

Echocardiographic Predictors of Clinical Outcome in Patients With Left Ventricular Dysfunction Enrolled in the SOLVD Registry and Trials: Significance of Left Ventricular Hypertrophy

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- OBJECTIVES** To assess the relation of left ventricular (LV) and left atrial (LA) dimensions, ejection fraction (EF) and LV mass to subsequent clinical outcome of patients with LV dysfunction enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) Registry and Trials.
- BACKGROUND** Data are lacking on the relation of LV mass to prognosis in patients with LV dysfunction and on the interaction of LV mass with other measurements of LV size and function as they relate to clinical outcome.
- METHODS** A cohort of 1,172 patients enrolled in the SOLVD Trials (n = 577) and Registry (n = 595) had baseline echocardiographic measurements and follow-up for 1 year.
- RESULTS** After adjusting for age, New York Heart Association (NYHA) functional class, Trial vs. Registry and ischemic etiology, a 1-SD difference in EF was inversely associated with an increased risk of death (risk ratio, 1.62; p = 0.0008) and cardiovascular (CV) hospitalization (risk ratio, 1.59; p = 0.0001). Consequently, the other echo parameters were adjusted for EF in addition to age, NYHA functional class, Trial vs. Registry and ischemic etiology. A 1-SD difference in LV mass was associated with increased risk of death (risk ratio of 1.3, p = 0.012) and CV hospitalization (risk ratio of 1.17, p = 0.018). Similar results were observed with the LA dimension (mortality risk ratio, 1.32; p < 0.02; CV hospitalizations risk ratio, 1.18; p < 0.04). Likewise, LV mass \geq 298 g and LA dimension \geq 4.17 cm were associated with increased risk of death and CV hospitalization. An end-systolic dimension $>$ 5.0 cm was associated with increased mortality only. A protective effect of EF was noted in patients with LV mass \geq 298 g (those in the group with EF $>$ 35% had lower mortality) but not in the group with LV mass $<$ 298 g.
- CONCLUSIONS** In patients with LV dysfunction enrolled in the SOLVD Registry and Trials, increasing levels of hypertrophy are associated with adverse events. A protective effect of EF was noted in patients with LV mass \geq 298 g (those in the group with EF $>$ 35% fared better) but not in the group with LV mass $<$ 298 g. These data support the development and use of drugs that can inhibit hypertrophy or alter its characteristics. (J Am Coll Cardiol 2000;35:1237-44) © 2000 by the American College of Cardiology

Over the past two decades, a number of physiologic, biochemical and clinical variables have been identified as important contributors to the prognosis of patients with left

ventricular (LV) dysfunction. Included among them are the following: advanced age, diabetes, etiology of LV dysfunction and symptomatic status (1-3), LV size and parameters of systolic and diastolic function (3-8), pulmonary pressures (9,10), ventricular arrhythmias (11), electrolyte abnormalities and neurohormonal alterations (4,12). More recently, LV hypertrophy has been proved to be a powerful and independent predictor of increased morbidity and mortality in population studies as well as in patients with systemic hypertension or coronary artery disease (13-19). Furthermore excessive hypertrophy has been associated with devel-

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
CHF	=	congestive heart failure
CV	=	cardiovascular
EF	=	ejection fraction
LA	=	left atrium
LV	=	left ventricle
NYHA	=	New York Heart Association
SD	=	standard deviation
SOLVD	=	Studies of Left Ventricular Dysfunction

opment of LV dysfunction in animal models and in patients with hypertension or other forms of heart disease (20–23). However, the influence of hypertrophy on the prognosis of patients with systolic LV dysfunction and/or heart failure is not well described.

The Studies of Left Ventricular Dysfunction (SOLVD) trials were designed to assess the effects of the angiotensin-converting enzyme (ACE) inhibitor, enalapril, in patients with LV dysfunction regardless of the presence or absence of heart failure symptoms (24). Concomitant with the SOLVD trials, a Registry of patients with LV systolic dysfunction was established (25). A cohort of patients from the Trials and Registry participated in substudies that included echocardiographic evaluation of LV function at the time of enrollment. All patients were observed by the SOLVD investigators for a minimum of one year. The present investigation represents an analysis of these data with the purpose of determining the relation between echocardiographic measurements of LV size and function, LV mass and left atrial (LA) size to one-year mortality and rate of cardiovascular (CV) hospitalizations.

METHODS

Patient population. The SOLVD Registry consisted of 6,273 patients with one of the following entry criteria: an ejection fraction (EF) \leq 45% measured by echocardiography, contrast ventriculography or radionuclide techniques, or a hospitalization for congestive heart failure (CHF) confirmed by radiographic evidence of pulmonary venous congestion, regardless of the resting EF (25). A subgroup of 898 patients from 21 participating centers were enrolled in a Registry substudy to investigate the relation of clinical, functional, structural and neurohormonal variables to morbidity and mortality. These patients were randomly selected within strata organized according to varying etiologies of LV dysfunction so as to reduce the frequency of ischemic and hypertensive etiologies relative to other forms of heart diseases. The demographic and clinical characteristics of the 898 patients have been described previously (25). They all underwent a baseline two-dimensional echocardiogram. One third of these patients were randomized to the SOLVD main Trials. The SOLVD Trials enrolled 6,797 patients with a resting EF \leq 35%. Patients with history of

overt heart failure were enrolled in the Treatment Trial and those with no history of heart failure were entered into the Prevention Trial (26,27). A subset of 311 patients (216 from the Prevention and 95 from the Treatment Trial) had baseline echocardiograms as part of a substudy that evaluated the effects of enalapril therapy on LV size, hypertrophy and function (28,29). For the purpose of this investigation, we added these patients to the Registry Substudy, increasing the total sample to 1,209 patients.

The following events were registered: all cause mortality, CV mortality, heart failure death, total hospitalization, CV hospitalizations and heart failure hospitalizations. Follow-up in the Registry patients was limited to one year.

Echocardiographic evaluation. The study protocol was approved by the Institutional Review Boards at each of the participating centers and each patient signed an informed consent form. A two-dimensional echocardiographic examination was performed with each patient lying in the left lateral recumbent position. The views obtained consisted of the parasternal long and short axis, and the apical four- and two-chamber view. A minimum of 10 cardiac cycles were recorded in each view. All video tapes were copied and the original sent for analysis to the SOLVD echocardiographic core laboratory at Baylor College of Medicine, The Methodist Hospital, Houston, Texas.

All of the LV and LA measurements were taken directly from the two-dimensional images by experienced observers blinded to any clinical information or to the assignment of Trial patients into the Treatment or Prevention trial, or the placebo or enalapril limb. Measurements were made using an off-line computerized analysis station equipped with internal calipers (Digisonics, Inc., Houston, Texas) using techniques previously described in detail (28). In brief, the end-diastolic and systolic LV dimensions, the thickness of the septum and posterior wall and the LA systolic dimension were measured in the parasternal long axis view. In $>$ 50% of studies, the use of a low parasternal window resulted in an angulated short axis appearance of the LV that precluded the use of either the area-length or the truncated ellipsoid method of deriving LV mass (30). LV mass was therefore estimated by applying the cube formula to the end-diastolic dimension and the septal and posterior wall thickness measured in the parasternal long axis view (28). LV mass was reported in absolute terms given that height was not consistently available and thus correction for body mass could not be obtained. Accurate measurement of end-diastolic and end-systolic volumes by two-dimensional echocardiography requires apical views that avoid foreshortening of the LV cavity (30), otherwise the results are inaccurate. Unfortunately, this level of technical quality could not be achieved consistently in the 18 centers participating in the Registry. Consequently, LV volumes were not incorporated into the analysis. Instead, EF was derived using the multiple diameter method that does not require volumetric measurements (31).

Table 1. Echocardiographic Measurements at Baseline

	n	Mean ± SD	Median	Range
LV end-diastolic dimension (cm)				
All patients	1,077	6.0 ± 0.97	6.0	3.90-9.10
Trial	535	6.22 ± 0.89*	6.2	3.91-9.10
Registry	542	5.79 ± 0.99	5.7	3.90-9.00
LV end-systolic dimension (cm)				
All patients	1,068	5.0 ± 1.19	4.93	2.10-8.50
Trial	529	5.30 ± 1.04*	5.32	2.10-8.50
Registry	539	4.62 ± 1.23	4.50	2.10-8.30
LVEF (%)				
All patients	1,049	34.5 ± 13.4	32	5-79
Trial	512	30.2 ± 10*	29	10-70
Registry	537	38.5 ± 15.1	36	5-79
LV mass (g)				
All patients	1,045	298 ± 103	282	86-1,023
Trial	521	290 ± 99†	275	86-1,023
Registry	524	306 ± 107	288	102-866
LA dimension (cm)				
All patients	1,077	4.17 ± 0.82	4.1	2-10.5
Trial	536	4.15 ± 0.73	4.1	2.3-7
Registry	541	4.18 ± 0.89	4.1	2-10.5

*p < 0.0001 Trial vs. Registry. †p = 0.02 Trial vs. Registry.
 LV = left ventricle; EF = ejection fraction; LA = left atrium.

Data analysis. All of the echocardiographic data were stored in computer and sent to the data coordinating center at the University of North Carolina, Chapel Hill, where they were stored with demographic and clinical information that included age, gender, New York Heart Association (NYHA) classification, heart rate and systemic blood pressure. Follow-up data included all-cause mortality, deaths from CV causes and from heart failure (CHF), number of hospitalizations, CV hospitalizations and CHF hospitalizations. Given that most deaths and hospitalizations were cardiovascular in nature, we have limited the statistical analyses to include only all-cause mortality and CV hospitalizations, although descriptive statistics for other events are included in this report. The nonparametric Wilcoxon two-sample test was used for comparisons of continuous variables between Trial and Registry patients. The Fisher exact test or the Pearson chi-square statistic was used to compare distributions of nominal variables. The relation between a 1-SD difference in an echocardiographic parameter between any two patients and risk of death and CV hospitalization was evaluated using Cox proportional hazard regression analysis. The association of an echo parameter above and below its mean value to mortality and rate of CV hospitalization was also examined by Cox proportional hazards regression. All of the analyses relating an echo parameter to an event rate were adjusted initially for age, NYHA functional class, Trial versus Registry assignment and ischemic etiology. Subsequently the analyses were adjusted for EF in addition to the other factors (see following text). Kaplan-Meier survival plots were also constructed.

RESULTS

Of the 1,209 patients, 1,172 had at least one of the echocardiographic measurements listed in Table 1 available for analysis. The clinical characteristics of these patients are

Table 2. Clinical Characteristics of Study Population

	All Patients (n = 1,172)	Trial Patients (n = 577)	Registry Patients (n = 595)
Age (yr)	59.7 ± 11.6	59 ± 11	60.4 ± 12
Weight (kg)	79.9 ± 16.8	81.7 ± 15.9*	78.2 ± 17.43
Male subjects (%)	80	86*	74
Race (%)			
White	86.2	85.2	87.1
Black	11.6	11.8	11.4
Other	2.2	3	1.5
CHF etiology (%)			
Ischemic	58.3	68.7	48.3†
Nonischemic	36.6	21.2	51.7†
Unknown	5.1	10.1	
NYHA class (%)			
I	38.8	44.5	33.2
II	46.3	44.5	48
III-IV	15	11*	18.8

*p ≤ 0.001 Trial vs. Registry patients.
 †Difference between Trials and Registry was by design.
 CHF = congestive heart failure; NYHA = New York Heart Association.

Table 3. Frequency of Events at One Year

	All Patients, No. (%) (n = 1,172)
Death	111 (9.5)
CV death	93 (7.9)
CHF death	49 (4.2)
Hospitalization	465 (40)
CV hospitalization	351 (30)
CHF hospitalization	132 (11.3)

CV = cardiovascular; CHF = congestive heart failure.

listed in Table 2. The mean age was 59.7 years, 80% of the patients were male and white was the predominant race. Ischemic heart disease was the most common etiology of LV dysfunction. Most patients (85%) were in NYHA functional class I or II at the time of enrollment into the study. Comparison of the subgroup of patients that participated in the SOLVD Trials (n = 577) with the subgroup that participated only in the Registry (n = 595) demonstrated that the Registry group had fewer men and consequently, lower body weight. In addition, the Registry group had a lower frequency of ischemic etiology (by design) and a higher frequency of NYHA functional class III-IV than the Trials group (Table 2). The Trials subgroup in the current investigation resembled the Trial population in everything but the frequency of an ischemic etiology (79.6% in the Trial and 68% in the subgroup; p < 0.02). The Registry subgroup resembled the overall Registry population in everything but the frequency of NYHA functional class I (50% in the Registry vs. 33% in the subgroup; p < 0.004). Mean ± 1 SD, median and range of values for the echocardiographic measurements are listed in Table 1. Comparison between Trial and Registry subgroups (Table 1) revealed larger LV dimensions (diastolic and systolic) and lower EF in the Trial subgroup, and larger LV mass in the Registry. No differences were observed in LA dimensions.

The one-year all-cause mortality for all patients was 9.5% with most deaths (84%) being CV in nature (Table 3). Based on available data, only 44% of the deaths were listed as secondary to CHF. Forty percent of the patients experienced one or more hospitalizations and 75% of these were for CV cause of which 38% consisted of CHF.

EF was a strong predictor of events even after adjusting for age, NYHA functional class, Trials versus Registry and ischemic etiology. A 1-SD difference in EF was highly associated with an increase in all-cause mortality (risk ratio of 1.62 [1.22, 2.14]; p = 0.0008) and CV hospitalization (risk ratio of 1.59 [1.27, 2.00]; p = 0.0001). In addition, an EF below the mean of 35% was associated with an increased risk in all-cause mortality (risk ratio of 1.8 [1.01, 3.21], p = 0.05). Figure 1 illustrates the cumulative mortality rate over a period of 12 months for patients with EF at or above vs. below 35%, showing survival advantage for the higher EF group (p = 0.012).

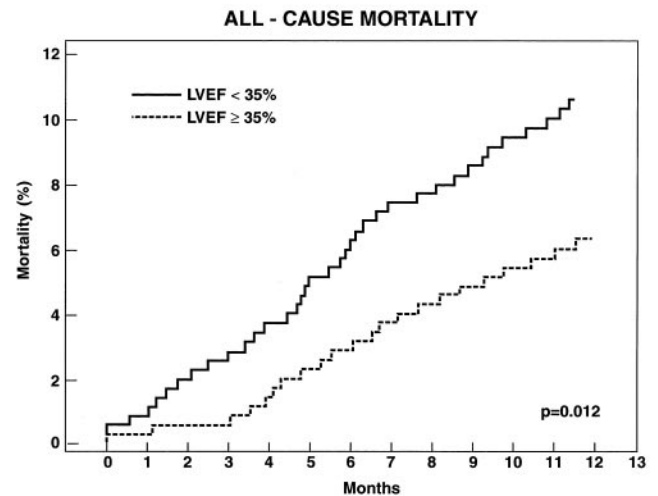


Figure 1. Kaplan-Meier unadjusted survival curves (expressed as cumulative 1-year mortality) observed in patients with LVEF at or above vs. below 35%.

Because of the influence of EF on survival, the analysis for the other echocardiographic variables was adjusted for EF in addition to age, NYHA class, Trial vs. Registry and ischemic etiology. A significant relation was observed between a 1-SD difference in LV mass and all-cause mortality (risk ratio of 1.3 [1.06, 1.60]; p = 0.012) as well as CV hospitalization (risk ratio of 1.17 [1.03, 1.31]; p = 0.018). Similar findings were observed with the LA dimension (mortality: risk ratio, 1.32; p < 0.02; CV hospitalizations: risk ratio, 1.18; p < 0.04). Neither systolic nor diastolic LV dimension was associated with higher event rates.

The association of an echo parameter above and below its mean value to mortality and rate of CV hospitalizations was examined by Cox proportional hazards regression adjusting for age, NYHA class, Trial vs. Registry, ischemic etiology and EF (Table 4). LV mass and LA dimensions greater than the mean were significantly associated with increased risk of death and CV hospitalization. End-systolic LV dimensions larger than the mean were associated with increased mortality.

Figure 2 illustrates the Kaplan-Meier unadjusted survival curves (expressed as cumulative one-year mortality) observed in patients with an LV mass at or above vs. below the mean value of 298 g. Mortality at 1 year reached 12% in patients with LV mass ≥298 g and 5% in those with lesser degree of hypertrophy (p = 0.0017). The effect of combining EF with LV mass on mortality rates is graphically displayed in Figure 3. The log-rank statistic p value (0.0014) compares the event rate experience of the four groups. An interaction between EF and LV mass on event rates was observed for mortality and CV death (Table 5). A protective effect of EF was noted in the group with LV mass ≥298 g (the subgroup with EF >35% fared better), whereas in the group with LV mass <298 g, mortality and CV deaths were lower independent of the EF.

Table 4. Relation of Echocardiographic Parameters to Event Rate, by Cox Proportional Hazards Regression

	All-Cause Mortality		CV Hospitalization	
	Risk-Ratio*	P Value	Risk-Ratio*	P Value
LV mass	2.75 (1.62, 4.66)	0.0002	1.81 (1.39, 2.36)	0.0001
LV end-systolic dimension	2.73 (1.43, 5.20)	0.003	NS	NS
LA dimension	1.84 (1.08, 3.15)	0.03	1.37 (1.05, 1.78)	0.02

*Above vs. below the mean group comparison adjusted for age, NYHA class, ischemic etiology and EF.
 CV = cardiovascular; LV = left ventricle; LA = left atrium; NYHA = New York Heart Association; EF = ejection fraction.

DISCUSSION

The patients in the SOLVD Registry and Trials were representative of the spectrum of patients with LV dysfunction seen in this country. However, by design, ischemic etiology was underrepresented in the Registry substudy to allow inclusion of other etiologies of LV dysfunction such as hypertension, valvular and myocardial diseases. Most patients (80%) were male and white was the predominant race (86%), with blacks representing close to 12% of the sample. From the standpoint of symptoms and LV function, our study population represented an ambulatory well-compensated group of patients. Most (85%) were in NYHA functional class I or II with a mean EF of 35%. Despite this, the one-year mortality of the group approached 10% with most of the deaths resulting from a CV event. Furthermore, 40% of the patients experienced one or more hospitalizations with three quarters of them being CV in nature. As in many other studies of patients with ischemic, valvular or myocardial diseases, (1,3,4,32-34), EF was a strong predictor of survival even after adjusting for age, NYHA functional class, Trial vs. Registry and ischemic etiology. For

this reason, the other echocardiographic parameters were adjusted for EF in addition to the other factors.

This study demonstrates for the first time (to our knowledge) an association between LV hypertrophy and CV events in patients with chronic LV dysfunction independent of the presence or absence of heart failure symptoms. Although increasing LV mass was associated with higher mortality and rate of CV hospitalizations after adjusting for EF, an interaction between the two was noted. EF was protective in patients with LV mass ≥ 298 g (the subgroup with EF >0.35 had lower mortality and CV deaths) whereas in the group with LV mass <298 g, mortality and CV deaths were lower regardless of the EF.

The interaction of myocardial function with LV mass relative to adverse events has been noted previously in hypertensive patients by de Simone and associates (35). They observed the highest event rates in patients who were in the highest two quartiles of LV mass as well as in those in the lowest two quartiles of midwall shortening. Furthermore, in patients with increased LV mass, event-free

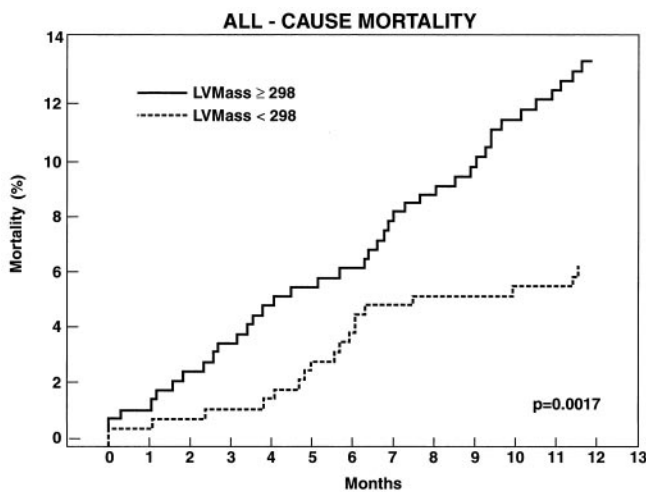


Figure 2. Kaplan-Meier unadjusted survival curves (expressed as cumulative 1-year mortality) observed in patients with LV mass at or above vs. below the mean value of 298 g.

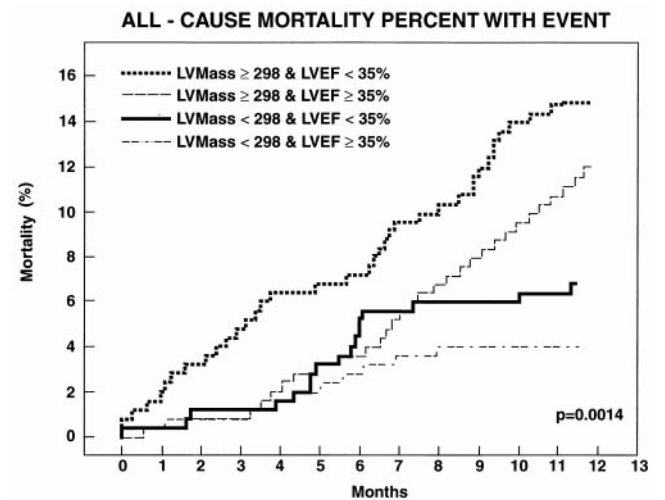


Figure 3. Kaplan-Meier unadjusted survival curves (expressed as cumulative 1-year mortality) observed in patients grouped according to LV mass and EF. The log-rank statistic p value (0.0014) compares nonparametrically the event rate experience of the four groups.

Table 5. Association of Left Ventricular Mass and Ejection Fraction With Clinical Events

	All-Cause Mortality, %	Death, %		Hospitalization, %		
		CV	CHF	Any	CV	CHF
LV mass <298 and EF <35%	6	5	3	35	24	9
LV mass ≥298 and EF <35%	12	10	5	39	32	18
LV mass <298 and EF ≥35%	4	3	1	27	19	4
LV mass ≥298 and EF ≥35%	6	6	4	39	27	11

CV = cardiovascular; CHF = congestive heart failure; LV = left ventricle; EF = ejection fraction.

survival was lower in the subgroup with reduced midwall shortening. We have observed a similar interaction in patients with chronic LV dysfunction. Although statistical associations are not proof of causality, these data are concordant with the concept that pathologic hypertrophy is associated with higher rates of CV events (13-19).

Left ventricular remodeling appears to be an important risk factor for increased mortality in patients with chronic volume overload lesions and following myocardial infarction (5,23,32,36,37). In our group of patients, dilatation and hypertrophy often coexisted with each other and therefore, the influence of one is closely linked to the other. Nevertheless, LV mass had a statistically stronger association with adverse events than LV dimensions. This may be due in part to the inclusion of patients with heart failure and normal EF (many of whom had hypertension) into the SOLVD Registry. Thus, relative to Trial patients, the Registry subgroup had smaller ventricles with higher EF and LV mass (i.e., more concentric hypertrophy). It is also possible that the use of dimensions, instead of volumes, underestimated the severity of LV dilation (38,39).

Although hypertrophy is often thought as a beneficial compensation to increased load, there are several factors that may be detrimental to clinical outcome. Increases in muscle mass may lead to an imbalance in myocardial oxygen supply and demand based on a relative reduction in the number of capillaries, increased intercapillary distance and relative reduction in energy-producing mitochondria. The expression of key genes may be altered in the hypertrophic ventricle and this may lead to abnormalities in function (40-44). Furthermore, pathologic hypertrophy (in contrast to physiologic hypertrophy) is associated with increased collagen deposition in the extracellular matrix and around the intramyocardial coronary arteries (41,45). The resulting interstitial and perivascular fibrosis has been linked to increased LV stiffness and impaired coronary reserve (46-48), both of which may worsen heart failure and ischemia (40,41,47,49,50). Therapy with ACE inhibitors has been

shown to partially reverse LV dilation and hypertrophy in survivors of acute myocardial infarction with depressed LV function and in patients enrolled in the SOLVD Trials (51-54). In addition, regression of hypertrophy and improvement in EF have been observed in patients with dilated cardiomyopathy treated with metoprolol (55). All of these observations combined suggest that regression of hypertrophy is possible even in advance stages of heart failure and may be linked to the clinical benefits observed with ACE inhibitors and beta-adrenergic blocking agents.

Enlargement of the LA, as assessed by the LA dimension, was also associated with an increased risk of death and CV hospitalization after adjusting for clinical variables and EF. This finding is not surprising since the LA dilates commonly in response to a variety of LV diseases, particularly those associated with hypertrophy and diastolic dysfunction.

Study limitations. The echocardiographic studies were performed by multiple clinical laboratories with a wide range of image quality, thus precluding the accurate measurement of LV volumes or the application of the area-length or truncated ellipsoid methods for the quantification of LV mass (30). However, the parasternal long axis view was available in most patients and this allowed for the use of ventricular dimensions to assess LV size and estimate mass with the cube formula. In a subgroup of patients from the SOLVD Trials with echocardiograms of excellent quality, we observed an excellent correlation between LV mass derived in this manner with LV mass determined by the area-length method (28). However, regardless of the equation used, two-dimensional echocardiography is limited in its accuracy for measuring LV mass since all methods assume a uniform thickness of the LV, which is not the case in areas of chronic infarction or with geometric deformity of the LV cavity (30,56). Despite its limitations, the method used in this study was applied in a blinded fashion to a large sample of patients and thus the association between increased LV mass and CV events is likely to be real.

CONCLUSIONS

In patients with LV dysfunction enrolled in the SOLVD Registry and Trials, echocardiographic measurements of LV mass, LA size and EF were significantly associated with mortality and rate of CV hospitalizations. A protective effect of EF was noted in patients with LV mass ≥ 298 g, whereas in the group with smaller mass, mortality was low irrespective of EF. These findings suggest that in patients with LV dysfunction (with or without clinical heart failure), pathologic hypertrophy is associated with higher rates of adverse CV events and support the development and use of drugs that inhibit hypertrophy or alter its characteristics. The echocardiographic measurements obtained in this study are all within the capacity of any clinical laboratory and thus are applicable to any patient presenting with LV dysfunction.

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