ISSN 1936-878X/08/$34.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2008.05.012

Prognostic Implications of Left Ventricular Mass and Geometry Following Myocardial Infarction

The VALIANT (VALsartan In Acute myocardial iNfarcTion) Echocardiographic Study

Anil Verma, MD,* Alessandra Meris, MD,* Hicham Skali, MD,* Jalal K. Ghali, MD,† J. Malcolm O. Arnold, MD,‡ Mikhail Bourgoun, MD,* Eric J. Velazquez, MD,§ John J. V. McMurray, MD,‖ Lars Kober, MD,¶ Marc A. Pfeffer, MD, PHD,* Robert M. Califf, MD,# Scott D. Solomon, MD*

Boston, Massachusetts; Detroit, Michigan; London, Ontario, Canada; Durham, North Carolina; Glasgow, Scotland; and Copenhagen, Denmark

OBJECTIVES This study sought to understand prognostic implications of increased baseline left ventricular (LV) mass and geometric patterns in a high risk acute myocardial infarction.

BACKGROUND The LV hypertrophy and alterations in LV geometry are associated with an increased risk of adverse cardiovascular events.

METHODS Quantitative echocardiographic analyses were performed at baseline in 603 patients from the VALIANT (VALsartan In Acute myocardial iNfarcTion) echocardiographic study. The left ventricular mass index (LVMi) and relative wall thickness (RWT) were calculated. Patients were classified into 4 mutually exclusive groups based on RWT and LVMi as follows: normal geometry (normal LVMi and normal RWT), concentric remodeling (normal LVMi and increased RWT), eccentric hypertrophy (increased LVMi and normal RWT), and concentric hypertrophy (increased LVMi and increased RWT). Cox proportional hazards models were used to evaluate the relationships among LVMi, RWT, LV geometry, and clinical outcomes.

RESULTS Mean LVMi and RWT were 98.8 $\pm$ 28.4 g/m^2 and 0.38 $\pm$ 0.08. The risk of death or the composite end point of death from cardiovascular causes, reinfarction, heart failure, stroke, or resuscitation after cardiac arrest was lowest for patients with normal geometry, and increased with concentric remodeling (hazard ratio [HR]: 3.0; 95% confidence interval [CI]: 1.9 to 4.9), eccentric hypertrophy (HR: 3.1; 95% CI: 1.9 to 4.8), and concentric hypertrophy (HR: 5.4; 95% CI: 3.4 to 8.5), after adjusting for baseline covariates. Also, baseline LVMi and RWT were associated with increased mortality and nonfatal cardiovascular outcomes (HR: 1.22 per 10 g/m^2 increase in LVMi; 95% CI: 1.20 to 1.30; $p < 0.001$) (HR: 1.60 per 0.1-U increase in RWT; 95% CI: 1.30 to 1.90; $p < 0.001$). Increased risk associated with RWT was independent of LVMi.

CONCLUSIONS Increased baseline LV mass and abnormal LV geometry portend an increased risk for morbidity and mortality following high-risk myocardial infarction. Concentric LV hypertrophy carries the greatest risk of adverse cardiovascular events including death. Higher RWT was associated with an increased risk of cardiovascular complications after high-risk myocardial infarction. (J Am Coll Cardiol Img 2008;1:582–91) © 2008 by the American College of Cardiology Foundation

From *Brigham and Women's Hospital, Boston, Massachusetts; †Wayne State University, Detroit, Michigan; ‡University Hospital, London Health Sciences Centre, London, Ontario, Canada; §Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; ‖Western Infirmary, Glasgow, Scotland; ¶Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; and #Duke Translational Medicine Institute, Duke University Medical Center, Durham, North Carolina. Drs. Ghali, Arnold, McMurray, Pfeffer, Califf, and Solomon have received research funding from Novartis Pharmaceuticals. Dr. Velazquez has served as a consultant for or has received honorariums from Novartis Pharmaceuticals.

Manuscript received February 26, 2008; revised manuscript received May 1, 2008, accepted May 28, 2008.

Increased left ventricular (LV) mass and LV hypertrophy are independent predictors of cardiovascular morbidity and mortality irrespective of etiology (1–3). The risk of death or nonfatal complications is increased 2- to 4-fold in the presence of LV hypertrophy in patients with hypertension, coronary artery disease, or uncomplicated myocardial infarction (MI) (1). The prevalence of LV hypertrophy is closely associated with advancing age and severity of hypertension, ranging from 6% in persons <30 years of age to 43% in those >69 years (4) and from 20% to 50% in populations with mild-to-severe hypertension (1,4).

See page 592

The LV adaptation to arterial hypertension can result in different LV geometric responses, and further classification of hypertensive patients by their ventricular geometry may provide incremental value beyond ventricular mass for further cardiovascular risk stratification (5–9). Hypertensive patients with concentric LV hypertrophy have the highest incidence of cardiovascular events including death (9).

Despite the association of LV hypertrophy with prognosis in patients with hypertension, uncertainty still persists with regard to the independent prognostic value of LV geometric patterns (10,11). In addition, the independent contribution of LV geometry, relative wall thickness (RWT), and LV mass to prognosis have not been well characterized in a high-risk post-MI population. To explore the prognostic value of LV mass and geometry in high-risk MI, we studied patients enrolled in the echocardiographic substudy of the VALIANT (VALsartan In Acute myocardial iNfarcTion) trial.

METHODS

Study design and patients. The VALIANT trial was designed to test the hypothesis that the angiotensin receptor blocker valsartan, either alone or in combination with the proven angiotensin-converting enzyme inhibitor captopril, would be superior or not inferior to a proven dose of captopril in reducing cardiovascular morbidity or mortality after MI (12). A total of 14,703 patients with heart failure, LV systolic dysfunction (ejection fraction [EF] ≤35% on echocardiography or ≤40% on contrast angiography), or both were enrolled within 12 h to 10 days after acute MI (12). The median duration of follow-up was 24.7 months. Patients were randomly assigned in a 1:1:1 ratio to treatment with either captopril (target dose 50 mg 3 times daily), valsartan (target dose 160 mg twice daily), or the combination of valsartan and captopril (target doses of 50 mg 3 times daily and 80 mg twice daily) (12). Clinical sites participating in the main VALIANT study were invited to enroll patients in the VALIANT echocardiographic study, and patients enrolled in the VALIANT trial at these sites were eligible for inclusion in the VALIANT echocardiographic study. Entry criteria were identical to those for the main VALIANT study. Patients were included regardless of infarct location or ST-segment characteristics. A total of 610 patients from the total VALIANT population (N = 14,703) were enrolled in the echocardiographic substudy and underwent baseline 2-dimensional echocardiography at a mean time of 5.0 ± 2.5 days following the index MI (13). A total of 94 clinical sites in 13 countries participated in the VALIANT echocardiographic substudy. The details of patient characteristics have been previously described (13) and the inclusion and exclusion criteria were identical to those of the main VALIANT study. The demographics of the echocardiographic participants were similar to the overall study group (13).

ABBREVIATIONS AND ACRONYMS

EF = ejection fraction
LA = left atrial
LV = left ventricular
LVMi = left ventricular mass index
MI = myocardial infarction
RV = right ventricular
RWT = relative wall thickness

Echocardiographic analysis. Echocardiograms from videotape were digitized and analyses were performed on an offline analysis workstation in a core laboratory. Of the initial cohort, 7 patients were excluded before analysis because of insufficient echocardiographic images and 603 patients were available at baseline for quantitative echocardiographic analysis.

The LV endocardial borders were manually traced at end diastole and end systole at the mitral and papillary short axis level and apical 4- and 2-chamber views from 3 separate cardiac cycles by a single experienced observer. The LV volumes were derived according to the modified biplane Simpson's rule in the apical 4- and 2-chamber views and indexed to body surface area. The EF was calculated in the standard fashion from LV end-diastolic and -systolic volume. Right ventricular (RV) function expressed as the RV fractional area change was assessed quantitatively as the percentage of change in cavity area from end diastole to end systole. Left atrial (LA) volume was assessed by the biplane area-length method from apical 4- and 2-chamber views at end systole from the frame preceding mitral valve opening. The LA volume index was calculated

JACC: CARDIOVASCULAR IMAGING, VOL. 1, NO. 5, 2008
SEPTEMBER 2008:582–91

as LA volume/body surface area (ml/m^2). Mitral flow velocity was assessed by pulsed wave Doppler study from the apical 4-chambers view by positioning the sample volume at the tip of the mitral leaflets.

The LV mass was calculated from LV linear dimensions using the following formula (14,15):

$$\text{LV mass (g)} = 0.80 \times \{1.04 \times [(\text{septal wall thickness in diastole} + \text{LV internal diastolic diameter} + \text{posterior wall thickness in diastole})^3 - (\text{LV internal diastolic diameter})^3]\} + 0.6\ \text{g}$$

The LV mass was indexed to body surface area and LV hypertrophy was considered present when echocardiographically derived LV mass index (LVMi) was >115 g/m^2 for men and >95 g/m^2 for women (15). The RWT was calculated as 2 × (posterior wall thickness in diastole) / (LV internal diastolic diameter). Increased RWT was present when this ratio was >0.42 (15). The sample was divided into 4 mutually exclusive groups on the basis of LV geometry: concentric hypertrophy (LV hypertrophy and increased RWT), eccentric hypertrophy (LV hypertrophy and normal RWT), concentric remodeling (normal LVMi and increased RWT), and normal geometry (normal LVMi and normal RWT) (15).

Statistical analysis. Echocardiographic measurements were made in triplicate by a single experienced observer blinded to outcome data using quantitative analysis software. Reproducibility was assessed after studies were randomly chosen and reanalyzed with the observer blinded to the initial results. The coefficient of variability based on the intraobserver reproducibility assessment was 8.3%, 2.7%, 3.0%, and 5.3% for LV volumes, LV mass, LA volume, and RV fractional area change assessment, respectively, and the coefficient of variability based on the interobserver reproducibility assessment for LV mass was 3.0%.

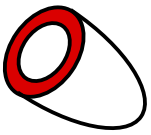
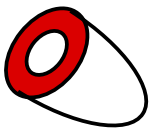
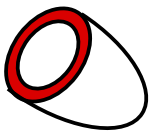
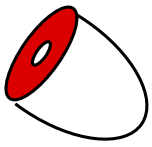
Continuous data were expressed as mean ± standard deviation. Among the 4 categories of LV geometrical patterns, categorical variables were analyzed with the chi-square test. Continuous variables were analyzed with analysis of variance (Scheffe post-hoc) test.

Defined time-dependent clinical outcomes included the primary end point of all-cause mortality and the composite cardiovascular end point and its individual components of cardiovascular death, recurrent MI, heart failure, stroke, and resuscitated sudden death (12). Clinical outcomes were adjudicated by an independent Clinical Endpoints Committee (12). To determine the independent prognostic value of baseline LVMi, LV mass to end-diastolic volume ratio, and RWT and LV geometric patterns, we used a multivariable Cox proportional hazards model. The adjustment model included predictors of mortality identified from the overall VALIANT study: age (in years), primary percutaneous transluminal coronary angioplasty, atrial fibrillation complicating MI, history of diabetes, history of hypertension, prior MI, Killip class, history of congestive heart failure, new left bundle branch block, history of angina, LVEF, estimated glomerular filtration rate, and a history of chronic obstructive pulmonary disease. Both stepwise elimination and backward selection were used to select the most parsimonious set of predictive variables. In addition, we also included in our adjusted model baseline measures of LV end-diastolic volume, LA volume index, and infarct length. To assess the independent prognostic value of RWT above that of LV mass, multivariable analysis was performed after adjustment for LV mass as a continuous variable and the candidate variables listed above in a Cox proportional hazards model. Kaplan-Meier estimates for all-cause mortality and the cardiovascular composite end point were determined according to LV geometric patterns and were presented as event curves. All p values were 2-sided; $p < 0.05$ was used to determine statistical significance. Statistical analyses were performed using STATA software, version 8.2 (Stata Corp., College Station, Texas).

RESULTS

Baseline characteristics. The baseline LVMi and RWT for the 603 patients in the VALIANT echocardiographic cohort were normally distributed. The mean LVMi (g/m^2) was 98.8 ± 28.4 (range: 40.1 to 203.7) and the mean RWT was 0.38 ± 0.08 (range: 0.19 to 0.70). In the VALIANT echocardiographic cohort concentric hypertrophy was present in 76 (12.6%) patients, eccentric hypertrophy in 112 (18.6%) patients, and concentric remodeling was present in 110 (18.2%) patients at baseline. Increased LVMi was associated with higher rates of prior MI, history of hypertension, diabetes mellitus, prior congestive heart failure, and stroke when compared with patients with normal geometry. Moreover, patients with LV hypertrophy were older, more likely to be female, had lower baseline estimated glomerular filtration rate, and

Table 1. Baseline Characteristics Stratified by LV Geometric Patterns

Characteristics	Normal Geometry (n = 305)	Concentric Remodeling (n = 110)	Eccentric Hypertrophy (n = 112)	Concentric Hypertrophy (n = 76)	p Value
					
Age, yrs	60.8 ± 12.5	64.5 ± 11.8	66.9 ± 11.5*	70.2 ± 9.8*	<0.001
White, %	97	93	93	92	0.13
Female, %	23	28	44	55	<0.001
Medical history, %					
MI	26	21	38	30	0.02
Hypertension	47	60	64	76	<0.001
Diabetes mellitus	16	30	29	30	0.001
HF	12	9	28	24	<0.001
Stroke	3	12	11	12	0.002
Site of qualifying MI, %					
Anterior	59	60	60	59	0.98
Inferior	35	37	33	24	0.23
Type of qualifying MI, %					
Q-wave	69	69	63	53	0.08
Non–Q-wave	30	30	36	46	0.053
BMI, kg/m^2	28.3 ± 5.2	27.9 ± 5.4	27.2 ± 4.4	27.8 ± 5.6	0.32
eGFR, ml/min/1.73 m^2	75.6 ± 20.2	73.7 ± 19.2	64.1 ± 18.1*	61.7 ± 21.1*	<0.0001
Killip class >I, %	69	78	77	80.3	0.07
Heart rate, beats/min	76.0 ± 12.9	75.0 ± 11.4	76.0 ± 12.2	75.0 ± 11.8	0.84
Blood pressure, mm Hg					
Systolic	120.2 ± 14.7	120.2 ± 13.7	121.1 ± 15.0	125.5 ± 16.4	0.047
Diastolic	70.3 ± 10.4	70.3 ± 10.4	71.9 ± 11.6	69.6 ± 12.0	0.49
Medications at randomization, %					
Beta-blocker	76	76	69	67	0.22
Aspirin	93	90	93	92	0.81
Calcium channel blocker	6	7	12	4	0.15
Statin	39	38	27	38	0.11
Study medications, %					
Captopril	34	34	33	34	
Valsartan	31	35	38	33	0.86
Captopril/valsartan	35	31	29	33	
Thrombolytic therapy,† %	43	44	29	29	0.01
PTCA,† %	19	30	5	12	<0.001
CABG,† %	2	2.7	1	0	0.45

Values are presented as mean ± standard deviation, unless otherwise indicated. *p < 0.001 versus patients with normal LV geometry. †The procedure took place in the interval after the MI and before the patients were randomly assigned to a treatment group.
BMI = body mass index; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; HF = heart failure; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

lower rates of primary percutaneous transluminal coronary angioplasty (Table 1). No differences were observed among groups with regard to treatment with aspirin, calcium channel blocker, statins, and beta-blockers.

The LV volumes were significantly increased and LVEF and RV function were significantly reduced in patients with eccentric hypertrophy (Table 2). The LA volume index increased significantly with increasing LV mass and was significantly higher in patients with eccentric and concentric hypertrophy. The LV mass to end-diastolic volume ratio and average LV wall thickness increased from normal geometry to concentric hypertrophy. Infarct seg-

Table 2. Baseline Echocardiographic Characteristics Stratified by LV Geometric Patterns

Echocardiographic Characteristics	Normal Geometry (n = 305)	Concentric Remodeling (n = 110)	Eccentric Hypertrophy (n = 112)	Concentric Hypertrophy (n = 76)	p Value
EDVi, ml/m^2	59.3 ± 13.9	55.2 ± 10.6	71.2 ± 18.1*	62.6 ± 15.0	<0.001
ESVi, ml/m^2	36.2 ± 10.7	32.7 ± 7.1†	45.0 ± 14.1*	38.9 ± 11.8	<0.001
LVEF, %	39.5 ± 5.5	40.8 ± 4.7	37.4 ± 6.4†	38.3 ± 6.0	<0.001
RWT	0.35 ± 0.04	0.48 ± 0.05*	0.35 ± 0.05	0.48 ± 0.05*	<0.0001
Average LV wall thickness, cm	0.9 ± 0.09	1.0 ± 0.1*	1.0 ± 0.1*	1.2 ± 0.09*	<0.0001
LV mass, g	168.1 ± 39.2	166.3 ± 35.4	246.5 ± 55.4*	246.3 ± 54.5*	<0.0001
LVMi, g/m^2	84.2 ± 16.9	85.5 ± 14.8	129.1 ± 23.4*	132.4 ± 23.9*	<0.0001
LV mass/EDV	1.5 ± 0.3	1.6 ± 0.3†	1.9 ± 0.4*	2.2 ± 0.5*	<0.0001
LAVi, ml/m^2	22.1 ± 7.0	21.5 ± 5.9	29.5 ± 9.7*	28.3 ± 8.2*	<0.0001
RVFAC, %	42.5 ± 4.0	42.1 ± 4.0	40.4 ± 5.3‡	41.5 ± 3.9	<0.001
Infarct length, cm	7.3 ± 2.2	6.4 ± 1.8†	8.1 ± 2.9†	7.0 ± 2.2	<0.001
Doppler					
E/A ratio	1.4 ± 0.7	1.1 ± 0.6†	1.5 ± 0.8	1.2 ± 0.7	0.003
DT, ms	156.2 ± 38.6	161.6 ± 37.4	154.3 ± 40.9	158.6 ± 39.2	0.60
MR grade, %					
No	52.5	62	22.6	37.1	
Mild	40	26.2	54.8	43.5	<0.001
Moderate or severe	7.5	12	22.6	19.4	

Values are presented as mean ± standard deviation, unless otherwise indicated. *p < 0.001 versus patients with normal LV geometry. †p < 0.05 versus patients with normal LV geometry. ‡p < 0.01 versus patients with normal LV geometry.
A = peak late diastolic velocity; DT = deceleration time; E = peak early diastolic velocity; EDV = end-diastolic volume; EDVi = end-diastolic volume index; ESVi = end-systolic volume index; LAVi = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass index; MR = mitral regurgitation; RVFAC = right ventricular fractional area change; RWT = relative wall thickness.

ment length was lower in patients with LV concentric remodeling and higher in patients with eccentric hypertrophy. Patients with concentric remodeling had significantly lower LV end-systolic volume and transmitral E/A ratio (E = peak early diastolic velocity; A = peak late diastolic velocity). There were no differences at baseline across the 4 groups with regard to deceleration time.

Relationship between baseline LV mass, geometry, and clinical outcomes. Of the 603 patients in the VALIANT echocardiographic cohort, 103 (17%) patients died, 162 (27%) experienced a composite of death or development of heart failure, and 187 (31%) experienced composite cardiovascular outcomes generated by adding important nonfatal cardiovascular events (recurrent MI, hospitalization for heart failure, resuscitation from cardiac arrest, and stroke) to death from cardiovascular causes after randomization. There were no significant differences in the number of events by treatment group in this cohort (13). When analyzed as a continuous variable, baseline LVMi was a potent univariate predictor of all-cause mortality (hazard ratio [HR]: 1.28; 95% confidence interval [CI]: 1.2 to 1.3), cardiovascular death (HR: 1.30; 95% CI: 1.2 to 1.36), death or heart failure hospitalization (HR: 1.30; 95% CI: 1.30 to 1.40), and cardiovascular composite (HR: 1.28; 95% CI: 1.23 to 1.30), all p < 0.001. In a multivariable adjusted model, each 10 g/m^2 increase in LVMi and each 0.1 unit increase in LV mass to end-diastolic volume ratio were independently associated with increased risk for all-cause mortality, cardiovascular death, and death or heart failure hospitalization (each p < 0.001) (Figs. 1A and 1B).

After adjusting for LV mass in addition to other covariates in the model, each 0.1 unit (10%) increase in RWT was independently associated with increased risk for the previously defined end points (each p < 0.001) (Fig. 1C). Both concentric and eccentric hypertrophy were significantly associated with increased risk of adverse outcome, with the highest mortality rates observed for patients with concentric hypertrophy (Figs. 2A, 2B, and 3). There was a wide spectrum of risk across the categories of LV geometrical patterns, with early divergence of the Kaplan-Meier curves for the composite end point (Fig. 2B). In a multivariable adjusted model, patients with concentric remodeling or with eccentric or concentric LV hypertrophy had worse outcomes than the patients with normal LV geometry. In particular, patients in the concen-

tric LV hypertrophy group had the highest rate of fatal and nonfatal events (Table 3).

DISCUSSION

In this high-risk cohort of patients with LV systolic dysfunction, heart failure, or both following MI, echocardiographically determined LV mass, RWT, and LV geometry are significant independent predictors of increased cardiovascular morbidity and mortality. Concentric hypertrophy carried the greatest cardiovascular risk, followed by eccentric hypertrophy, and then concentric remodeling. Our results confirm the importance of LV mass and geometry following MI and argue for their routine assessment in high-risk patients with LV systolic dysfunction, heart failure, or both following MI.

Increased LV mass results from increased hemodynamic load and is an independent predictor of subsequent cardiovascular morbidity and all-cause mortality (1,2). Volume and pressure overloads, or a combination of both, cause different LV geometric adaptations including concentric ventricular remodeling, eccentric hypertrophy, and concentric hypertrophy. Geometric patterns identify distinctive pathophysiologic patterns and may be added to LV mass for risk stratification (5–11). Even though cardiovascular risk associated with LV mass is well established in patients with hypertension, the prognostic implication of LV geometry and RWT has not been clearly demonstrated in a high-risk post-MI population (16,17). Our analysis of the VALIANT echocardiographic cohort provides comprehensive information concerning significant cardiovascular risk associated with LV mass and RWT in a population of high-risk post-MI individuals. An important finding of this study shows that concentric LV hypertrophy carries the highest risk of adverse events, even after adjusting for well-established risk factors such as LVEF, hypertension, and estimated glomerular filtration rate, and adds incremental prognostic value over the other known predictors of outcome. Several factors including hypertension and activation of the renin-angiotensin-aldosterone system induce LV hypertrophy and progression of atherosclerosis. Pathologic increase in LV mass beyond the need to compensate for increased cardiac load is found when LV geometry is concentric (18,19) and is associated with increased collagen deposition in the extracellular matrix and around the intramyocardial coronary arteries with medial thickening of the

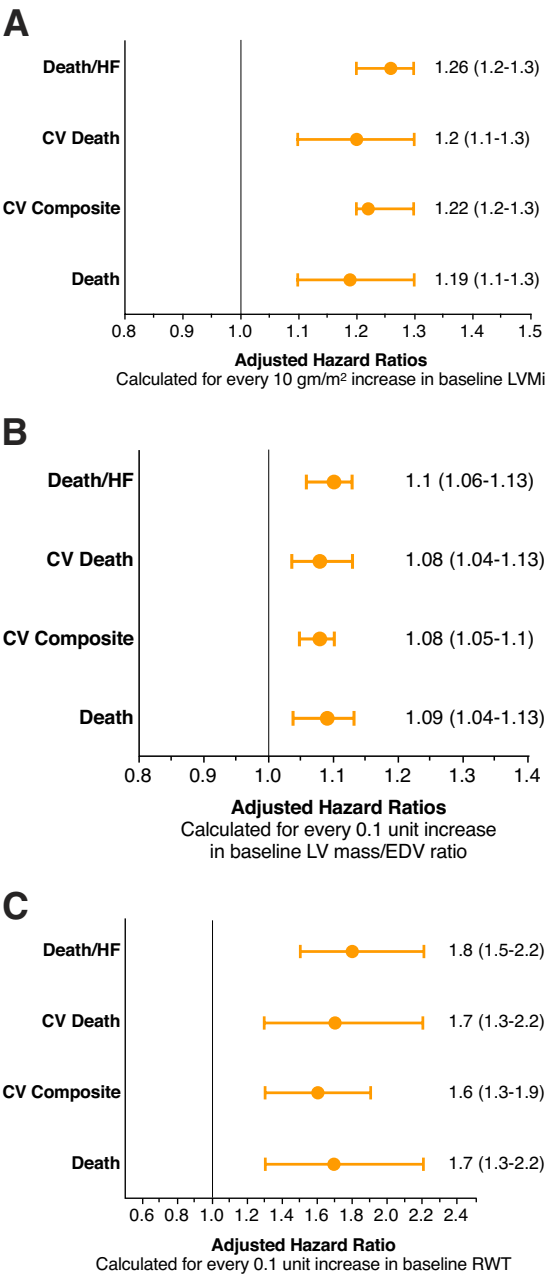


Figure 1. Adjusted Hazard Ratios (95% Confidence Intervals) for Adverse Outcomes

Multivariable Cox proportional hazards models were used to determine the independent prognostic value of left ventricular mass index (LVMi), LV mass/end-diastolic volume (EDV), and relative wall thickness (RWT). The models were adjusted for age (years), primary percutaneous transluminal coronary angioplasty, atrial fibrillation complicating myocardial infarction (MI), history of diabetes, history of hypertension, prior MI, Killip class, history of congestive heart failure (HF), new left bundle branch block, history of angina, LV ejection fraction, estimated glomerular filtration rate, and a history of chronic obstructive pulmonary disease. Each 10 g/m^2 increase in LVMi **(A)**, 0.1-U (10%) increase in LV mass to end-diastolic volume ratio **(B)**, and 0.1-U (10%) increase in RWT **(C)** were independently associated with increased risk for death, cardiovascular (CV) death, and death or heart failure hospitalization (each $p < 0.001$). Echocardiographically determined LV mass and RWT are significant independent predictors of increased cardiovascular morbidity and mortality in high-risk post-MI patients warranting their routine assessment.

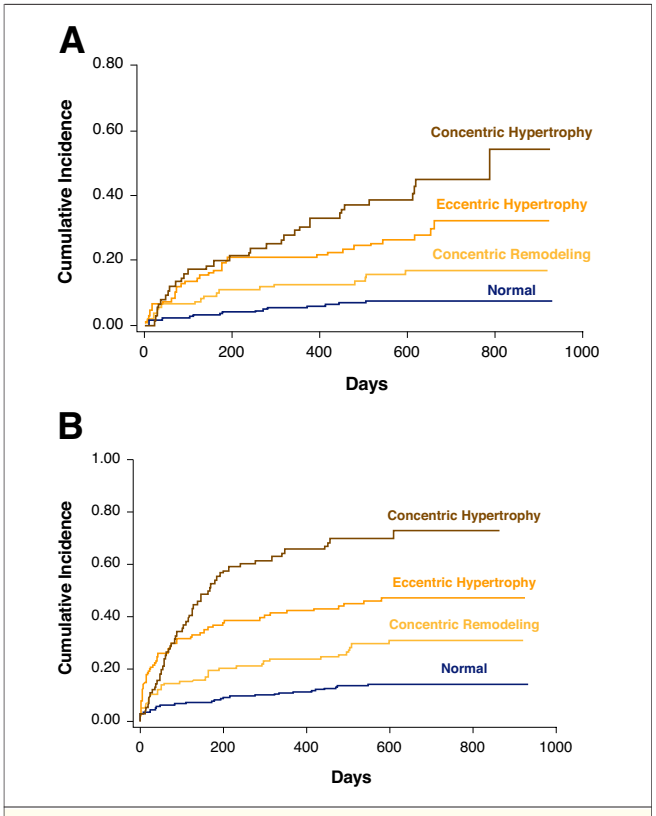


Figure 2. Unadjusted Kaplan-Meier Curves Stratified by LV Geometric Patterns

Kaplan-Meier estimates for clinical outcomes for all-cause mortality **(A)** and the CV composite end point (CV death, recurrent MI, heart failure, stroke, and resuscitated sudden death) **(B)** were determined for LV geometric patterns and were presented as event curves. There was a wide spectrum of risk across the categories of LV geometrical patterns, with early divergence of the Kaplan-Meier curves for mortality and composite end point, particularly between patients with normal geometry and those with concentric hypertrophy. Concentric hypertrophy carried the greatest CV risk, followed by eccentric hypertrophy, and then concentric remodeling, underscoring the importance of increased LV mass and RWT as important risk predictors following high risk MI. Abbreviations as in Figure 1.

intramyocardial coronary arteries and disturbances of myocardial blood flow (20,21). Although myocardial afterload is the prime stimulus that promotes the cascade of biological events leading to ventricular hypertrophy to reduce wall stress, concentric LV hypertrophy is eventually associated with increased cardiovascular risk (22). Left ventricular hypertrophy secondary to hypertension, infarction, obesity, or valvular heart disease leads to shifts toward glycolytic metabolism, disorganization of the sarcomere, alterations in calcium handling, changes in contractility, loss of myocytes with fibrotic replacement, systolic and diastolic dysfunction, and electrical remodeling resulting in alterations in myocardial metabolism, structure, and function with increasing severity of LV hypertrophy (23). These structural, metabolic, and functional alterations possibly associate LV hypertrophy with adverse cardiovascular risk and heart failure development.

In addition, the present study demonstrates that increasing baseline LV mass is also associated with increasing incidence of resuscitated sudden death. Left ventricular hypertrophy has long been known to be associated with sudden cardiac death and increased risk of ventricular arrhythmias (24–26), and it may be related to prolongation of action potential, increased dispersion of refractoriness, and lowering of the ventricular fibrillation threshold (24). Of note, we also observed increasing incidence of stroke associated with abnormal LV geometry, both concentric hypertrophy and concentric remodeling were associated with an increased risk of stroke. Left ventricular hypertrophy has long been associated with risk of ischemic stroke (27–29). Recently, Di Tullio et al. (30) reported association of abnormal LV geometry and RWT with stroke risk in a population-based case control study. Our study extends those findings to a high-risk post-MI population.

It is also noteworthy that despite being associated with similar left and right systolic function, concentric LV remodeling was also associated with poor prognosis compared with patients with normal LV geometry in this high-risk post-MI population. In our observations, concentric remodeling was associated with a 3-fold increase in fatal and nonfatal cardiovascular events following a high-risk MI. The association of concentric remodeling with increased risk is supported by Verdecchia et al. (11), who demonstrated that in the presence of normal LV mass, concentric LV remodeling reflecting a nearly pure pressure overload was associated with worse outcome. These observations suggest that both chamber dilation in the form of eccentric hypertrophy and increased RWT in the form of concentric LV hypertrophy and concentric remodeling are independently related to adverse cardiovascular events.

Study limitations. Although our findings are strengthened by involving a larger cohort of randomized subjects receiving contemporary post-MI therapy and the nearly complete follow-up associated with this trial, some limitations should be noted. First, 2-dimensional echocardiography is limited in its accuracy for measuring LV mass because all methods assume a uniform LV thickness, which is not the case in areas of chronic MI or with geometric deformity of the LV cavity. However, the M-mode methods based on the simple

cube-function formula have repeatedly been shown to give reasonably accurate LV mass measurements in necropsy validation studies. In addition, the simplicity and ease of this technique has made it possible for application to large-scale clinical and epidemiological studies and to relate LV mass and its change over time to clinical outcomes (31). On the other hand, the 2-dimensional methods for measuring LV mass that are based on the area-length formula and the truncated ellipsoid model might be more accurate, but because this is also expertise-dependent and time-consuming, its applicability is limited to a large-scale study. None of the methods described to measure LV mass are validated in the post-MI setting. However, despite its limitations, we do not expect the degree of wall thickness to change abruptly after an acute MI and the method used in this study was applied in a blinded fashion to a large sample of patients; therefore, the association between increased LV mass, abnormal LV geometry, and cardiovascular risk is likely to be real. In addition, first, baseline echocardiograms in the VALIANT echocardiographic study were obtained during the early post-MI period, thus precluding any significant LV enlargement and were devoid of any LV aneurysm. Second, we did not assess for serial changes in blood pressure and in LV mass and its geometrical patterns and potential influence on cardiovascular risk. Finally, our results are predominantly applicable to the high-risk cohort of VALIANT, which limits generalization to the broader group of post-MI patients.

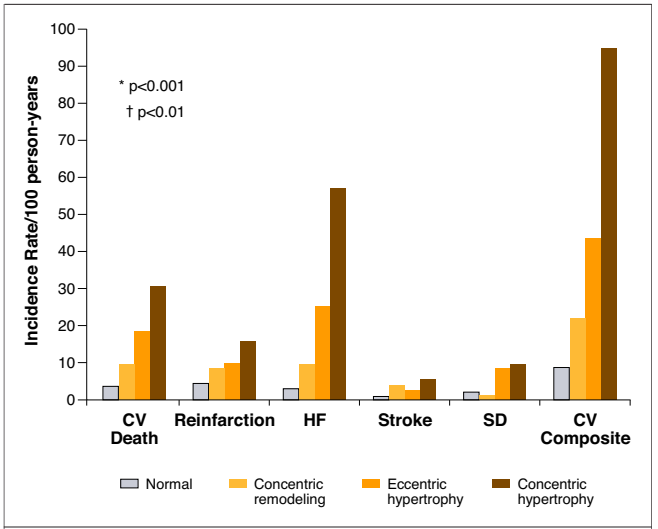


Figure 3. Crude Incidence Rates per 100-Person Years

Crude incidence rates per 100 person-years were calculated for the defined time-dependent clinical CV outcomes and depicted as bar graph, for LV geometrical patterns. Concentric hypertrophy carried the greatest incidence rate for adverse CV outcomes including CV mortality, recurrent MI, heart failure, stroke and sudden cardiac death. Even concentric remodeling was associated with poor prognosis compared with patients with normal LV geometry. Concentric hypertrophy had higher incidence rates for CV mortality and heart failure development and also recurrent MI, stroke, and sudden cardiac death. Routine echocardiographic assessment of LV mass and its geometry following a high-risk MI is important. SD = sudden death; other abbreviations as in Figure 1.

CONCLUSIONS

Echocardiographically determined LV mass and its geometrical patterns are important independent predictors of increased morbidity and mortality following high-risk MI. Concentric LV hypertro-

Table 3. HR (Chi-Square: 95% CI) Stratified by LV Geometric Patterns Group

Outcome	Normal Geometry	Concentric Remodeling	Eccentric Hypertrophy	Concentric Hypertrophy
Death				
Unadjusted HR	Ref	2.7 (7.1: 1.4–5.0)*	5.0 (32.1: 2.9–8.8)†	8.0 (4.6–13.9)†
Adjusted HR‡	Ref	3.5 (10.7: 1.6–7.3)*	3.4 (7.5: 1.3–5.1)*	6.1 (26.7: 3.1–12.1)†
CV death				
Unadjusted HR	Ref	2.6 (7.9: 1.3–5.1)*	5.0 (28.8: 2.8–9.0)†	7.9 (48.3: 4.4–14.3)†
Adjusted HR‡	Ref	3.4 (8.9: 1.5–7.5)*	2.6 (6.4: 1.2–5.3)*	6.5 (28.8: 3.1–13.6)†
Death or HF				
Unadjusted HR	Ref	2.9 (16.1: 1.7–4.9)†	6.3 (61.8: 4.0–9.9)†	11.7 (113.0: 7.4–18.5)†
Adjusted HR‡	Ref	4.2 (21.4: 2.1–6.3)†	3.5 (19.6: 2.6–7.0)†	8.9 (68.5: 5.4–14.9)†
CV composite				
Unadjusted HR	Ref	2.4 (14.1: 1.5–3.8)†	4.5 (52.2: 3.0–6.7)†	7.7 (96.4: 5.1–11.6)†
Adjusted HR‡	Ref	3.0 (19.9: 1.9–4.9)†	3.1 (12.0: 1.9–4.8)*	5.4 (51.7: 3.4–8.5)†

Values presented as hazard ratio (HR) (chi-square: 95% confidence interval [CI]). *$p < 0.01$. †$p < 0.001$. ‡Adjusted for age (in years), primary PTCA, atrial fibrillation complicating MI, history of diabetes, history of hypertension, prior MI, Killip class, history of congestive HF, new left bundle branch block, history of angina, LVEF, LVEDV, infarct length, LAVi, eGFR, and a history of chronic obstructive pulmonary disease.
CV = cardiovascular death; LVEDV = left ventricular end-diastolic volume; Ref = referent value; other abbreviations as in Tables 1 and 2.

JACC: CARDIOVASCULAR IMAGING, VOL. 1, NO. 5, 2008
SEPTEMBER 2008:582–91

phy carries the greatest risk of adverse cardiovascular events including death. Even the presence of concentric geometry in the absence of increased LV mass is associated with an increased risk of subsequent cardiovascular complications, underscoring the importance of increased baseline LV mass and RWT as important risk predictors in patients following high-risk MI. Our findings demonstrate that routine assessment of LV mass and RWT can be used to better risk-stratify patients following high-risk MI with LV systolic dysfunction, heart failure, or both, and raise the question of whether specific therapies can be developed to improve prognosis in these high-risk patients.

Reprint requests and correspondence: Dr. Scott D. Solomon, Associate Professor of Medicine, Director of Noninvasive Cardiology, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. *E-mail: ssolomon@rics.bwh.harvard.edu.*

REFERENCES

1. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J 2001; 141:334–41.
2. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.
3. Ghali JK, Kadakia S, Cooper RS, Liao YL. Impact of left ventricular hypertrophy on ventricular arrhythmias in the absence of coronary artery disease. J Am Coll Cardiol 1991;17: 1277–82.
4. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol 1987; 59:956–60.
5. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 1992;19:1550–8.
6. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. Hypertension 1994;23:600–6.
7. Muiesan ML, Salvetti M, Monteduro C, et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension 2004;43:731–8.
8. Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. Am J Cardiol 2006; 97:959–63.
9. Koren M J, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–52.
10. Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. J Am Coll Cardiol 1995;25: 879–84.
11. Verdecchia P, Schillaci G, Borgioni C, et al. Adverse prognostic significance of concentric remodelling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol 1995;25:871–8.
12. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906.
13. Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation 2005; 111:3411–9.
14. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
15. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
16. Bolognese L, Dellavesa P, Rossi L, Sarasso G, Bongo AS, Scianaro MC. Prognostic value of left ventricular mass in uncomplicated acute myocardial infarction and 1-vessel coronary artery disease. Am J Cardiol 1994;73: 1–5.
17. Boden WE, Kleiger RE, Schechtman KB, Capone RJ, Schwartz DJ, Gibson RS. Clinical significance and prognostic importance of left ventricular hypertrophy in non–Q-wave acute myocardial infarction. Am J Cardiol 1988; 62:1000–4.
18. Mureddu GF, Pasanisi F, Palmieri V, Celentano A, Contaldo F, de Simone G. Appropriate or inappropriate left ventricular mass in the presence or absence of prognostically adverse left ventricular hypertrophy. J Hypertens 2001;19:1113–9.
19. de Simone G, Verdecchia P, Pede S, Gorini M, Maggioni AP. Prognosis of inappropriate left ventricular mass in hypertension: the MAVI Study. Hypertension 2002;40:470–6.
20. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991; 83:1849–65.
21. Weber KT, Janicki JS, Shroff SG, Pick R, Chen RM, Bashey RJ. Collagen remodeling of the pressure-overloaded, hypertrophied nonhuman primate myocardium. Circulation Res 1988;62:757–65.
22. Aurigemma GP, Devereux RB, de Simone G, et al. Myocardial function and geometry in hypertensive subjects with low levels of afterload. Am Heart J 2002;143:546–51.
23. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med 2008;358:1370–80.
24. Kahan T, Bergfeldt L. Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. Heart 2005; 91:250–6.
25. McLenachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. N Engl J Med 1987;317:787–92.
26. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992;117:831–6.
27. Bikkina M, Levy D, Evans JC, et al. Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. JAMA 1994; 272:33–6.

28. Fox ER, Taylor HA Jr., Benjamin EJ, et al. Left ventricular mass indexed to height and prevalent MRI cerebrovascular disease in an African American cohort: the Atherosclerotic Risk in Communities study. Stroke 2005;36: 546–50.
29. Verdecchia P, Angeli F, Gattobigio R, Sardone M, Pede S, Reboldi GP. Regression of left ventricular hypertrophy and prevention of stroke in hypertensive subjects. Am J Hypertens 2006;19:493–9.
30. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S. Left ventricular mass and geometry and the risk of ischemic stroke. Stroke 2003;34: 2380–4.
31. Devereux RB, Pini R, Aurigemma GP, Roman MJ. Measurement of left ventricular mass: methodology and expertise. J Hypertension 1997;15:801–9.

Key Words: left ventricular mass ■ left ventricular geometry ■ myocardial infarction ■ relative wall thickness ■ echocardiography ■ prognosis.

▶ APPENDIX

For an accompanying slide set on the VALIANT study, please see the online version of this article.