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Severity of Left Ventricular Remodeling Defines Outcomes and Response to Therapy in Heart Failure

Valsartan Heart Failure Trial (Val-HeFT) Echocardiographic Data

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OBJECTIVES The objective of this study was to test the hypothesis that the severity of left ventricular remodeling predicts the response to treatment and outcomes in chronic heart failure.

BACKGROUND Reversal of remodeling should produce the most favorable outcome in patients with the most severe remodeling.

METHODS In 5,010 heart failure patients on background therapy and randomized to valsartan and placebo, serial recordings of left ventricular internal diastolic diameter (LVIDd) and ejection fraction (EF) were read at sites that had to meet qualifying standards before participating. Baseline LVIDd and EF were pooled across treatments and retrospectively grouped by quartiles Q1 to Q4, representing best to worst. Kaplan-Meier survival curves were obtained by the log-rank test. Q1 was compared with Q4 for mortality and combined mortality and morbidity (M + M) from Cox regression risk ratios (RRs). Valsartan versus placebo changes from baseline in LVIDd and EF were analyzed by quartiles from analysis of covariance. Valsartan and placebo were compared by RRs for M + M.

RESULTS Survival rates were greater in the better quartiles for LVIDd and EF ($p < 0.00001$). The RR for Q1 versus Q4 in events approached 0.5 for both LVIDd and EF ($p < 0.0001$). An LVIDd decrease and EF increase were quartile-dependent and greater with valsartan than placebo at virtually all time points. The RR for M + M outcomes favored valsartan in the worse quartiles.

CONCLUSIONS Stratification by baseline severity of remodeling showed that patients with worse LVIDd and EF are at highest risk for an event, yet appear to gain the most anti-remodeling effect and clinical benefit with valsartan treatment. (J Am Coll Cardiol 2004;43:2022–7) © 2004 by the American College of Cardiology Foundation

Clinical trials in heart failure (HF) establish entry criteria that ensure the severity of disease sufficient to detect a favorable effect of therapy on a mortality or morbidity end point. Left ventricular (LV) ejection fraction (EF), a marker for the extent of functional and structural abnormalities of the ventricle, has been identified as a guide to the risk of death and morbid events (1,2). Therefore, most HF trials have set a low EF as an entrance criterion, and in previous trials, the severity of a low EF has served as a guide to the risk of adverse events.

Therapy aimed at reversing or slowing the progression of LV remodeling would be expected to exert the most favorable effect in patients with the greatest severity of remodeling. However, in most previous trials, the sample size of the echocardiographic data was inadequate to evaluate the relationship between remodeling and outcome in individual patients.

The Valsartan Heart Failure Trial (Val-HeFT) was carried out in over 5,000 patients with HF, all of whom had core laboratory-monitored echocardiography performed at baseline and during follow-up after randomization to valsartan or placebo, in addition to all background HF therapy (3). Because the entrance criteria included both a low EF (<40%) and a dilated ventricle (left ventricular internal diastolic diameter [LVIDd] >2.9 cm/m^2 body surface area), all patients recruited into the trial had confirmed remodeling of the LV. Valsartan treatment in the overall population led to a 13.2% reduction in combined mortality and morbidity (M + M) and an improvement in remodeling of the LV (4,5). The large sample size allowed us to further examine the extent to which the degree of remodeling contributed to outcomes and the response to valsartan (6).

METHODS

Echocardiography, both the recording and interpretation, was carried out at 291 multi-national sites. Participation in the trial was dependent on meeting specific core laboratory standards for recording and reading of LVIDd from two-dimensionally directed M-mode echocardiography, and EF was derived from LV volumes using the area-length

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ANCOVA = analysis of covariance
BB = beta-blocker
EF = ejection fraction
HF = heart failure
LV = left ventricle/ventricular
LVIDd = left ventricular internal diastolic diameter
M + M = combined mortality and morbidity
RR = risk ratio
Val-HeFT = Valsartan Heart Failure Trial

method. Total study reproducibility determined from duplicate echocardiograms showed detectable treatment differences for LVIDd and EF, with a power of 90% and alpha level of 5%. During the trial, quality control was monitored from random sampling of patient studies, and this was satisfactorily maintained (6).

Serial echocardiograms in 5,010 patients were obtained at baseline before randomization and at 4, 12, 18, 24, and 30 months after randomization. Baseline measurements of LVIDd and EF for the pooled population of valsartan and placebo patients were retrospectively grouped according to quartiles Q1 to Q4, defined by increasing severity from best to worst. Kaplan-Meier survival curves were constructed to compare baseline quartiles for LVIDd and EF. Differences among quartiles were assessed by the log-rank test. Cox proportional hazard analysis was performed to investigate the relation between the two primary study end points and baseline quartiles for LVIDd and EF. Cox regression risk ratios (RRs), comparing Q1 with Q4 for mortality (time to death) and for M + M (time to death or first morbid event: sudden death with resuscitation, intravenous inotropic or vasodilator therapy, or hospitalization for HF), were calculated from pooled patient data. The treatment effects with valsartan were also analyzed within the baseline quartiles. Inter-treatment differences in change from baseline in LVIDd and EF at months 4, 12, and 24 and end point by quartiles of LVIDd and EF were based on least-squares mean values by analysis of covariance (ANCOVA), which were adjusted for differences among patients with respect to other effects in the ANCOVA model. In addition to treatment, the ANCOVA model included effects for baseline, continent, angiotensin-converting enzyme (ACE) inhibitor use, beta-blocker (BB) use, and treatment-by-baseline interaction. Separate analyses were performed for each quartile and time point using this model. For each time point, the consistency of treatment differences across quartiles was assessed in an analysis of all quartile data by adding treatment-by-quartile interaction (and quartile) effects to the ANCOVA model already described. Risk ratios and 95% confidence intervals comparing valsartan with placebo for M + M were calculated separately for each LVIDd and EF quartile, using Cox regression analysis, including adjustment for New York Heart Association (NYHA) functional class, baseline ACE inhibitor and BB co-therapy, etiology, and age group; these were summarized graphically. Treatment-by-quartile interaction was assessed in a separate

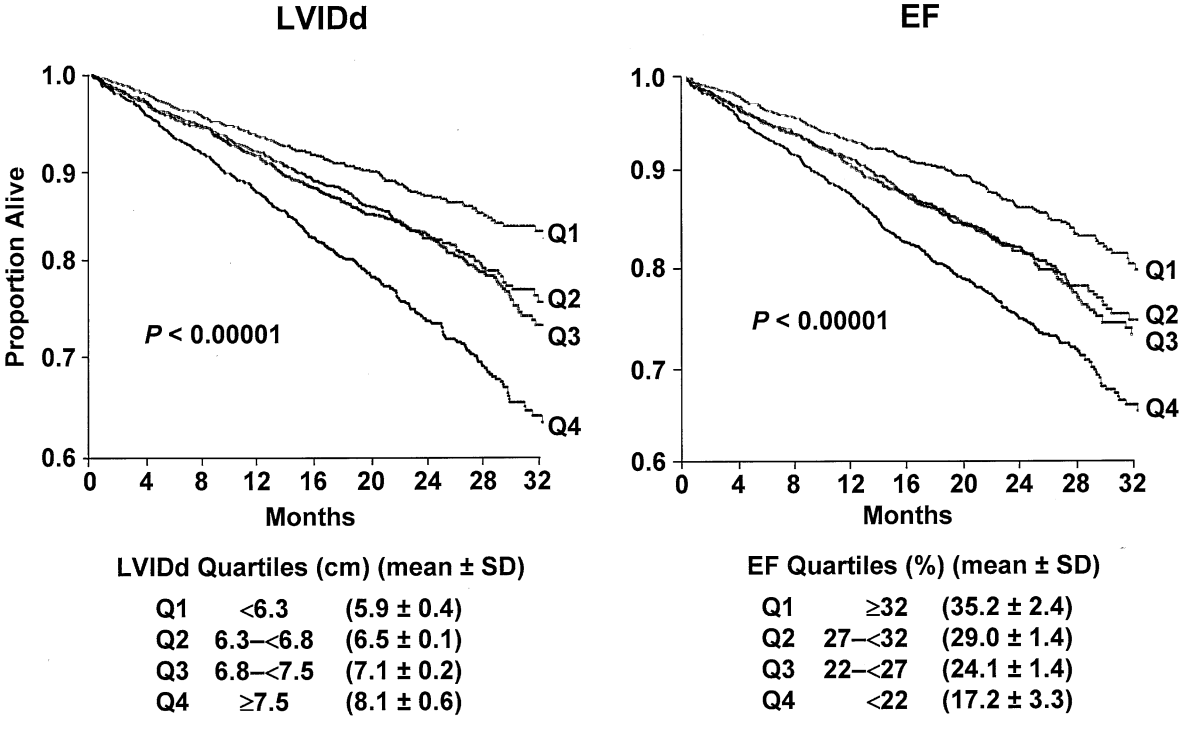

Figure 1. Kaplan-Meier survival curves by baseline quartiles of left ventricular internal diastolic diameter (LVIDd) and ejection fraction (EF) from pooled valsartan and placebo data acquired over an average of 23 months of observation after randomization. Differences among quartiles are significant ($p < 0.00001$ by the log-rank test).

Table 1. Outcomes by Baseline Quartiles

	Q1 n (%)	Q4 n (%)	Q1/Q4 RR*	Q1/Q4 95% CI
LVIDd				
Mortality	153 (13.2)	351 (27.3)	0.442	0.365–0.534
M + M	245 (21.1)	501 (39.0)	0.485	0.416–0.565
EF				
Mortality	202 (13.9)	325 (26.4)	0.501	0.420–0.597
M + M	329 (22.6)	495 (40.2)	0.506	0.440–0.582
LVIDd + EF				
Mortality	55 (10.7)	155 (30.6)	0.319	0.234–0.434
M + M	87 (16.9)	227 (44.9)	0.323	0.253–0.414

*$p < 0.0001$. LVIDd, EF, and combined quartiles at baseline are compared with outcomes (mortality and M + M) from pooled valsartan and placebo data, using univariate Cox proportional hazards analysis.

CI = confidence interval; EF = ejection fraction; LVIDd = left ventricular internal diastolic diameter; M + M = combined mortality and morbidity; n = number of patients with baseline left ventricular measurements who had an event; Q_= quartile; RR = risk ratios by Cox regression.

analysis by incorporating the effects for treatment-by-quartile interaction with those for treatment and LVIDd and EF quartiles. In addition, the odds of an event during the trial for high (≥median) versus low LVIDd were compared across high (≥median) and low EF categories, using the Breslow-Day test for homogeneity of odds ratios. This comparison was made for mortality and M + M, based on pooled patient data.

RESULTS

In this symptomatic population of patients in NYHA functional class II to IV, baseline quartiles of LVIDd from the pooled (valsartan and placebo) population ranged from marginal dilation of <6.3 cm to gross dilation of ≥7.5 cm. Baseline quartiles of EF ranged from a high of ≥32% to a low of <22% (Fig. 1). Survival rates were significantly better in the best quartile (Q1) compared with the worst quartile (Q4) for both LVIDd and EF. Survival rates in the intermediate quartiles (Q2 and Q3) were similar and virtually the same as in the overall population.

Mortality and M + M outcomes at the end of the trial (mean follow-up of 23 months) in the best (Q1) compared with the worst (Q4) quartile for LVIDd and EF are shown in Table 1. The combined LVIDd and EF groups (LVIDd + EF) represent the subgroup of patients in Q1 or Q4 for both LVIDd and EF. The RR for Q1 versus Q4 on either mortality or M + M was highly significantly reduced. For LVIDd or EF, the RR approached 0.5, whereas combining LVIDd and EF identified subgroups in which the risk for patients with the least remodeled ventricles (Q1) was nearly 70% lower than that for the group with the greatest remodeled ventricles (Q4). Tests for homogeneity of high/low odds ratios for LVIDd across high/low categories of EF were not significant for either mortality ($p = 0.334$) or M + M ($p = 0.456$), indicating consistency of high/low values of LVIDd in predicting outcome risk, regardless of high/low values of EF.

Changes over time in LVIDd and EF in the four quartiles are displayed by treatment in Figure 2. The absolute magnitude of LVIDd and EF change was least in both treatment groups in Q1 (the quartile with the lowest baseline LVIDd and the highest baseline EF) and greatest in Q4 (the quartile with the highest LVIDd and lowest EF). These quartile-dependent changes would be anticipated on the basis of regression to the mean. Nonetheless, in each quartile, the magnitude of LVIDd decrease and EF increase at all time points was greater in the valsartan arm than in the placebo arm. The one exception was EF in Q2 at month 24. Placebo-subtracted valsartan effects on LVIDd and EF in the four quartiles at each time point are summarized in Table 2. Significantly greater decreases in LVIDd and increases in EF were observed in various quartiles in the 4- and 12-month data, as well as at the end point with valsartan compared with placebo.

The effects of valsartan treatment on M + M are expressed as RRs by baseline quartiles of LVIDd and EF (Fig. 3). Valsartan reduced the risk for M + M in Q2, Q3, and Q4 for LVIDd by 12%, 20%, and 16%, and for EF by 11%, 15%, and 22%, respectively. Statistically significant RRs in favor of valsartan were observed in Q3 for LVIDd ($p = 0.046$) and Q4 for EF ($p = 0.024$). The effects of valsartan in Q1 were neutral for both LVIDd and EF. Although point estimates tended to demonstrate greater risk reductions with valsartan in the higher quartiles of LVIDd and EF, the global trends were not statistically significant.

DISCUSSION

The present subgroup analysis of Val-HeFT data confirms that the degree of LV structural and functional abnormality is directly related to mortality and morbidity, even when the analysis is limited to patients manifesting systolic dysfunction and ventricular dilation. A low EF is conventionally viewed as a functional abnormality, and in patients with stable HF, it is usually accompanied by a dilated LV chamber, evidence viewed as structural remodeling (7). By including the increased transverse diameter as an entrance criterion for Val-HeFT, the population was confined to those patients with structural remodeling.

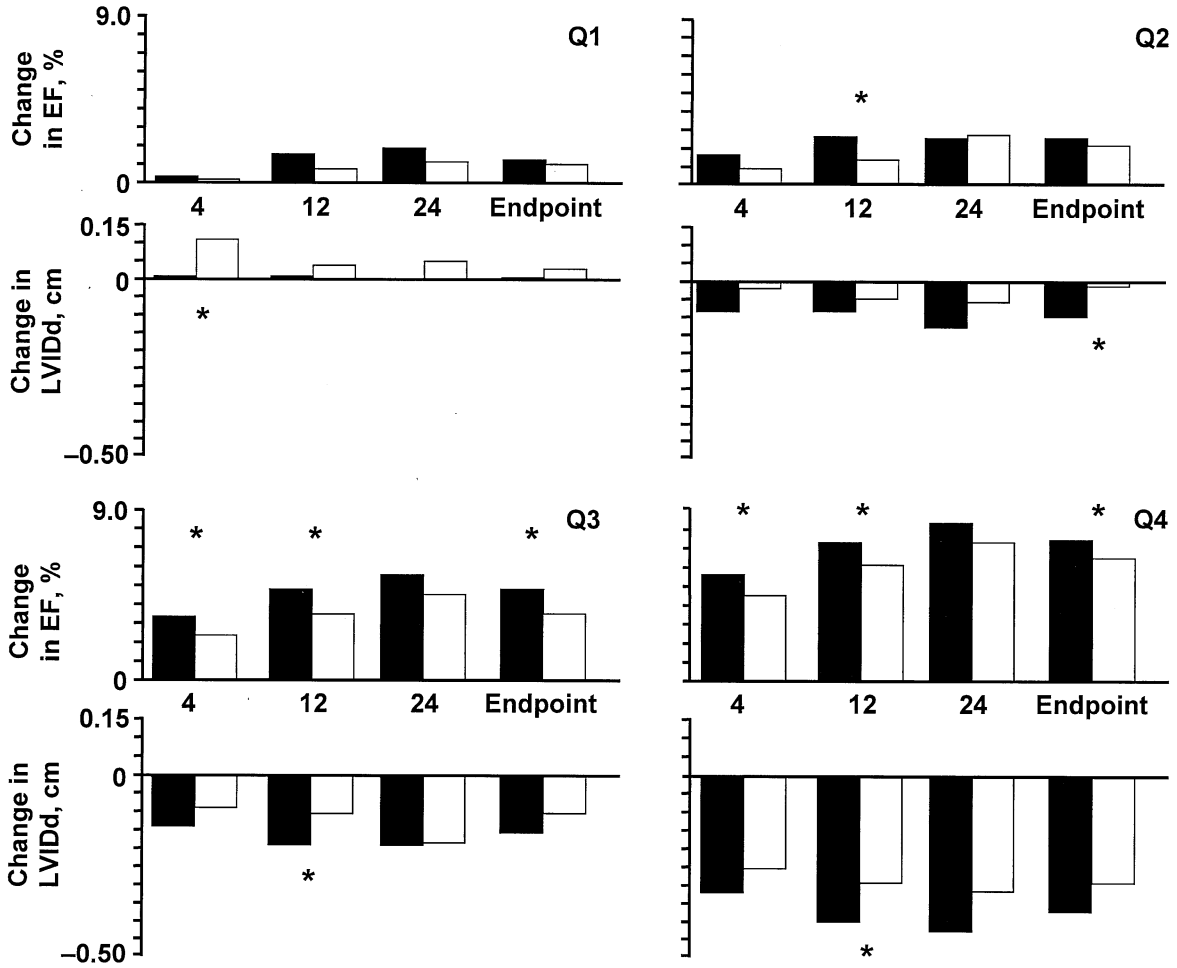

Figure 2. Response to treatment by baseline quartiles. Inter-treatment changes from baseline quartiles of left ventricular internal diastolic diameter (LVIDd) and ejection fraction (EF) at months 4, 12, and 24 and the end point are least-squares mean values by analysis of covariance. **Open bars** = placebo; **solid bars** = valsartan. **Asterisks** indicate significant placebo-subtracted changes from baseline, based on least-square mean values ($p < 0.05$). Global, across-quartile treatment differences at each time point are not significant.

The aims of the retrospective stratification of the echocardiographic data were to differentiate those HF subgroups at higher risk of mortality and morbidity and to assess any differential responses to therapy. The study showed that when baseline LVIDd and EF were grouped according to quartiles of severity, patients with the most severely dilated ventricles and depressed systolic function, irrespective of treatment, were at the greatest risk of mortality and M + M. The finding that both LVIDd and EF were powerful predictors of outcome suggests that they are both markers for the severity of the remodeling process.

In Val-HeFT, valsartan compared with placebo exerted a

Table 2. Placebo-Subtracted Changes From Baseline by Quartiles

	Month 4		Month 12		Month 24		End Point	
	V-P	n	V-P	n	V-P	n	V-P	n
LVIDd (cm)								
Q1	**−0.10***	520	−0.02	466	−0.05	232	−0.05	528
Q2	−0.06	527	−0.03	468	−0.07	229	**−0.09***	537
Q3	−0.06	636	**−0.08***	556	−0.00	293	−0.05	649
Q4	−0.06	559	**−0.11***	467	−0.11	220	−0.09	574
EF (%)								
Q1	0.21	659	0.87	588	0.83	283	0.20	667
Q2	0.78	516	**1.33***	449	−0.16	225	0.58	527
Q3	**1.00***	511	**1.66***	456	1.04	229	**1.40***	521
Q4	**1.07***	535	**1.26***	454	1.19	223	**1.12***	542

*The letter "n" represents the lower sample size for either valsartan or placebo. Values with an asterisk and in **bold** are for $p < 0.05$. Across-quartile changes are not significant. P = placebo; V = valsartan; V-P = placebo-subtracted changes from baseline, based on least-square mean values by analysis of co-variance; other abbreviations as in Table 1.

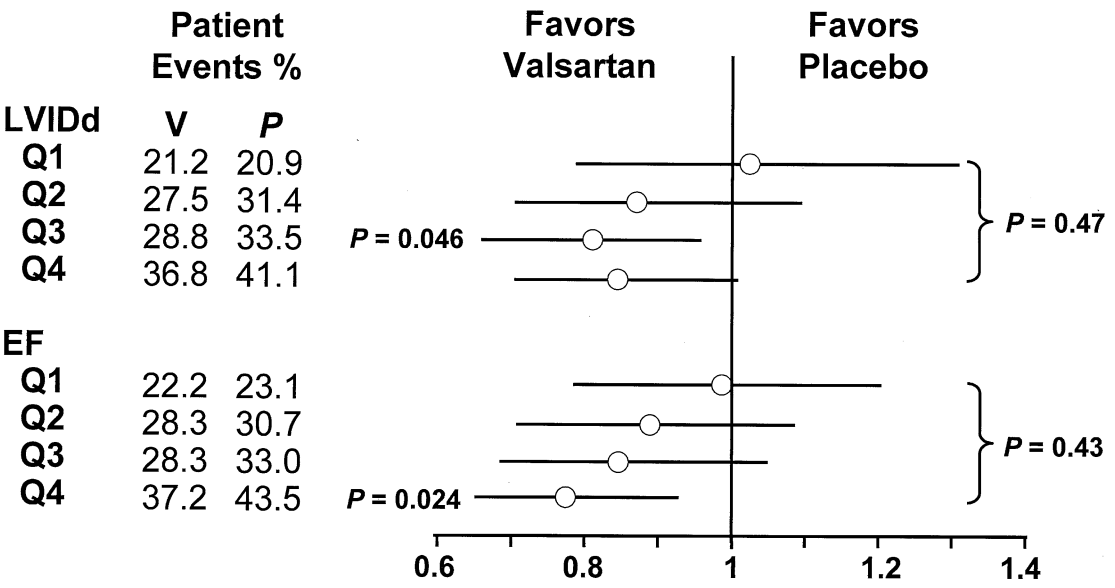

Figure 3. Risk by baseline quartiles—effect of valsartan (V) on the combined end point. Valsartan is compared with placebo (P) for M + M, summarized as percentage of events, risk ratios, and 95% confidence intervals, calculated using Cox regression analysis. The p values on the **right** are for global, across-quartile change. EF = ejection fraction; LVIDd = left ventricular internal diastolic diameter.

favorable effect on LVIDd and EF in the overall population. Between 12 and 24 months, when changes reached a plateau, the absolute maximal mean decrease with valsartan in LVIDd was −0.20 cm, and the maximal mean increase in EF was +4.5% (results not shown for month 18). The corresponding placebo-subtracted changes were −0.10 cm and +1.28%, respectively, which met detectable thresholds for treatment differences (5). Therefore, small changes were statistically significant and physiologically meaningful given the overall clinical outcome (4). As the anti-remodeling effect of valsartan in subgroups based on background therapy appeared to correlate with outcomes (4), we hypothesized that the magnitude of effect of valsartan on LVIDd and EF would be dependent on the baseline severity of remodeling, and that outcomes would correspond to the magnitude of reversal in remodeling.

Analysis of changes from baseline in LVIDd and EF can be influenced by regression to the mean, and when baseline values are truncated by cut-points, subsequent changes will tend to drift toward more normal values. With entry criteria set at abnormal levels for all quartile subgroups, all changes will tend to go in the same direction toward normal, with the largest changes occurring in the subgroup furthest from normal. This appeared to occur; nonetheless, the decrease in LVIDd and increase in EF recorded in the valsartan arm tended to be greater than in the placebo arm in all quartiles and for virtually all time periods (Fig. 2). Although the absolute changes were largest in Q3 and Q4, the placebo-subtracted changes were similar to the mean changes in the overall population, but the smaller sample size in each quartile restricted statistical power (Table 2).

Because the peak effect of valsartan on LVIDd and EF is delayed, we conjecture that the mechanism operates by blocking tissue angiotensin II, which directly affects LV structure by known mitogenic actions (8–10). The finding that the more dysfunctional and dilated LVs were associated with greater reversal of remodeling and a greater risk reduction seemed consistent with evidence showing that the release of angiotensin II is mediated through stretch of sarcomeres (11,12). However, changes in LVIDd and EF were quartile-dependent (Fig. 2), whereas placebo-subtracted changes tended to be similar across quartiles (Table 2). Therefore, the angiotensin II-blocking effects of valsartan remain inferential in explaining the results of this study.

The ideal surrogate for predicting prognosis and for testing treatment efficacy must have, in addition to a statistical relationship, a direct pathophysiologic pathway to the outcome. A change in the surrogate should result in a proportional change in outcome (13,14). The treatment effects on the outcome, therefore, must be mediated through the surrogate and not by another causal pathway (15). Val-HeFT, which included serial echocardiograms in all patients randomized, confirmed the relationship between attenuation or reversal of remodeling and clinical benefit (5). A preliminary report also revealed that changes in EF over time were associated with corresponding changes in mortality and morbidity risks (16). In the current study, baseline LVIDd and EF were found to be strong predictors of mortality and morbidity, and in combination, an even stronger prognosticator. From the Studies Of Left Ventricular Dysfunction (SOLVD) data, patients grouped by median values for LV mass and EF showed a two- to three-fold increase in mortality for those with EF less than the median combined with LV mass greater than the median, as compared with patients with EF above and LV mass below the median (17). The greater predictability is likely due to both structure and function being indepen-

dently informative rather than interactive, as the testing of Val-HeFT data for the relationship between LVIDd and EF found that LVIDd consistently predicted the risk of mortality and M + M, regardless of EF values. The basis for both structure and function as surrogates lies within the concept of remodeling, which is thought to express neurohormonal overcompensation to cardiac injury, and manifested as changes in LV size, shape, and function. This construct is the underpinning for regression of LV remodeling that has emerged as a prime surrogate, based on experimental and clinical experience (18).

Substudies from ACE inhibitor (19,20) and BB trials (21) showed that treatment improved EF and attenuated or decreased ventricular volumes and was associated with a survival benefit reported across the whole study population (22,23). The anti-remodeling and clinical benefit attained in these studies and the Val-HeFT trials (4,5) have raised the prospect of tracking EF and cardiac dimensions to determine efficacy of treatment (18,24). The present study supports the supposition and further suggests that severity of remodeling can predetermine which patients are most likely to derive benefit.

Mortality was not significantly reduced by valsartan in the overall population, but treatment was associated with a significant 13.2% reduction in the combined end point of mortality and morbidity. Was the morbidity benefit influenced by the severity of baseline remodeling? The data are suggestive but not definitive. A mortality/morbidity advantage with valsartan therapy was not observed in the best quartile (Q1) of LVIDd and EF (Fig. 3). The favorable effects of valsartan on outcomes and LV structure and function appeared to be greatest in the quartiles with the widest LVIDd and lowest EF.

Conclusions. Val-HeFT has confirmed that stratification of baseline LVIDd and EF can identify those patients with HF who are most likely to have a fatal or nonfatal event. Those patients with LVIDd ≥7.5 cm and EF <22% are at the highest risk and, at the same time, appear to gain the most improvement in structure and function in response to valsartan. Although all subgroups seemed to respond with some reversal of remodeling, the clinical benefit with valsartan was greatest for those with the more severely dilated and dysfunctional ventricles.

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