA dimension, E/A and E/E' ratios, and MR severity; and (2) lesser LVEF and Dec Time. This study also extends our previous findings (4) that baseline Doppler-echo measures of LV diastolic function—including E/A and E/E'—were modest, but better independent predictors in this cohort of baseline aerobic exercise capacity (peak VO_2) and ventilatory efficiency (VE/VCO_2 slope) than was LVEF.

Measures of LV systolic function, LV mass, and LV diastolic function/filling—e.g., E/A, E/E', and Dec Time—have been shown to predict CVD events in patients with systolic HF. In the SOLVD Registry and Trials, LV mass ≥298 g and LA dimension ≥4.17 cm were associated with increased risk of death and CVD hospitalization in 1,172 patients with LV dysfunction. A protective effect of LVEF >35%—i.e., better outcomes—was noted only in patients with LV mass ≥298 g (11). In 207 consecutive patients with dilated cardiomyopathy, indexed LA size was the best predictor of death in patients >70 years old, whereas a "restrictive mitral flow pattern" (Dec Time <140 ms) was independently associated with cardiac death or HF hospitalization (12). In smaller studies of ischemic and non-ischemic cardiomyopathy patients, with LVEF cutpoints ranging from <50% to <35% and E/E' cutpoints ranging from 13.5 to 16, E/E' ratio was a good predictor of cardiac death or HF rehospitalization and of a combined endpoint including death, heart transplantation, and HF hospitalization (8,13–16). Dokainish, et al., reported that E/E' and pre-discharge brain natriuretic peptide blood levels were incremental predictors of cardiac death or rehospitalization for HF (17). Our study extends previous work by demonstrating that, in our cohort, echo-Doppler E/A and E/E' ratios and MR grade are stronger predictors of HF hospitalization or CVD mortality than are LV mass, LVEF, and LA dimension.

There are a number of likely reasons why the resting echo-Doppler variables studied were not better predictors—e.g., as compared to peak VO2—of the primary or secondary outcomes. Tests that examine cardiopulmonary function during stress—e.g., exercise CPX tests—often have more robust diagnostic and prognostic capabilities than those examining only resting function. Furthermore, echo-Doppler variables do not assess non-cardiac HF components—e.g., abnormalities of skeletal muscle or peripheral vasculature—or multiple comorbidities that may drive many events in HF patients (17,18). Of importance, age alone is a strong predictor of overall and CVD-related outcomes; after adjustment for age in a multivariate model, echo-Doppler variables have substantially less prognostic power.

Several limitations of the current study are apparent. First, echo variables were not available in many patients. M-mode echo variables—e.g., LVDD, LV mass, and LA dimension—and pulsed Doppler E/A and Dec Time—were available in 2/3rd, whereas tissue Doppler-based variables—E' velocity and E/E'—were available in only 1/3rd of the cohort. In

approximately 1/3rd, 2D-derived M-mode measurements of LVDD, LV mass, and LA dimension could not be reliably performed, thereby limiting the usefulness of echo in these patients and others outside the study in whom these measurements cannot be reliably made. Nonetheless, as reported previously (3), our findings should be generalizable to the entire cohort because there were no meaningful differences in demographic or clinical variables between subgroups in whom all echo variables were available and the entire cohort. Second, there are well-known limitations in using Doppler-echo measurements to evaluate LV systolic and diastolic function. Potential difficulties include LV foreshortening, inadequate visualization of LV endocardium, and mathematical over-simplifications in 2D models used to estimate three-dimensional LV volumes, mass, and EF. In patients with severe HF, E/E' ratio has been reported unreliable in predicting intracardiac filling pressures—especially in patients with large LV volumes (19). E/E' may reflect either a "restrictive" filling pattern or "pseudonormalization" in patients with high filling pressures (20). Factors including loading conditions and regional contractility may modify the E/E'. Currently, there is no single perfect Doppler-echo measurement of diastolic dysfunction. Nonetheless, the HF-ACTION core echo laboratory has previously reported measurements for inter-reader variability of 2 ± 1% (mean ± standard deviation) for E velocity and 5 ± 2–3% for Dec Time and E' velocity (21). Third, since a follow-up echo was not performed, we cannot comment on 3-month changes in echo variables potentially associated with either baseline-to-3 month change in peak VO_2 or primary or secondary endpoints. Fourth, because patients included in this study were preselected on the basis of their ability to participate in the exercise training protocol, the results of this study cannot be extrapolated to all patients with advanced systolic HF. Finally, plasma natriuretic peptides, strong predictors of outcomes in systolic HF (22), were not routinely measured, preventing assessment of the independent prognostic power of echo variables in this context.

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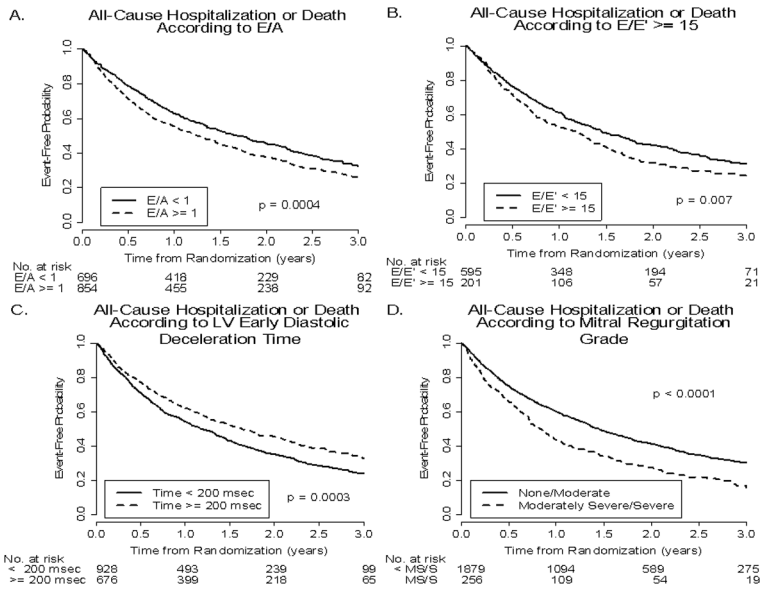

Figure 1.

Kaplan-Meier curves for the event-free probabilities for all-cause hospitalization or death (primary outcome) as a function of E/A ratio <1.0 versus ≥1.0 (panel A); E/E' <15 versus ≥15 (panel B); Dec Time <200 versus ≥200 msec (panel C); and MR, none-to-moderate versus moderately severe or severe (panel D).

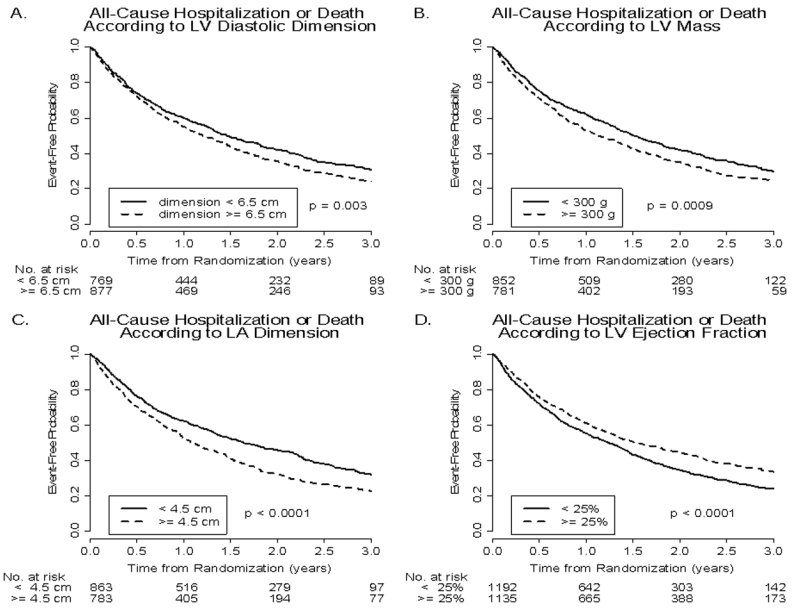

Figure 2.

Kaplan-Meier curves for the event-free probabilities for all-cause hospitalization or death (primary outcome) as a function of LVDD <6.5 vs ≥6.5 cm (Panel A), LV mass <300 vs ≥300 g (Panel B), LA dimension <4.5 vs ≥4.5 cm (Panel C), and LVEF <25% vs ≥25% (Panel D).

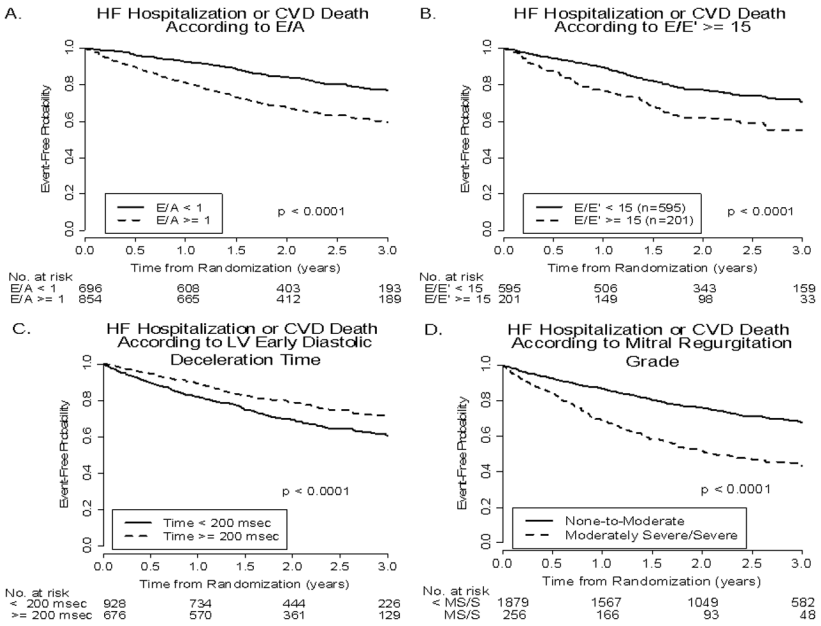

Figure 3.

Kaplan-Meier curves for the event-free probabilities for HF hospitalization or CVD death (secondary outcome) as a function of E/A, E/E', Dec Time, and MR. Format is the same as in Figure 1.

Table 1

Baseline Demographic, Clinical and Echocardiographic Characteristics of Participants as a Function of Echocardiographic Measurement Availability

Parameter	Overall cohort (n = 2331)	Cohort with complete echo data for primary endpoint (n = 519)
Age (years)	59 (51, 68)	59 (50, 68)
Men	72%	69%
White/Black/Other	62%, 33%, 5%	59%, 34%, 7%
Body surface area (m^2)	2.1 (1.9, 2.3)	2.1 (1.9, 2.3)
Blood urea nitrogen (mg/dL)	20 (15, 28)	20 (14, 28)
Diabetes mellitus	32%	32%
Left ventricular ejection fraction	25% (20, 30)	25% (21, 31)
New York Heart Association Class (II, III)	63%, 36%	65%, 35%
Peak oxygen consumption (ml/kg/min)	14.4 (11.5, 17.7)	15.8 (11.8, 17.8)
Ventricular conduction	13%, 17%, 43%, 24%, 4%	13%, 15%, 47%, 21%, 4%

Continuous variables are expressed as median (25^{th} percentile, 75^{th} percentile)

Ventricular conduction is categorized as interventricular conduction delay, left bundle branch block, normal, paced rhythm, and right bundle branch block, respectively.

Table 2

Univariate Predictors of HF-ACTION Primary Endpoint (All-Cause Death or All-Cause Hospitalization)

Echo Parameters	Sample Size	Hazard Ratio (95% confidence interval)	Chi-Square Value	p-value
Left ventricular diastolic dimension (cm)	1646	1.09 (1,04, 1.15)	12.3	0.0005
Left ventricular mass (per 100g)	1646	1.08 (1.04, 1.12)	13.5	0.0002
Left ventricular ejection fraction (per 5%)	2327	0.89 (0.86, 0.92)	49.7	<0.0001
Left atrial dimension (cm)	1646	1.30 (1.21, 1.41)	48.1	<0.0001
Peak mitral early diastolic-to-peak late diastolic velocity ratio	1550	1.15 (1.08, 1.22)	19.5	<0.0001
Early diastolic deceleration time (msec)	1604	0.91 (0.87, 0.95)	18.6	<0.0001
Tissue Doppler peak early diastolic myocardial velocity (cm/sec)	909	0.98 (0.96, 1.00)	6.4	0.01
Peak mitral early diastolic velocity-to-tissue Doppler peak early diastolic myocardial velocity ratio	796	1.03 (1.01, 1.04)	18.7	<0.0001
Mitral regurgitation grade(grades 0–4 vs. 5–6)	2135	1.53 (1.31, 1.77)	27.8	<0.0001
Peak oxygen consumption(ml/kg/min)	2275	0.92 (0.91, 0.93)	199.0	<0.0001

Abbreviations are as in text.

Table 3

Multivariate Models for HF-ACTION Primary Endpoint (n=519 with complete data)

Multivariate Model	Multivariate Model Chi-Square Value	Multivariate p-value of added predictor(s) beyond the Basic model	C-index
Basic	57.8		0.61
Basic + Left ventricular diastolic dimension	58.4	0.49	0.61
Basic + Left ventricular mass	58.0	0.69	0.61
Basic + Left ventricular ejection fraction	58.1	0.60	0.61
Basic + Left atrial dimension	61.1	0.07	0.61
Basic + Peak mitral early diastolic-to-peak late diastolic velocity ratio	66.6	0.003	0.62
Basic + Early diastolic deceleration time	60.2	0.12	0.61
Basic + Peak mitral early diastolic velocity-to-tissue Doppler peak early diastolic myocardial velocity ratio	65.6	0.005	0.61
Basic + Mitral regurgitation grade	62.7	0.08	0.61
Basic + All 8 echo variables	74.6	multiple added predictors	0.62
Basic + Peak oxygen consumption	92.5	<0.0001	0.64
Basic + Peak oxygen consumption + Peak mitral early diastolic-to-peak late diastolic velocity ratio	94.8	0.13 (E/A) <0.0001 (peak VO_2)	0.64

Basic multivariate model for primary endpoint includes beta blocker dose (truncated at 50mg/day), body surface area, BUN, gender, KCCQ symptom stability score, region (U.S. vs. non-U.S.), ventricular conduction.

Table 4

Univariate Predictors of HF-ACTION for Secondary Endpoint (Cardiovascular Disease Mortality or Heart Failure Hospitalization)

Echo Parameters	Sample Size	Hazard Ratio (95% confidence interval)	Chi-Square Value	p-value
Left ventricular diastolic dimension (cm)	1646	1.14 (1.06, 1.23)	12.7	0.0004
Left ventricular mass (per 100g)	1646	1.10 (1.04, 1.17)	10.8	0.001
Left ventricular ejection fraction (per 5%)	2327	0.82 (0.78, 0.87)	58.3	<0.0001
Left atrial dimension (cm)	1646	1.48 (1.33, 1.65)	49.7	<0.0001
Peak mitral early diastolic-to-peak late diastolic velocity ratio	1550	1.43 (1.33, 1.54)	71.2	<0.0001
Early diastolic deceleration time (per 50msec)	1604	0.83 (0.77, 0.89)	27.9	<0.0001
Tissue Doppler peak early diastolic myocardial velocity(cm/sec)	909	0.98 (0.95, 1.01)	2.24	0.13
Peak mitral early diastolic velocity-to-tissue Doppler peak early diastolic myocardial velocity ratio	796	1.23 (1.15, 1.33)	25.5	<0.0001
Mitral regurgitation grade(grades 0–4 vs. 5–6)	2135	2.3 (1.9, 2.8)	61.1	<0.0001
Peak oxygen consumption(ml/kg/min)	2275	0.86 (0.85, 0.88)	255.3	<0.0001

Table 5

Multivariate Models for HF-ACTION Cardiovascular Disease Mortality or Heart Failure Hospitalization Endpoint (n=512 with complete data)

Multivariate Model	Multivariate Model Chi-Square Value	Multivariate p-value of added predictor(s) beyond the basic model	C-index
Basic	100.4		0.70
Basic + Left ventricular diastolic dimension	107.1	0.009	0.71
Basic + Left ventricular mass	105.3	0.03	0.70
Basic + Left ventricular ejection fraction	103.8	0.06	0.70
Basic + Left atrial dimension	101.3	0.33	0.70
Basic + Peak mitral early diastolic-to-peak late diastolic velocity ratio	127.4	<0.0001	0.73
Basic + Early diastolic deceleration time	105.6	0.02	0.71
Basic + Peak mitral early diastolic velocity-to-tissue Doppler peak early diastolic myocardial velocity ratio	121.2	<0.0001	0.72
Basic + Mitral regurgitation grade	111.6	0.0008	0.71
Basic + All 8 echo variables	149.5	multiple added predictors	0.74
Basic + Peak oxygen consumption	132.6	<0.0001	0.74
Basic + Peak oxygen consumption + Peak mitral early diastolic-to-peak late diastolic velocity ratio	146.4	0.0002 (E/A) <0.0001 (peak VO_2)	0.75

Basic multivariate model for secondary endpoint includes age (truncated at 62 years), body surface area, BUN (truncated at 39mg/dL), gender, KCCQ symptom stability score, loop diuretic dose (truncated at 100mg), race, ventricular conduction.