Journal of the American College of Cardiology Vol. 45, No. 7, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.12.069

Echocardiographic Predictors of Morbidity and Mortality in Patients With Advanced Heart Failure

The Beta-blocker Evaluation of Survival Trial (BEST)

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OBJECTIVES The aim of this study was to determine echocardiographic predictors of outcome in patients with advanced heart failure (HF) due to severe left ventricular (LV) systolic dysfunction in the Beta-blocker Evaluation of Survival Trial (BEST).

BACKGROUND Previous studies indicate that echocardiographic measurements of LV size and function, mitral deceleration time, and mitral regurgitation (MR) predict adverse outcomes in HF. However, complete quantitative echocardiograms evaluating all of these parameters have not been reported in a prospective randomized clinical trial in the era of modern HF therapy.

METHODS Complete echocardiograms were performed in 336 patients at 26 sites and analyzed by a core laboratory. A Cox proportional-hazards regression model was used to determine which echocardiographic variables predicted the primary end point of death or the secondary end point of death, HF hospitalization, or transplant. Significant variables were then entered into a multivariable model adjusted for clinical and demographic covariates.

RESULTS On multivariable analysis adjusted for clinical covariates, only LV end-diastolic volume index predicted death (events = 75), with a cut point of 120 ml/m^2. Three echocardiographic variables predicted the combined end point of death (events = 75), HF hospitalization (events = 97), and transplant (events = 9): LV end-diastolic volume index, mitral deceleration time, and the vena contracta width of MR. Optimal cut points for these variables were 120 ml/m^2, 150 ms, and 0.4 cm, respectively.

CONCLUSIONS Echocardiographic predictors of outcome in advanced HF include LV end-diastolic volume index, mitral deceleration time, and vena contracta width. These variables indicate that LV remodeling, increased LV stiffness, and MR are independent predictors of outcome in patients with advanced HF. (J Am Coll Cardiol 2005;45:1064–71) © 2005 by the American College of Cardiology Foundation

According to the American College of Cardiology/American Heart Association practice guidelines, echocardiography is "the single most useful test in the evaluation of patients with heart failure (HF)" (1). Among other things, it offers the ability to assess chamber size, shape, and function, filling pressures, pulmonary artery pressure, valvular disease, congenital abnormalities, and restrictive physiology (2). Despite its obvious clinical utility, it is difficult to demonstrate that echocardiography influences patient outcomes or predicts response to specific therapy (3). Although numerous variables can be measured echocardiographically, it is not clear which of these variables predicts outcome in HF. In the Vasodilators in Heart Failure Trial (V-HeFT) (4), the Studies Of Left Ventricular Dysfunction (SOLVD) (5), and the Valsartan in Heart Failure Trial (Val-HEFT) (6,7), echocardiographic assessment of left ventricular (LV) size and left ventricular ejection fraction (LVEF) predicted outcomes. However, these studies did not assess other echocardiographic variables, such as mitral deceleration time (8,9) or severity of mitral regurgitation (MR) (10), that have been shown in single-center or small retrospective studies to predict outcome in HF. This study reports the results of the Beta-blocker Evaluation of Survival Trial (BEST) echocardiographic substudy, in which we prospectively sought to determine echocardiographic predictors of outcome in patients with advanced HF due to severe LV systolic dysfunction in the absence of a reversible cause. We hypothesized that baseline measurements of LV geometry and function, mitral deceleration time, and MR would predict adverse outcomes independently of clinical covariates.

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Manuscript received October 11, 2004; revised manuscript received December 3, 2004, accepted December 20, 2004.

Abbreviations and Acronyms

BEST = Beta-blocker Evaluation of Survival Trial
CHF = congestive heart failure
EROA = effective regurgitant orifice area
HF = heart failure
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
NYHA = New York Heart Association
SAVE = Survival And Ventricular Enlargement trial
SOLVD = Studies Of Left Ventricular Dysfunction trial
Val-HeFT = Valsartan in Heart Failure Trial

METHODS

The design and primary results of the BEST study have been previously published (11). Briefly, patients with New York Heart Association (NYHA) functional class III or IV HF and LVEF ≤35% were randomly assigned to placebo or bucindolol therapy, with mortality as a primary end point. Patients were excluded if they had HF due to a reversible cause, uncorrected primary valvular disease, hypertrophic cardiomyopathy, untreated thyroid disease, pericardial disease, amyloidosis, active myocarditis, prosthetic valve dysfunction, or recent myocardial infarction (<6 months). All patients were at least 18 years old and provided written, informed consent for the main trial and for the echocardiographic substudy.

Complete two-dimensional and Doppler echocardiograms were performed in 355 patients enrolled in the BEST study at 26 clinical sites. Sites were selected on the basis of experience in echocardiographic clinical research, interest in this substudy, and submission of three protocol-specific qualifying echocardiograms. All BEST participants at these sites were asked to participate in the echocardiographic substudy. Echocardiograms of poor technical quality were excluded in 19 patients (5%); the remaining 336 patients comprise this report.

Echocardiography. Blood pressure was taken by cuff at the time of echocardiography. A thorough two-dimensional and Doppler echocardiographic study was then performed according to a specific imaging protocol. Each site received a training manual and videotape detailing the specific views and measurements required to assess LV systolic and diastolic function, LV geometry, LV mass, and MR. All echocardiographic data were recorded on S-VHS videotape labeled with the date, BEST study patient identification number, and patient initials, and sent to the core laboratory for analysis and quality control. Studies were interpreted without knowledge of clinical characteristics or treatment assignment.

Analysis of LV systolic function and geometry. At each participating site, sonographers were instructed to adjust gain settings to optimize visualization of the LV endocardial contours while avoiding excessive gain artifact. Standard parasternal, apical, and subcostal views were obtained. Specific instruction included placing the transducer as far laterally and caudally as possible in the apical windows to maximize LV cavity size and avoid foreshortening. Technically difficult studies were excluded by the core laboratory when inadequate endocardial border visualization in the apical views precluded measurement of LV volumes. Left ventricular end-systolic and end-diastolic dimensions, posterior wall thickness, septal wall thickness, and left atrial dimension were measured according American Society of Echocardiography recommendations (12). The LV volumes and LVEF were quantified at the core laboratory using the biplane Simpson's rule (12). Stroke volume and cardiac output were determined by pulsed Doppler technique as recommended by the American Society of Echocardiography (13). The LV geometry was assessed by a ratio of the major-to-minor axis at end-diastole (14) and as the sphericity index, which is the ratio of the LV end-diastolic volume to a sphere whose radius equals the length of the LV (15). The LV mass was assessed by the 5/6 area-length method as recommended by the American Society of Echocardiography (12). Circumferential wall stress was calculated from cuff systolic blood pressure and end-systolic echocardiographic measurements (16).

Analysis of LV diastolic function. Left ventricular filling patterns were determined by pulsed Doppler technique with a 1- to 2-mm sample volume positioned between the tips of the mitral leaflets parallel to mitral inflow from the four-chamber view (8,9). Mitral inflow patterns were analyzed for maximal E and A velocities, E/A ratio, A-wave duration, and deceleration time. Deceleration time was calculated as the time between the peak E-wave and its deceleration slope extrapolated to the zero baseline. By slightly repositioning the sample volume to overlap mitral inflow and aortic outflow, isovolumic relaxation time was assessed as the time from the end of aortic ejection to the start of mitral inflow. Pulmonary venous flow velocities were obtained with a 2- to 4-mm sample volume positioned 1 to 2 cm into the right and left upper pulmonary veins from a modified four-chamber view (13). Peak systolic and diastolic flow velocities were recorded. In addition, the peak A-wave reversal and A duration were measured.

Assessment of MR. Doppler color flow mapping was used to identify the presence or absence of MR. Gain settings were optimized by reducing the gain to the point where background noise disappeared. Frame rate was maximized by minimizing the sector angle and depth settings to allow visualization of the entire contour of the left atrium. The left atrium was interrogated from multiple acoustic windows using adjustments in transducer angulation to identify the largest MR velocity profile. The direction of the MR jet was assessed from both parasternal and apical views, and the area of the largest clearly definable color flow disturbance was traced in each view as an index of the severity of MR (17,18). The width of the jet vena contracta as it emerges from the valve leaflets was measured in each view (19). Quantitative Doppler assessment of regurgitant volume, regurgitant fraction, and effective regurgitant orifice

Table 1. Clinical Characteristics of Patients in the BEST Echocardiographic Substudy by Treatment Assignment Compared to the BEST Cohort

	Echo Substudy		
	Placebo (n = 167)	Bucindolol (n = 169)	BEST Cohort (n = 2,708)
Demographics			
Age (yrs)	61 ± 12	60 ± 13	60 ± 12
Female	27 (16%)	37 (22%)	593 (22%)
Caucasian	127 (76%)	117 (69%)	1,896 (70%)
African American	31 (19%)	42 (25%)	627 (23%)
Hispanic	7 (4%)	7 (4%)	143 (5%)
Clinical variables			
Heart rate (beats/min)	81 ± 13	82 ± 13	81 ± 13
Systolic blood pressure (mm Hg)	118 ± 18	115 ± 18	117 ± 18
Diastolic blood pressure (mm Hg)	71 ± 11	69 ± 11	71 ± 11
NYHA functional class III	151 (90%)	156 (92%)	2,482 (92%)
NHYA functional class IV	16 (10%)	13 (8%)	226 (8%)
Diabetes mellitus	50 (30%)	54 (32%)	964 (36%)
Hypertension	92 (55%)	91 (54%)	1,596 (59%)
Prior CABG	47 (28%)	52 (31%)	782 (29%)
Ischemic cardiomyopathy	99 (59%)	91 (54%)	1,587 (59%)
Medications			
ACE inhibitor	146 (87%)	157 (93%)	2,470 (91%)
Angiotensin II antagonist	20 (12%)	11 (7%)	174 (6%)
Digoxin	149 (89%)	152 (90%)	2,501 (92%)
Diuretics	161 (96%)	159 (94%)	2,537 (94%)
Vasodilators	81 (49%)	72 (43%)	1,271 (47%)
Antiarrhythmic agent	3 (2%)	5 (3%)	73 (3%)

ACE = angiotensin-converting enzyme; BEST = Beta-blocker Evaluation of Survival Trial; CABG = coronary artery bypass graft; NYHA = New York Heart Association.

area (EROA) was performed using established methods (20). Similarly, the proximal isovelocity surface area method was also used to determine peak regurgitant flow rate and EROA (20). In patients without MR, vena contracta width and EROA were considered to be 0 for purposes of statistical analysis. Finally, pulsed Doppler spectra from the pulmonary veins were assessed in a modified four-chamber view for systolic flow reversal (20). All measurements of MR severity were made at the core laboratory; results were sent to the data coordinating center where all statistical analysis was performed.

Statistical analysis. Continuous variables are reported as mean ± one standard deviation. Group comparisons were made by paired *t* test or Wilcoxon rank sum test, as appropriate. Categorical variables are reported as proportions; comparisons were made by chi-square test or Fisher exact test, as appropriate. The primary end point was death; the secondary end point was death, transplant, or hospitalization for HF. Survival was determined by the Kaplan-Meier method and p values were calculated by the log-rank test. All echocardiographic variables were assessed for univariate statistical significance using a Cox proportional hazard regression model. Variables with a p value <0.1 were then entered into a multivariable model, which was adjusted for the baseline covariates age, diabetes, creatinine, NYHA functional class, and treatment group. Optimal cut points for variables that were predictive of outcome on multivariable analysis were selected by examining box plots showing whether or not an event occurred. For all analyses, a p value ≤ 0.05 was considered statistically significant.

RESULTS

Table 1 compares the clinical characteristics of the patients in the echocardiographic substudy, by treatment assigned, to those in the main BEST study. There were no significant differences between patients in the echocardiographic substudy and those in the main trial, nor were there differences between substudy patients randomized to placebo and those treated with bucindolol. There were no significant differences in the echocardiographic measurements between groups (Table 2). In the 336 patients in the echocardiographic substudy, baseline LVEF by multiple gated acquisition was 22.7 ± 7.7%, compared with 24.9 ± 9.5% by echocardiography ($p = 0.0001$).

Of the 336 patients in the BEST echocardiographic substudy, there were 75 (22%) deaths, 9 (3%) heart transplants, and 97 (29%) hospitalizations for congestive heart failure (CHF). As shown in Table 3, several echocardiographic variables predicted outcome by univariate analysis. However, multivariable analysis showed that only three echocardiographic variables were predictors of these outcomes after adjustment for clinical covariates. Only LV end-diastolic volume index was predictive of death on multivariable analysis. Figure 1 shows a Kaplan-

Table 2. Baseline Echocardiographic and Doppler Variables by Treatment Group

	Placebo (n = 167)	Bucindolol (n = 169)
LV end-diastolic dimension (cm)	6.6 ± 0.9	6.7 ± 0.9
LV end-systolic dimension (cm)	5.8 ± 0.9	5.9 ± 1.0
Septal wall thickness (cm)	0.9 ± 0.2	0.9 ± 0.2
Posterior wall thickness (cm)	1.0 ± 0.2	0.9 ± 0.2
LA dimension (cm)	4.5 ± 0.6	4.5 ± 0.8
LVOT diameter (cm)	2.2 ± 0.2	2.2 ± 0.2
Mitral annulus diameter (PLAX) (cm)	3.0 ± 0.4	3.0 ± 0.4
Mitral annulus diameter (4-chamber) (cm)	3.0 ± 0.4	3.0 ± 0.4
LVOT velocity-time integral (cm)	13.2 ± 4.2	12.7 ± 3.9
Systolic ejection period (ms)	248 ± 38	247 ± 37
Mitral E velocity (m/s)	0.8 ± 0.3	0.8 ± 0.3
Mitral A velocity (m/s)	0.6 ± 0.3	0.6 ± 0.3
Mitral A wave duration (ms)	140 ± 32	141 ± 29
Deceleration time (msec)	162 ± 64	168 ± 70
Isovolumic relaxation time (ms)	97 ± 31	96 ± 33
Mitral annulus velocity-time integral (cm)	9.1 ± 3.6	8.5 ± 3.2
Pulmonary vein S_1 velocity (m/s)	0.3 ± 0.1	0.3 ± 0.1
Pulmonary vein S_2 velocity (m/s)	0.4 ± 0.2	0.4 ± 0.2
Pulmonary vein D velocity (m/s)	0.5 ± 0.2	0.5 ± 0.2
Pulmonary vein A velocity (m/s)	0.3 ± 0.1	0.3 ± 0.1
Pulmonary vein A duration (ms)	139 ± 27	144 ± 26
Pulmonary vein systolic flow reversal	10 (7%)	7 (6%)
Tricuspid regurgitation peak velocity (m/s)	2.9 ± 0.7	2.8 ± 0.6
LV end-diastolic volume index (ml/m^2)	113 ± 35	115 ± 42
LV end-systolic volume index (ml/m^2)	85 ± 31	88 ± 40
LVEF (%)	25 ± 10	24 ± 9
LV mass index (g/m^2)	144 ± 36	146 ± 43
Fractional area shortening (%)	18 ± 9	18 ± 9
LV length (cm)	9.6 ± 1.0	9.5 ± 1.0
Sphericity index	0.3 ± 0.1	0.3 ± 0.1
Major-to-minor axis ratio	1.5 ± 0.2	1.4 ± 0.2
LV end-systolic stress, meridional (dynes/cm^2)	153 ± 65	146 ± 67
LV end-systolic stress, circumferential (dynes/cm^2)	542 ± 406	563 ± 419
MR	124 (75%)	130 (78%)
MR jet area (cm^2)	9.0 ± 5.4	9.3 ± 5.8
MR vena contracta width (cm)	0.4 ± 0.1	0.3 ± 0.1
MR jet velocity-time integral (cm)	133 ± 29	137 ± 36
MR jet peak velocity (m/s)	4.3 ± 0.7	4.3 ± 0.7
MR jet dp/dt (mm Hg/s)	803 ± 747	789 ± 720
PISA radius (cm)	0.5 ± 0.1	0.5 ± 0.2
EROA, PISA (cm^2)	0.2 ± 0.1	0.1 ± 0.1
EROA, quantitative Doppler (cm^2)	0.1 ± 0.1	0.0 ± 0.1
Regurgitant fraction, quantitative Doppler	0.1 ± 0.4	0.1 ± 0.5

EROA = effective regurgitant orifice area; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MR = mitral regurgitation; PISA = proximal isovelocity surface area; PLAX = parasternal long axis.

Meier survival plot for patients stratified according to an LV end-diastolic volume index ≤120 ml/m^2. Left ventricular end-diastolic volume index, mitral deceleration time, and vena contracta width (a marker of MR severity) were significant predictors of the combined end point of death, transplant, or hospitalization for CHF. Figure 2 shows the Kaplan-Meier event-free survival plots for these three variables using cut points of ≤120 ml/m^2 for LV end-diastolic volume index, ≥150 ms for mitral deceleration time, and ≤0.4 cm for MR vena contracta width.

Table 4 shows the echocardiographic and clinical predictors of outcome by multivariable analysis. For all patients in the echocardiographic substudy, LV end-diastolic volume index, creatinine, and treatment group (bucindolol vs. placebo) were significant predictors of mortality. Predictors of the combined end point included LV end-diastolic volume index, mitral deceleration time, MR vena contracta width, diabetes, creatinine, and treatment group.

DISCUSSION

Although echocardiography is widely used to evaluate cardiac structure and function in patients with HF, few data are available regarding its ability to predict outcomes (21). A large number of variables can be measured or calculated by echocardiographic and Doppler imaging, many of which are physiologically or even mathematically related. Thus, it is not clear which echocardiographic measurements provide independent prognostic information. This substudy of the BEST study demonstrates that echocardiographic measures of LV end-diastolic volume index, mitral deceleration time, and MR vena contracta width predict outcomes in patients

Table 3. Echocardiographic Predictors of Outcomes on Univariate Analysis

Variable	n	Death	Combined End Point
LVEF	335		0.0679
Fractional area shortening	327		0.0097
Isovolumic relaxation time	295		
LV end-diastolic dimension	336	0.0339	0.0130
LV end-systolic dimension	336	0.0048	0.0034
LV length	336	0.0854	0.0064
LA dimension	335	0.0738	0.0462
LV end-systolic stress, meridional	320		0.0060
LV septal wall thickness	336		0.0789
LV sphericity index	335		0.0344
LV end-diastolic volume index	335	0.0015	0.0001
LV end-systolic volume index	335	0.0018	0.0001
LV mass index	327	0.0804	0.0046
LVOT velocity-time integral	328	0.0207	0.0034
Mitral annulus diameter, 4-chamber	332	0.0378	0.0050
Mitral annulus diameter, long-axis	332		0.0736
Mitral E velocity	316	0.0233	0.0003
Mitral A velocity	282	0.0226	0.0001
Mitral A duration	279		0.0022
Mitral deceleration time	302	0.0464	0.0001
Mitral annulus velocity-time integral	293	0.0273	0.0518
MR	332	0.0722	
MR vena contracta width	235	0.0996	0.0003
MR PISA radius	220	0.0889	0.0078
MR EROA, PISA	195	0.0609	0.0012
MR EROA, volumetric	259		0.0001
MR regurgitant fraction, volumetric	301		0.0515
MR jet area	247		0.0002
MR jet dp/dt	250	0.0535	
TR jet peak velocity	214		0.0007

Only parameters with p values <0.10 are shown. These were entered into the multivariable model.
Abbreviations as in Table 2.

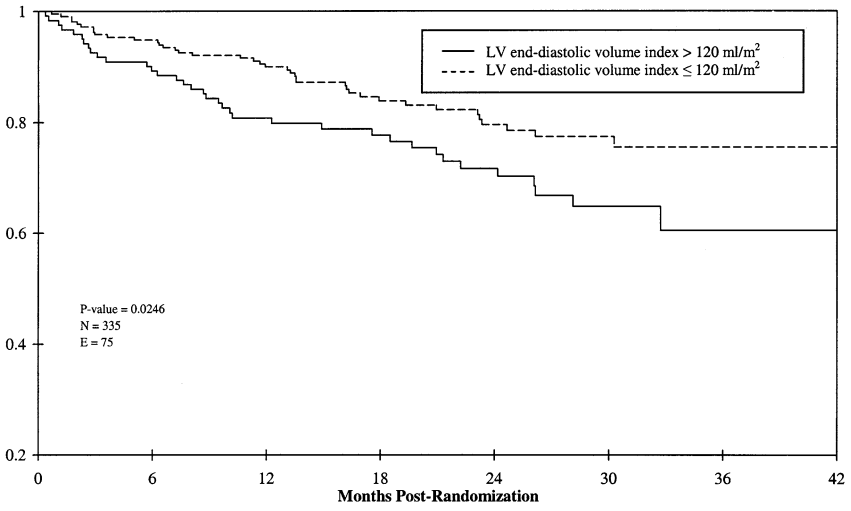

Figure 1. Kaplan-Meier plot showing time to death by left ventricular (LV) end-diastolic volume index. Patients are stratified according to LV end-diastolic volume index ≤120 ml/m^2 versus >120 ml/m^2. E = events.

with advanced HF (NYHA functional class III or IV symptoms and LVEF ≤35%).

LV end-diastolic volume index. Left ventricular volumes are important predictors of outcome after acute myocardial infarction. White et al. (22) showed that LV end-systolic volume index was an independent predictor of survival after acute myocardial infarction. In the Survival And Ventricular Enlargement (SAVE) trial, LV cavity area, measured in a short-axis view, was reduced by captopril, and this reduction was associated with improved outcomes (23). Moreover, baseline LV cavity area predicted cardiovascular outcome regardless of treatment assigned (24). The SAVE trial also showed that LV remodeling after myocardial infarction was associated with ventricular arrhythmias (25).

Echocardiographic LV volume data has also been reported in HF clinical trials. In the SOLVD prevention and treatment arms (26), enalapril significantly reduced LV end-diastolic volume, LV end-systolic volume, and LV mass over 12 months compared with placebo in 301 patients enrolled in an echocardiographic substudy. Carvedilol has also been shown to reduce LV volumes and increase LVEF, in 123 patients in the Australia-New Zealand Heart Failure Research Collaborative Group (27). The Val-HeFT echocardiographic substudy (6) showed a reduction in LV end-diastolic dimension and an increase in LVEF with valsartan therapy compared to placebo in 5,010 patients. Although these studies showed favorable effects on LV remodeling of drugs known to improve survival in HF, they did not report the relation of echocardiographic variables measured at baseline to outcomes in HF, nor did they evaluate other important echocardiographic variables such as LV filling velocities or MR severity. In this substudy of the BEST trial, LV end-diastolic volume index was the only echocardiographic variable that predicted the primary outcome of death when adjusted for clinical covariates.

Many echocardiography laboratories do not measure LV volumes, but instead rely on LV dimensions, in part because of their ease of measurement and many years of clinical familiarity. In this study, LV dimensions were predictive of death and the combined end point on univariate, but not on multivariable, analysis. Recent studies using contrast echocardiography have shown that the accuracy of LV volumes is improved in technically difficult patients by the use of contrast (28,29), thus enabling measurement of LV volumes and LVEF in nearly all patients. The present data support routine measurement and reporting of LV volumes by echocardiography in patients with HF. Moreover, the prognostic importance of LV end-diastolic volume index highlights the interest in newer surgical techniques to reduce LV volumes in ischemic cardiomyopathy (30). A large clinical trial has been initiated to determine whether reducing LV volumes by surgical ventricular restoration will improve mortality in HF (31).

Mitral deceleration time. This study confirms the results of previous single-center studies that showed that mitral deceleration time predicts outcome in HF (8,9,32,33). In this large, multicenter trial of patients with advanced HF, mitral deceleration time independently predicted the combined end point of death, heart failure hospitalization, or transplant. The optimal cut point for mitral deceleration time was 150 ms. The pathophysiologic basis for this finding is that mitral deceleration time is a marker of increased LV stiffness (34) and decreased myocardial viability (35), factors associated with extensive fibrosis and necrosis.

MR vena contracta width. Functional MR is a common complication of ischemic heart disease and is widely considered to contribute to symptoms and mortality. Two large clinical trials have shown that functional MR occurring either early or late (>16 days) after acute myocardial infarction is associated with increased mortality (36,37). However, until recently, studies in dilated cardiomyopathy were small and limited mainly to nonischemic etiology (10,38–40). A recent retrospective study by Trichon et al. (41) reported that the angiographic severity of MR predicts mortality in patients with HF and LVEF ≤40%. This study confirms the prognostic impor-

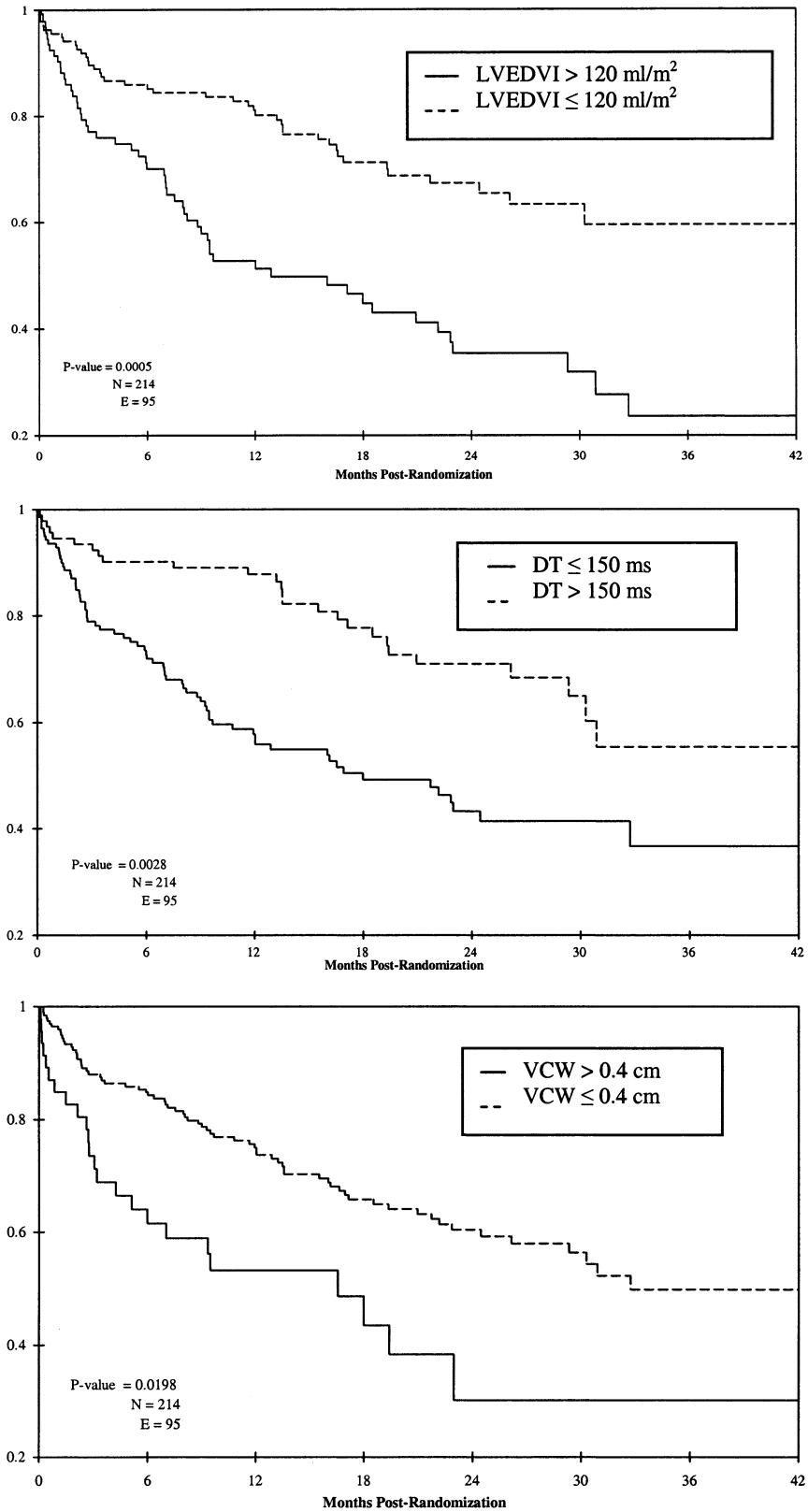

Figure 2. Kaplan-Meier plots showing time to the combined end point of death, heart failure hospitalization, or transplant for patients with a left ventricular end-diastolic volume index (LVEDVI) ≤120 ml/m^2 versus >120 ml/m^2 **(top panel)**, a mitral deceleration time (DT) ≥150 ms versus <150 ms **(middle panel)**, and a mitral regurgitation vena contracta width (VCW) of ≤0.4 cm versus >0.4 cm **(bottom panel)**. Variables included in the model were LVEDVI, mitral DT, and mitral regurgitation VCW. E = events.

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Table 4. Predictors of Outcome on Cox Proportional Hazards Multivariable Analysis Adjusted for Baseline Covariates

Primary End Point of Death (E = 75)*			
Baseline Variable	**HR**	**95% CI**	**p Value**
LV end-diastolic volume index	1.009	1.003–1.014	0.0012
Creatinine	2.023	1.235–3.316	0.0052
Treatment group	0.566	0.355–0.902	0.0167
Secondary End Point of Death (E = 75), HF Hospitalization (E = 97), or Transplant (E = 9)†			
Baseline Variable	**HR**	**95% CI**	**p Value**
LV end-diastolic volume index	1.009	1.004–1.015	0.0008
Mitral deceleration time	0.992	0.987–0.997	0.0014
MR vena contracta width	10.669	2.331–48.823	0.0023
Creatinine	1.921	1.182–3.123	0.0085
History of diabetes	1.599	1.024–2.496	0.0390
Treatment group	0.503	0.326–0.775	0.0018

*Seven initial covariates entered into model: LV end-diastolic volume index, history of diabetes, creatinine, age, gender, NYHA functional class, treatment group. †Nine initial covariates entered into model: LV end-diastolic volume index, mitral deceleration time, MR vena contracta width, history of diabetes, creatinine, age, gender, NYHA functional class, treatment group.

CI = confidence interval; E = events; HF = heart failure; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

tance of MR in advanced HF in a prospective clinical trial. Although several echocardiographic measures of MR severity predicted the combined end point on univariate analysis, only vena contracta width remained predictive on multivariable analysis, even when adjusted for clinical covariates. Patients with a vena contracta width >0.4 cm had a greater likelihood of death, transplant, or HF hospitalization. Importantly, a vena contracta of 0.4 cm is generally considered to be only moderate MR (19).

Study limitations. The patients in this substudy were not randomly selected from all eligible patients in the BEST study. Instead, they were enrolled from expert sites, which underwent specific training in the acquisition of this study protocol. Although this method assured high-quality data, we cannot be certain that these results apply to the overall BEST study population. In fact, the finding that treatment with bucindolol predicted improved survival in this substudy indicates that these patients are not representative of the overall BEST study population, because bucindolol was not associated with a survival benefit in the main trial. Moreover, because this study was initiated in 1996, tissue Doppler, strain-rate imaging, harmonic imaging, and contrast agents were not used. Finally, LVEF was predictive of outcome on univariable, but not on multivariable, analysis. This differs from prior studies (4–7). Likely reasons include the narrow and limited range of LVEF in this substudy, a relatively small number of patients, and the fact the LV end-diastolic volume, which was a statistically significant predictor, is a mathematical determinant of LVEF.

Conclusions. Echocardiographic predictors of outcome in advanced HF include LV end-diastolic volume index, mitral deceleration time, and vena contracta width. These variables indicate that LV remodeling, increased LV stiffness, and MR severity are independent predictors of outcome in patients with advanced HF.

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REFERENCES

1. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101–13.
2. Vitarelli A, Gheorghiade M. Transthoracic and transesophageal echocardiography in the hemodynamic assessment of patients with congestive heart failure. Am J Cardiol 2000;86 Suppl:36G–40G.
3. Douglas PS. Justifying echocardiography: the role of outcomes research in evaluating a diagnostic test. J Am Soc Echocardiogr 1996;9:577–81.
4. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87 Suppl 6:V117–23.
5. Quinones MA, Greenberg BH, Kopelen HA, et al. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. J Am Coll Cardiol 2000;35:1237–44.
6. Wong M, Staszewsky L, Latini R, et al. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. J Am Coll Cardiol 2002;40:970–5.
7. Wong M, Staszewsky L, Latini R, et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan Heart Failure Trial (Val-HeFT) echocardiographic data. J Am Coll Cardiol 2004;43:2022–7.
8. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic, and hemodynamic correlations and prognostic implications. J Am Coll Cardiol 1993;22:808–15.
9. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol 1994;24:132–9.
10. Blondheim DS, Jacobs LE, Kotler MN, Costacurta GA, Parry WR. Dilated cardiomyopathy with mitral regurgitation: decreased survival despite a low frequency of left ventricular thrombus. Am Heart J 1991;122:763–71.
11. The Beta-blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659–67.
12. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.
13. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167–84.
14. Sabbah HN, Kono T, Stein PD, Mancini GBJ, Goldstein S. Left ventricular shape changes during the course of evolving heart failure. Am J Physiol 1992;263:H266–70.
15. Bashore TM, Grayburn PA. Quantitation of ventricular function. In: St. John Sutton MG, Rutherford JD, Leppo J, editors. Cardiac Imaging: A Companion to Braunwald's Heart Disease. New York, NY: Elsevier, 2004:77–104.
16. Douglas PS, Reichek N, Plappert T, Muhammad A, St. John Sutton MG. Comparison of echocardiographic methods for assessment of left ventricular shortening and wall stress. J Am Coll Cardiol 1987;9:945–51.
17. Spain MG, Smith MD, Grayburn PA, Harlamert EA, DeMaria AN. Quantitative assessment of mitral regurgitation by color Doppler flow imaging: angiographic and hemodynamic correlations. J Am Coll Cardiol 1989;13:585–90.
18. Helmcke F, Nanda NC, Hsiung MC, et al. Color-Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;75:175–83.

19. Hall SA, Brickner ME, Willett DL, Irani WN, Afridi I, Grayburn PA. Assessment of mitral regurgitation severity by Doppler color flow mapping of the vena contracta. Circulation 1997;95:636–42.
20. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
21. Friesinger GC. Outcomes research: evaluating the impact of echocardiography in congestive heart failure. J Am Coll Cardiol 1999;33:171–3.
22. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.
23. St. John Sutton M, Pfeffer MA, Plappert T, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction: the protective effects of captopril. Circulation 1994;89:68–75.
24. St. John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival And Ventricular Enlargement (SAVE) trial. Circulation 1997;96:3294–9.
25. St. John Sutton M, Lee D, Rouleau JL, et al. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. Circulation 2003;107:2577–82.
26. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiographic substudy. Circulation 1995;91:2573–81.
27. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. J Am Coll Cardiol 1997;29:1060–6.
28. Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Administration of an intravenous contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: a comparison with cine magnetic resonance imaging. J Am Coll Cardiol 1998;32:1426–32.
29. Thomson HL, Basmadjian AJ, Rainbird AJ, et al. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodeling measurements: a prospective, randomly assigned, blinded study. J Am Coll Cardiol 2001;38:867–75.
30. Athanasuleas CL, Stanley AWH Jr., Buckberg GD, Dor V, DiDonato M, Blackstone EH. Surgical anterior ventricular endocardial restoration (SAVER) in the dilated remodeled ventricle after anterior myocardial infarction. J Am Coll Cardiol 2001;37:1199–209.
31. Jones RH. Is it time for a randomized trial of surgical treatment of ischemic heart failure? J Am Coll Cardiol 2001;37:1210–3.
32. Rihal CS, Nishimura RA, Hatle LK, et al. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy: relation to symptoms and prognosis. Circulation 1994;90:2772–9.
33. Giannuzzi P, Temporelli PL, Bosimini E, et al. Independent and incremental prognostic value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. J Am Coll Cardiol 1996;28:383–90.
34. Little WC, Ohno M, Kitzman DW, et al. Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. Circulation 1995;92:1933–9.
35. Yong Y, Nagueh SF, Shimoni S, et al. Deceleration time in ischemic cardiomyopathy: relation to echocardiographic and scintigraphic indices of myocardial viability and functional recovery after revascularization. Circulation 2001;103:1232–7.
36. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival And Ventricular Enlargement Investigators. Circulation 1997;96:827–33.
37. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–64.
38. Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. Am J Cardiol 1984;54:147–52.
39. Stevenson LW, Fowler MB, Schroeder JS, Stevenson WG, Dracup DA, Fond V. Poor survival of patients with idiopathic cardiomyopathy considered too well for transplantation. Am J Med 1987;83:871–6.
40. Romeo F, Pelliccia F, Cianfrocca C, et al. Determinants of end-stage idiopathic dilated cardiomyopathy: a multivariable analysis of 104 patients. Clin Cardiol 1989;12:387–92.
41. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538–43.

APPENDIX

For a list of participants in the BEST Echocardiographic Substudy, please see the April 5, 2005, issue of *JACC* at http://www.onlinejacc.org.