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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Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (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 rest transthoracic echocardiographic measurements, the predictive value of 8 Doppler echocardiographic measurements—left ventricular (LV) diastolic dimension, mass, systolic (ejection fraction) and diastolic (mitral valve peak early diastolic/peak late diastolic [E/A] ratio, peak mitral valve early diastolic velocity/tissue Doppler peak early diastolic myocardial velocity [E/E′] ratio, and deceleration time) function, left atrial dimension, and mitral regurgitation severity—was examined for a primary end point of all-cause death or hospitalization and a secondary end point of cardiovascular disease death or HF hospitalization. Also compared was the prognostic value of echocardiographic variables versus peak oxygen consumption (Vo_2). Mitral valve E/A and E/E′ ratios were more powerful independent predictors of clinical end points than the LV ejection fraction but less powerful than peak Vo_2. In multivariate analyses for predicting the primary end point, adding E/A ratio to a basic demographic and clinical model increased the C-index from 0.61 to 0.62, compared with 0.64 after adding peak Vo_2. For the secondary end point, 6 echocardiographic variables, but not the LV ejection fraction or left atrial dimension, provided independent predictive power over the basic model. The addition of E/E′ or E/A to the basic model increased the C-index from 0.70 to 0.72 and 0.73, respectively (all p values <0.0001). Simultaneously adding E/A ratio and peak Vo_2 to the basic model increased the C-index to 0.75 (p <0.0005). No echocardiographic variable was significantly related to the change from baseline to 3 months in exercise peak Vo_2. In conclusion, the addition of echocardiographic LV diastolic function variables improves the prognostic value of a basic demographic and clinical model for cardiovascular disease outcomes. **(Am J Cardiol 2012;110:862–869)**

In the present analysis, we examined the prognostic power of baseline Doppler echocardiographic 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 patients enrolled in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION). The major hypothesis was increased LV mass, LV internal dimension, LA dimension, and MR severity, a decreased LV ejection fraction (LVEF), and decreased LV diastolic function, as measured at baseline by Doppler echocardiography, would (1) improve the prediction, over a basic model of demographic and clinical variables, of increased all-cause death or all-cause hospitalization (the primary end point), as well as CVD death or heart failure (HF) hospitalization (secondary end points), over a 30-month median follow-up period and (2) predict a poorer exercise training effect, as measured by the change from baseline to 3-months in exercise peak oxygen consumption (Vo_2), in the exercise training intervention group.

Methods

The design,[1] primary outcome,[2] and baseline Doppler echocardiographic findings[3] of the HF-ACTION study have been previously reported. Enrollment criteria included an LVEF ≤35%, New York Heart Association clinical class II to IV HF, and sufficient ability to undergo exercise training.

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Table 1
Baseline demographic, clinical, and echocardiographic characteristics of participants as a function of echocardiographic measurement availability

Parameter	Overall Cohort (n = 2,331)	Cohort With Complete Echocardiographic Data for Primary End Point (n = 519)
Age (years)	59 (51–68)	59 (50–68)
Men	72%	69%
Race		
White	62%	59%
Black	33%	34%
Other	5%	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%
LVEF (%)	25 (20–30)	25 (21–31)
New York Heart Association class		
II	63%	65%
III	36%	35%
Peak Vo2 (ml/kg/min)	14.4 (11.5–17.7)	15.8 (11.8–17.8)
Ventricular conduction		
Interventricular conduction delay	13%	13%
Left bundle branch block	17%	15%
Normal	43%	47%
Paced rhythm	24%	21%
Right bundle branch block	4%	4%

Continuous variables are expressed as median (interquartile range).

Patients were excluded if they were unable to exercise, were already exercising regularly, or had experienced CVD events in the previous 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 to receive usual care alone; the median follow-up period was approximately 2.5 years.

Doppler echocardiography was performed at baseline using standard methods; echocardiographic 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, Texas). The following echocardiographic variables were measured or derived: LV mass, LV diastolic dimension, LV volumes, and the LVEF; LA dimension, peak mitral valve early diastolic (E) velocity, the average of septal and lateral myocardial annular tissue velocities (E′), the E/E′ ratio, the peak early diastolic/peak late diastolic (E/A) velocity ratio, early diastolic deceleration time, and MR grade.[4–6] MR was graded from apical-view color Doppler echocardiographic images as follows: 0 = none, 1 = trace, 2 = mild, 3 = mild to moderate, 4 = moderate, 5 = moderately severe, and 6 = severe. 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 images.[7] Peak E and A mitral valve 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 deceleration time, increased E/E′ ratio, and increased LA dimension.[8]

Symptom-limited exercise testing with gas exchange measurement was completed using commercially available metabolic carts and motor-driven treadmills, using 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 (in milliliters per kilogram per minute) for a 15- or 20-second interval during the last 90 seconds of exercise or the first 30 seconds of recovery.[9] The independent relations of baseline demographic and clinical variables to clinical outcomes were assessed using bootstrapped, step-down variable selection. Partially on the basis of this assessment, the following were included in models to determine the independent predictive ability of echocardiographic variables for primary or secondary CVD outcomes: age, gender, race, body surface area, geographic region, Kansas City Cardiomyopathy Questionnaire symptom stability score, blood urea nitrogen, ventricular conduction, β-blocker dose, and loop diuretic dose.

Univariate and multivariate Cox regression were used to analyze relations of demographic and clinical, Doppler echocardiographic, and exercise training (peak Vo_2) variables to the primary and secondary outcomes. The bootstrap-corrected C-index was used to evaluate the predictive ability of multivariate models for the primary and secondary outcomes. In the exercise training group, univariate corre-

Table 2
Univariate predictors of heart failure: a controlled trial investigating outcomes of exercise training primary end point (all-cause death or all-cause hospitalization)

Echocardiographic Parameter	Sample Size	Hazard Ratio (95% Confidence Interval)	Chi-Square Value	p Value
LV diastolic dimension	1,646	1.09 (1.04–1.15)	12.3	0.0005
LV mass (per 100 g)	1,646	1.08 (1.04–1.12)	13.5	0.0002
LVEF (per 5%)	2,327	0.89 (0.86–0.92)	49.7	<0.0001
LA dimension	1,646	1.30 (1.21–1.41)	48.1	<0.0001
Peak mitral early diastolic/peak late diastolic velocity ratio	1,550	1.15 (1.08–1.22)	19.5	<0.0001
Early diastolic deceleration time	1,604	0.91 (0.87–0.95)	18.6	<0.0001
Tissue Doppler peak early diastolic myocardial velocity	909	0.98 (0.96–1.00)	6.4	0.01
Peak mitral early diastolic velocity/tissue Doppler peak early diastolic myocardial velocity ratio	796	1.03 (1.01–1.04)	18.7	<0.0001
MR grade (grades 0–4 vs 5 or 6)	2,135	1.53 (1.31–1.77)	27.8	<0.0001
Peak Vo2	2,275	0.92 (0.91–0.93)	199.0	<0.0001

Table 3
Multivariate models for heart failure: a controlled trial investigating outcomes of exercise training primary end point (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 + LV diastolic dimension	58.4	0.49	0.61
Basic + LV mass	58.0	0.69	0.61
Basic + LVEF	58.1	0.60	0.61
Basic + LA dimension	61.1	0.07	0.61
Basic + peak mitral early diastolic/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/tissue Doppler peak early diastolic myocardial velocity ratio	65.6	0.005	0.61
Basic + MR grade	62.7	0.08	0.61
Basic + all 8 echocardiographic variables	74.6	Multiple added predictors	0.62
Basic + peak Vo2	92.5	<0.0001	0.64
Basic + peak Vo2 + peak mitral early diastolic/peak late diastolic velocity ratio	94.8	0.13 (E/A), <0.0001 (peak Vo2)	0.64

The basic multivariate model for the primary end point included β-blocker dose (truncated at 50 mg/day), body surface area, blood urea nitrogen, gender, Kansas City Cardiomyopathy Questionnaire symptom stability score, region (United States vs non–United States), and ventricular conduction.

lations between Doppler echocardiographic 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 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a 2-tailed α level of 0.05, with no adjustment for multiple comparisons. Unless otherwise indicated, all p values are based on the likelihood ratio chi-square statistic.

Results

Table 1 lists selected demographic, clinical, and echocardiographic variables in the overall cohort (n = 2,331) and in the subgroup (n = 519) for whom complete data were available for the primary end point 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, gender, body mass index, and race), exercise, and LVEF variables between the overall cohort and the echocardiographic 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 lists univariate predictors of the primary end point (all-cause hospitalization or all-cause death). Among the 2,331 HF-ACTION patients, measurements for LV diastolic dimension, LV mass, LA dimension, E/A ratio, and deceleration time were available for 1,550 to 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 signifi-

Table 4
Univariate predictors of heart failure: a controlled trial investigating outcomes of exercise training for secondary end point (cardiovascular disease mortality or heart failure hospitalization)

Echocardiographic Parameter	Sample Size	Hazard Ratio (95% Confidence Interval)	Chi-Square Value	p Value
LV diastolic dimension	1,646	1.14 (1.06–1.23)	12.7	0.0004
LV mass (per 100 g)	1,646	1.10 (1.04–1.17)	10.8	0.001
LVEF (per 5%)	2,327	0.82 (0.78–0.87)	58.3	<0.0001
LA dimension	1,646	1.48 (1.33–1.65)	49.7	<0.0001
Peak mitral early diastolic/peak late diastolic velocity ratio	1,550	1.43 (1.33–1.54)	71.2	<0.0001
Early diastolic deceleration time (per 50 ms)	1,604	0.83 (0.77–0.89)	27.9	<0.0001
Tissue Doppler peak early diastolic myocardial velocity	909	0.98 (0.95–1.01)	2.24	0.13
Peak mitral early diastolic velocity/tissue Doppler peak early diastolic myocardial velocity ratio	796	1.23 (1.15–1.33)	25.5	<0.0001
MR grade (grades 0–4 vs 5 or 6)	2,135	2.3 (1.9–2.8)	61.1	<0.0001
Peak Vo2	2,275	0.86 (0.85–0.88)	255.3	<0.0001

Table 5
Multivariate models for heart failure: a controlled trial investigating outcomes of exercise training cardiovascular disease mortality or heart failure hospitalization end point (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 + LV diastolic dimension	107.1	0.009	0.71
Basic + LV mass	105.3	0.03	0.70
Basic + LVEF	103.8	0.06	0.70
Basic + LA dimension	101.3	0.33	0.70
Basic + peak mitral early diastolic/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/tissue Doppler peak early diastolic myocardial velocity ratio	121.2	<0.0001	0.72
Basic + MR grade	111.6	0.0008	0.71
Basic + all 8 echocardiographic variables	149.5	Multiple added predictors	0.74
Basic + peak Vo2	132.6	<0.0001	0.74
Basic + peak Vo2 + peak mitral early diastolic/peak late diastolic velocity ratio	146.4	0.0002 (E/A), <0.0001 (peak Vo2)	0.75

The basic multivariate model for the secondary end point included age (truncated at 62 years), body surface area, blood urea nitrogen (truncated at 39 mg/dl), gender, Kansas City Cardiomyopathy Questionnaire symptom stability score, loop diuretic dose (truncated at 100 mg), race, and ventricular conduction.

cant), all echocardiographic variables were highly statistically significant univariate predictors of the primary end point; however, peak Vo_2 was a better predictor than any echocardiographic variable.

Table 3 lists C-index and multivariate p values for the primary end point when each echocardiographic variable was separately added to the basic multivariate model (which included only 519 patients who had no missing data for all variables). Only E/A ratio increased (slightly) the C-index of the basic model (from 0.61 to 0.62, p = 0.003); nevertheless, the E/A and E/E′ ratios had highly significant chi-square p values. (A significant chi-square p value can indicate statistical improvement in model fit by the inclusion of a variable in the absence of substantive improvement in model discrimination between higher and lower risk patients, denoted by the C-index.[10]) The other 7 echocardiographic variables added little to prediction beyond that achieved by the basic multivariate model plus E/A ratio. Importantly, peak Vo_2 improved risk discrimination independently of the basic model and echocardiographic variables, increasing the C-index from 0.62 to 0.64, while echocardiographic variables did not improve risk discrimination of the basic model plus peak Vo_2, with the C-index remaining unchanged at 0.64.

Table 4 lists the univariate predictors for the secondary combined end point (CVD mortality or HF hospitalization). All echocardiographic variables, except for E′ velocity, were highly statistically significant predictors of the secondary end point. LA dimension, the LVEF, MR grade, E/A ratio, and E/E′ ratio were the most important echocardiographic predictors of the secondary end point, but peak Vo_2 was even more important. Table 5 lists multivariate p values and C-indexes for the secondary end point when each of the 8 echocardiographic variables was separately added to the

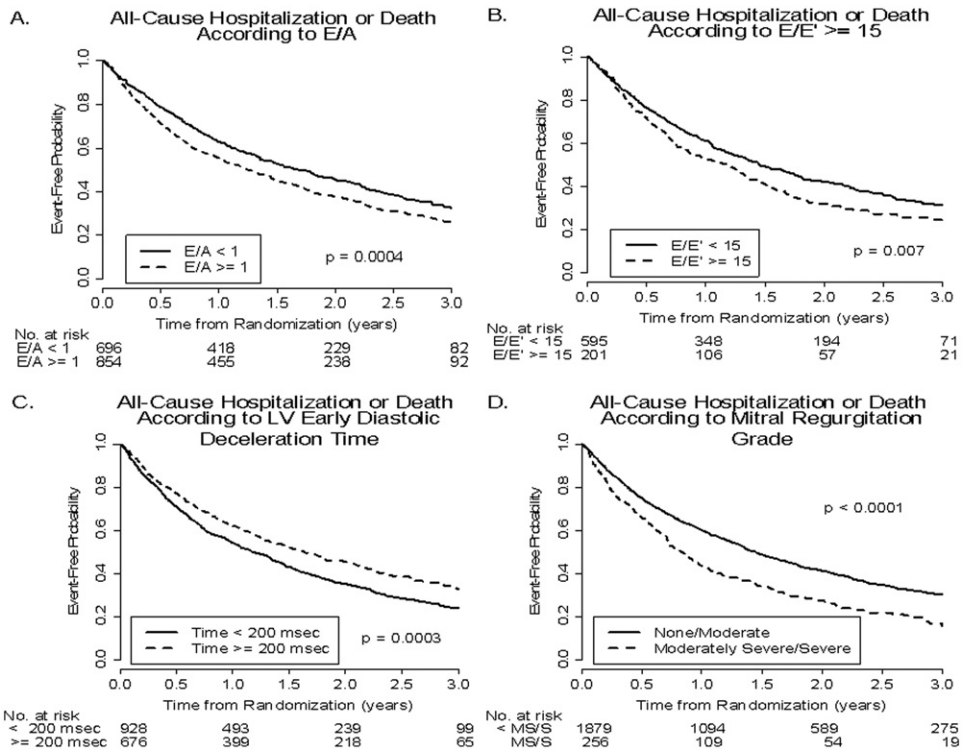

Figure 1. Kaplan-Meier curves for the event-free probabilities for all-cause hospitalization or death (primary outcome) as a function of E/A ratio <1.0 versus ≥1.0 *(A)*, E/E′ ratio <15 versus ≥15 *(B)*, deceleration time <200 versus ≥200 ms *(C)*, and none to moderate versus moderately severe or severe MR *(D)*.

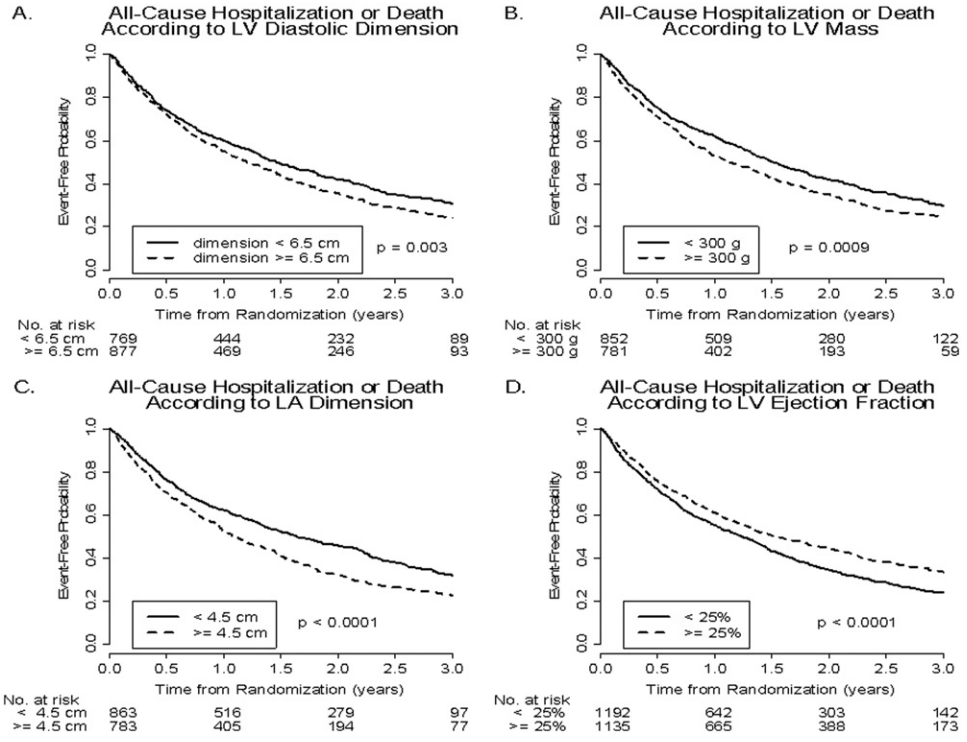

Figure 2. Kaplan-Meier curves for the event-free probabilities for all-cause hospitalization or death (primary outcome) as a function of LV diastolic dimension <6.5 vs ≥6.5 cm *(A)*, LV mass <300 vs ≥300 g *(B)*, LA dimension <4.5 vs ≥4.5 cm *(C)*, and LVEF <25% vs ≥25% *(D)*.

basic multivariate model. The multivariate models included only patients who had data for all variables. The E/A and E/E′ ratios were the most statistically significant echocardiographic variables; their addition to the basic model resulted in the most substantial increases in the C-index (from 0.70 for the basic model to 0.73 and 0.72, respectively).

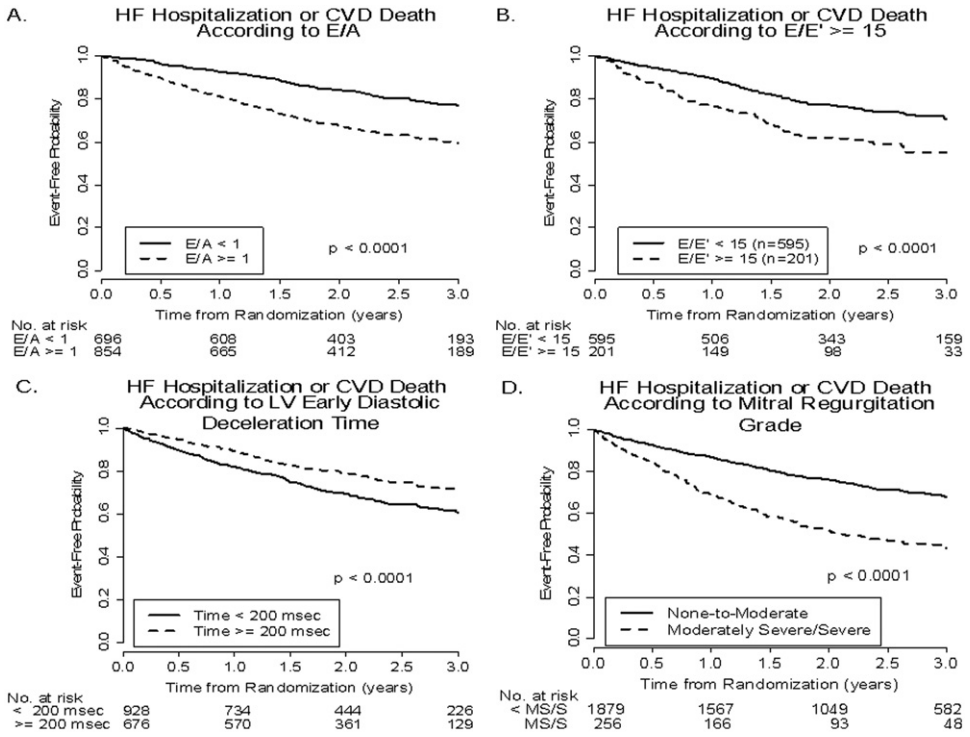

Figure 3. Kaplan-Meier curves for the event-free probabilities for HF hospitalization or CVD death (secondary outcome) as a function of E/A, E/E′, deceleration time, and MR. Format is the same as in Figure 1.

However, peak Vo_2 was a stronger independent predictor for the secondary end point (C-index = 0.74) than any echocardiographic variable. Moreover, peak Vo_2 was an independent predictor of outcomes even when all 8 echocardiographic variables were included. There was no difference in predictive ability between the basic model plus all 8 echocardiographic variables and peak Vo_2 versus the basic model plus E/A ratio and peak Vo_2. In the 972 patients in the exercise training arm with serial measurements, no echocardiographic variable was significantly related to the change from baseline to 3 months in peak Vo_2.

Figures 1 and 2 present Kaplan-Meier curves demonstrating the relation of the event-free probability for the primary outcome versus time from randomization in patients with each echocardiographic variable above and below a defined clinically relevant cut point. Note that event-free probability for the primary outcome was higher with an E/A ratio <1.0 versus ≥ 1.0, an E/E′ ratio <15 versus ≥ 15, deceleration time <200 versus ≥ 200 ms, and MR grades of less than moderately severe (0 to 4) versus moderately severe or severe (5 and 6) (Figure 1). Figure 2 presents similar relations in patients with LV diastolic dimensions <6.5 versus ≥ 6.5 cm, LV mass <300 versus ≥ 300 g, LA dimensions <4.5 versus ≥ 4.5 cm, and LVEFs $<25\%$ versus $\geq 25\%$. Event-free probabilities for the primary outcome were significantly higher in those with smaller LV diastolic dimensions, smaller LV mass, smaller LA dimensions, and higher LVEFs. Relations similar to those for the primary outcome were present between all 8 echocardiographic variables and the secondary outcome. Significant differences were present between the 2 curves for each echocardiographic variable, representing event-free probabilities for patients with echocardiographic measurements above and below the defined clinically relevant cut point. Figure 3 presents relations (all significant) between the secondary outcome and E/A ratio, E/E′ ratio, LV deceleration time, and MR grade. Visual differences between the 2 event-free curves were greatest for MR grade.

Discussion

We examined the predictive value for all-cause death or all-cause hospitalization (the primary end point) and CVD death or HF hospitalization (the secondary end point) of Doppler echocardiographic measures of LV and LA anatomy, and LV systolic and diastolic function, in the HF-ACTION cohort. For the primary end point, peak Vo_2 was a more powerful univariate and multivariate predictor than were echocardiographic variables when added to a basic demographic and clinical model. Moreover, peak Vo_2 improved risk prediction independently of the basic model and the echocardiographic variables, while the echocardiographic variables did not improve the predictive ability of the basic model once peak Vo_2 was included. Similarly, for the secondary end point, peak Vo_2 was a more important univariate predictor than the echocardiographic variables. Adding peak Vo_2 was equivalent as an independent multivariate predictor of the secondary end point to adding all 8 echocardiographic variables to a basic model. E/A ratio was the most important single echocardiographic predictor for the primary and secondary end points. For the secondary end point, including E/A ratio in the basic model with peak Vo_2 improved the C-index modestly. However, the LVEF

was not an independent predictor beyond the basic multivariate model for primary or secondary end points.

We believe the HF-ACTION cohort is the largest to measure echocardiographic variables and aerobic capacity using cardiopulmonary exercise testing in patients with systolic HF. Our study extends previous work by suggesting that in patients with systolic HF, a combination of commonly recorded rest echocardiographic variables may add modest prognostic value to peak Vo_2; however, peak Vo_2 is a stronger predictor of adverse outcomes than any individual echocardiographic variable. Kaplan-Meier event rate analysis showed significantly higher rates of overall and CVD or HF hospitalization and mortality in the groups with (1) greater LV diastolic dimensions, LV mass, LA dimensions, E/A and E/E′ ratios, and MR severity and (2) lower LVEFs and deceleration times. This study also extends our previous findings[4] that baseline Doppler echocardiographic 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 the LVEF.

Measures of LV systolic function, LV mass, and LV diastolic function and filling (e.g., E/A, E/E′, and deceleration time) have been shown to predict CVD events in patients with systolic HF. In the Studies of Left Ventricular Dysfunction (SOLVD) registry and trials, LV mass ≥298 g and LA dimension ≥4.17 cm were associated with increased risk for death and CVD hospitalization in 1,172 patients with LV dysfunction. A protective effect of an 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 aged >70 years, whereas a "restrictive mitral flow pattern" (deceleration time <140 ms) was independently associated with cardiac death or HF hospitalization.[12] In smaller studies of patients with ischemic and nonischemic cardiomyopathy, with LVEF cut points ranging from <50% to <35% and E/E′ cut points ranging from 13.5 to 16, the E/E′ ratio was a good predictor of cardiac death or HF rehospitalization and of a combined end point including death, heart transplantation, and HF hospitalization.[8,13–16] Dokainish et al[16] reported that E/E′ ratio and predischarge brain natriuretic peptide blood levels were incremental predictors of cardiac death or rehospitalization for HF. Our study extends previous work by demonstrating that in our cohort, Doppler echocardiographic E/A and E/E′ ratios and MR grade are stronger predictors of HF hospitalization or CVD mortality than are LV mass, the LVEF, and LA dimension.

There are a number of likely reasons why the rest Doppler echocardiographic variables studied were not better predictors (e.g., compared with peak Vo_2) of the primary or secondary outcome. Tests that examine cardiopulmonary function during stress (e.g., exercise cardiopulmonary exercise tests) often have more robust diagnostic and prognostic capabilities than those examining only rest function. Furthermore, Doppler echocardiographic variables do not assess noncardiac HF components (e.g., abnormalities of skeletal muscle or peripheral vasculature) or multiple co-morbidities that may drive many events in patients with HF.[17,18] Of importance, age alone is a strong predictor of overall and CVD-related outcomes; after adjustment for age in a multivariate model, Doppler echocardiographic variables have substantially less prognostic power.

Several limitations of the present study are apparent. First, echocardiographic variables were not available in many patients. M-mode echocardiographic variables (e.g., LV diastolic dimension, LV mass, and LA dimension) and pulsed Doppler E/A ratio and deceleration time were available in 2/3, whereas tissue Doppler–based variables (E′ velocity and E/E′ ratio) were available in only 1/3, of the cohort. In approximately 1/3, 2-dimensionally derived M-mode measurements of LV diastolic dimension, LV mass, and LA dimension could not be reliably performed, thereby limiting the usefulness of echocardiography 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 echocardiographic variables were available and the entire cohort. Second, there are well-known limitations in using Doppler echocardiographic measurements to evaluate LV systolic and diastolic function. Potential difficulties include LV foreshortening, inadequate visualization of LV endocardium, and mathematical oversimplifications in 2-dimensional models used to estimate 3-dimensional LV volumes, LV mass, and LVEF. In patients with severe HF, the E/E′ ratio has been reported unreliable in predicting intracardiac filling pressures, especially in patients with large LV volumes.[19] The E/E′ ratio 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′ ratio. Currently, there is no single perfect Doppler echocardiographic measurement of diastolic dysfunction. Nonetheless, the HF-ACTION core echocardiographic laboratory has previously reported measurements for interreader variability of 2 ± 1% for E velocity and 5 ± 2 to 3% for deceleration time and E′ velocity.[21] Third, because follow-up echocardiography was not performed, we cannot comment on 3-month changes in echocardiographic variables potentially associated with either the change from baseline to 3 months in peak Vo_2 or the primary or secondary end point. 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 echocardiographic variables in this context.

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