

Prognostic Significance of Left Ventricular Mass Change During Treatment of Hypertension

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DESPITE SUBSTANTIAL BENEFITS from lowering blood pressure (BP), conventional treatment does not normalize the risk of major cardiovascular (CV) events in patients with hypertension.¹⁻⁵ Progress has been made in predicting risk of hypertension by evaluating preclinical CV disease.⁶ Left ventricular hypertrophy (LVH), ie, pathologically increased left ventricular mass, independently predicts adverse outcomes in diverse populations,⁷⁻¹² including patients with hypertension.^{7,11} These findings suggest that the level of left ventricular mass and mass reduction during treatment of hypertension may provide independent information about disease progression or control. This hypothesis has been supported by data from some,^{13,14} but not other,^{15,16} electrocardiographic studies. Echocardiographic

See also pp 2343 and 2396 and Patient Page.

Context Increased baseline left ventricular (LV) mass predicts cardiovascular (CV) complications of hypertension, but the relation between lower LV mass and outcome during treatment for hypertension is uncertain.

Objective To determine whether reduction of LV mass during antihypertensive treatment modifies risk of major CV events independent of blood pressure change.

Design, Setting, and Participants Prospective cohort substudy of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) randomized clinical trial, conducted from 1995 to 2001. A total of 941 prospectively identified patients aged 55 to 80 years with essential hypertension and electrocardiographic LV hypertrophy had LV mass measured by echocardiography at enrollment in the LIFE trial and thereafter were followed up annually for a mean (SD) of 4.8 (1.0) years for CV events.

Main Outcome Measures Composite end point of CV death, fatal or nonfatal myocardial infarction, and fatal or nonfatal stroke.

Results The composite end point occurred in 104 patients (11%). The multivariable Cox regression model showed a strong association between lower in-treatment LV mass index and reduced rate of the composite CV end point (hazard ratio [HR], 0.78 per 1-SD (25.3) decrease in LV mass index; 95% confidence interval [CI], 0.65-0.94; $P=.009$) over and above that predicted by reduction in blood pressure. There were parallel associations between lower in-treatment LV mass index and lower CV mortality (HR, 0.62; 95% CI, 0.47-0.82; $P=.001$), stroke (HR, 0.76; 95% CI, 0.60-0.96; $P=.02$), myocardial infarction (HR, 0.85; 95% CI, 0.62-1.17, $P=.33$), and all-cause mortality (HR, 0.72; 95% CI, 0.59-0.88, $P=.002$), independent of systolic blood pressure and assigned treatment. Results were confirmed in analyses adjusting for additional CV risk factors, electrocardiographic changes, or when only considering events after the first year of study treatment.

Conclusion In patients with essential hypertension and baseline electrocardiographic LV hypertrophy, lower LV mass during antihypertensive treatment is associated with lower rates of clinical end points, additional to effects of blood pressure lowering and treatment modality.

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graphic studies¹⁷⁻¹⁹ have supported associations of regression of LVH or persistence of normal left ventricular mass with lower CV event rates. Thus, uncertainty persists concerning the relation between lower left ventricular mass and outcome during treatment for hypertension.

This study was undertaken to determine whether lower in-treatment left ventricular mass, as measured by echocardiography, is associated with reduced rates of major CV events independent of effects of BP, baseline left ventricular mass, and the greater effect of losartan-based vs atenolol-based treatment on left ventricular mass²⁰ in a prospectively planned substudy of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study.²¹

METHODS

Study Design

The LIFE study enrolled patients with hypertension and electrocardiographic LVH in a prospective, double-blind, multicenter, randomized study to determine whether greater reduction in CV events is achieved by losartan-based than atenolol-based treatment.^{22,23} More than 10% of LIFE participants enrolled in a substudy in which echocardiograms were performed at enrollment and annually thereafter^{21,24} with a goal of assessing the association of lower in-treatment echocardiographic left ventricular mass with rates of major CV events. Participants gave written informed consent under protocols approved by all ethics committees concerned. As described elsewhere,²² participants were aged 55 to 80 years; had seated BPs of 160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic, or both, during placebo treatment; had not experienced a myocardial infarction (MI) or stroke within 6 months; and did not require treatment with a β -blocker, angiotensin-converting enzyme inhibitor, or AT₁-receptor antagonist. Patients had LVH by either a product of QRS duration \times Cornell voltage ($R_{aVL} + S_{V3}$, +6 mm in women^{22,25}) greater than 2440 mm \times ms, or Sokolow-Lyon voltage ($S_{V1} + RV_{5/6}$) greater than 38 mm.

Treatment Regimens

Blinded treatment was begun with losartan, 50 mg, or atenolol, 50 mg, and matching double placebo and up-titrated by adding hydrochlorothiazide, 12.5 mg, followed by increasing study medication to 100 mg. If needed to reduce BP to less than 140/90 mm Hg, hydrochlorothiazide was increased to 25 mg and/or calcium channel blockade or other medications were added (excluding β -blockers, angiotensin-converting enzyme inhibitors, or AT₁-receptor antagonists).

Echocardiographic Methods

Sonographers underwent training using a procedure manual adapted from previous multicenter studies^{26,27} and courses that included didactic presentations, practical demonstrations, and hands-on studies of patients.

Echocardiograms were performed between October 1995 and September 2001 using phased-array echocardiographs. Recordings were made by a standardized protocol under which the parasternal window was used to record 10 or more consecutive beats of 2-dimensional and M-mode recordings of left ventricular internal diameter and wall thicknesses just below the mitral leaflet tips in long- and short-axis views.

Echocardiographic Measurements

Correct orientation of imaging planes was verified as described previously.²⁸ Left ventricular internal dimension and wall thicknesses were measured at end-diastole and end-systole by American Society of Echocardiography recommendations^{29,30} using a computerized review station; all measurements were verified (and often corrected) or made primarily by experienced investigators.

End-diastolic left ventricular septal and posterior wall thicknesses and internal dimensions were used to calculate left ventricular mass by a validated formula: left ventricular mass = 1.04×0.8 [(left ventricular wall thicknesses + internal dimension) - (internal dimension)] + 0.6 g. This formula correlates closely with left ven-

tricular mass at autopsy ($r=0.90$, $P<.001$ ³¹) and results in 91% to 98% yields of left ventricular mass measurements in previous studies in diverse populations.^{26,32,33} The resultant left ventricular mass values also showed excellent reproducibility (intraclass $r=0.93$; mean difference, 1.7 g; $P<.001$) without significant regression to the mean between 2 echocardiograms in a previous group of 183 patients with hypertension²⁷ and had excellent agreement ($r=0.94$; $P<.001$; mean difference, 0.9 [SD, 9.5] g) between experienced readers in a separate group of 22 adults.³⁴

End Points

The LIFE study used a composite end point of CV death, MI, or stroke.^{22,35} End points were ascertained by systematic surveillance at regular outpatient visits and investigator contact of patients and verified by an end point committee.^{22,35} The members of the end point committee were blinded to echocardiographic measurements of left ventricular mass. Survival status in patients otherwise lost to follow-up was ascertained using professional patient locators (the US National Death Index and, in Nordic countries, the Central Person Registers).

Statistical Analysis

A sample size of 1000 was chosen for this substudy to have 90% power for a 2-tailed α level of less than .05 to detect a significant association between lower in-treatment left ventricular mass and risk of a clinical end point. While the analysis used a Cox regression model with time-varying covariates, power was calculated by dichotomizing patients into left ventricular mass regressors (with 70% projected to decrease mass from baseline to year 1) and progressors (with no change or at least a minimal mass increase), treated as a 2×2 table. Since 2×2 analyses have less power than the Cox regression analysis, this was a conservative approach.

Data are expressed as mean (SD). Using predefined criteria reflecting the up-

Table 1. Serial Change in Blood Pressure, Heart Rate, and Left Ventricular Geometry During Treatment in the LIFE Trial*

Parameter	Mean (SD)					
	Baseline (n = 960)	12 mo (n = 879)	24 mo (n = 830)	36 mo (n = 785)	48 mo (n = 752)	60 mo (n = 352)
Systolic BP, mm Hg	174 (14)	150 (20)	149 (19)	147 (20)	149 (19)	146 (19)
Diastolic BP, mm Hg	98 (9)	84 (10)	83 (10)	82 (11)	83 (10)	82 (9)
Pulse BP, mm Hg	75 (16)	64 (16)	62 (16)	61 (15)	62 (15)	61 (15)
Heart rate, beats/min	68 (12)	63 (12)	63 (12)	62 (11)	63 (11)	67 (11)
LV mass, g	234 (56)	206 (50)	195 (44)	193 (47)	190 (46)	187 (45)
LV mass index	123 (26)	109 (23)	103 (20)	102 (22)	101 (23)	99 (21)
LVH, No. (%)†	660 (70)	368 (43)	217 (28)	201 (28)	193 (28)	78 (23)

Abbreviations: BP, blood pressure; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension; LV, left ventricular; LVH, left ventricular hypertrophy.

* $P < .001$ for all comparisons vs baseline, except for heart rate at 60 months.

†LVH defined as LV mass index of >116.0 in men and >104.0 in women.

per limit of the 95% confidence interval (CI) in ethnically diverse reference populations³⁴ and predicting an adverse prognosis.^{9,36} LVH was recognized by left ventricular mass index (LVMI), calculated as left ventricular mass in grams divided by body surface area in square meters, greater than 104.0 in women and 116.0 in men. Data management and analyses were primarily performed by the Clinical Biostatistics Department of Merck Research laboratories using SAS version 8 (SAS Institute Inc, Cary, NC), with independent validation performed by one of the authors (R.B.D.) All study data currently reside in the Merck & Co Inc database.

Analysis Plan

To test the hypothesis that lower LVMI during antihypertensive therapy results in reduction in clinical events independent of antihypertensive treatment type and degree of BP lowering, the effect of in-treatment LVMI on risk of clinical end points was analyzed by the intention-to-treat principle, assessing all randomized patients with baseline left ventricular mass values for end points for the entire duration of the study, regardless of protocol violations or discontinuation of study medication. The effect of in-treatment LVMI on the risk of clinical end points, expressed as the hazard ratio (HR) and its 95% CI per SD (25.3) of baseline LVMI was analyzed using multivariable Cox regression models. In the primary model the baseline LVMI, systolic and

diastolic BPs, and treatment group indicator were standard covariates, and LVMI and systolic and diastolic BP at annual evaluations were time-varying covariates carried forward until the next evaluation. The homogeneity of association between lower in-treatment LVMI and lower rate of composite end points was assessed in subset analyses comparing subgroups defined by sex, self-reported race, age, diabetes, and randomized treatment. Additional Cox models excluded events during the first year of treatment and added baseline age, diabetes, smoking, and previous MI, stroke, and heart failure as covariates. Conclusions based on the parameter for LVMI as a time-varying covariate were to be considered independent of treatment type if the interaction between treatment group and LVMI was not statistically significant. Secondary Cox analyses considered the presence or absence of LVH as a categorical variable.

Event rates over time for patients with or without LVH are illustrated using Kaplan-Meier curves modified to account for time-varying covariates. Daily event-free probabilities calculated for LVH categories (with/without LVH) on each individual day were used to construct Kaplan-Meier curves in the usual way. The modified Kaplan-Meier curves illustrate the effect of a time-varying covariate on risk that corresponds to the HR for that covariate calculated using Cox regression analysis. Just as in the Cox regression analysis with continuous time-varying covariates, the covar-

iate values for each patient at each event time are compared between those with an event and those at risk without an event. Thus, the modified Kaplan-Meier curves are to Cox regression analyses with a time-varying covariate what the ordinary Kaplan-Meier curves are to Cox regression analyses with time-invariant covariates.

RESULTS

Baseline Characteristics

Of 960 patients with full echocardiograms by the LIFE protocol, the 941 (98%) with measurable left ventricular mass at the baseline study were included in the present analyses. As previously described,²¹ participants in the LIFE echocardiography substudy were middle-aged to elderly (mean age, 66 years), predominately white (84%), had moderately severe hypertension (TABLE 1), were overweight (body mass index, 27.4 [SD, 4.7]), and had moderate prevalences of diabetes (11%), coronary heart disease (13%), stroke (8%), and peripheral vascular disease (5%), paralleling characteristics for the entire LIFE population.^{23,35}

Changes in Blood Pressure and Left Ventricular Mass

Blood pressure, heart rate, and left ventricular mass all decreased substantially during the first year in the LIFE study (Table 1). Thereafter, BP and heart rate decreased only slightly. In contrast, left ventricular mass decreased markedly from 12- to 24-month echocardiograms, with small

further decrements throughout the 60-month follow-up. Change in left ventricular mass was related to baseline left ventricular mass, with progressively greater mass reduction but also progressively higher in-treatment LVMI from the lowest to highest quartile of LVMI at enrollment (from 96 to 85 in the first baseline LVMI quartile, 114 to 98 in the second, 127 to 106 in the third, and 156 to 125 in the fourth quartile, $P < .001$ for trend). Greater reduction of LVMI was paralleled by greater reduction in systolic BP in higher quartiles of baseline LVMI (mean reduction by quartile: -27 , -28.7 , -30.1 , and -30.5 mm Hg).

Regression and Incidence of LVH

Of 660 LIFE participants with baseline echocardiographic LVH, the proportion with normal LVMI increased to 45% after 1 year and 68% after 60 months of treatment. In contrast, of patients with normal left ventricular mass at baseline, only 3% to 9% developed LVH at different annual reexaminations. Hypertrophy prevalence decreased from 70% at baseline to 23% after 5 years (Table 1). Medication use was similar in patients with or without hypertrophy at each annual visit, eg, randomized study drug was taken by 92% and 95%, respectively, hydrochlorothiazide by 59% and 64%, and other medications by 27% and 24% ($P > .05$ for all) after 1 year in the LIFE trial. Adherence to randomized study medication was similarly high among patients with or without LVH (eg, 78% and 85% at the last visit at which LVMI was measured).

Clinical End Points

Primary events occurred in 104 patients (11%), including 84 with events after the first year of treatment, during a mean follow-up of 4.6 years (median, 4.8; 25.1/1000 patient-years). A test for interaction between treatment with losartan and LVMI on the composite CV end point was not significant ($P = .12$).

The results of Cox multivariable proportional hazards analyses considering

Table 2. Association of In-Treatment LV Mass With Risk of Cardiovascular Events: Results of Cox Multivariable Proportional Hazards Analyses

In-Treatment LV Mass Measure and End Point	HR (95% CI)	P Value
LVMI decrease of 25.3*†		
Composite	0.78 (0.65-0.94)	.009
CV mortality	0.62 (0.47-0.82)	.001
Myocardial infarction	0.85 (0.62-1.17)	.33
Stroke	0.76 (0.60-0.96)	.02
All-cause mortality	0.72 (0.59-0.88)	.002
LVMI decrease of 25.3*‡		
Composite	0.84 (0.68-1.03)	.10
CV mortality	0.66 (0.49-0.90)	.009
Myocardial infarction	0.91 (0.64-1.32)	.63
Stroke	0.90 (0.67-1.20)	.48
All-cause mortality	0.74 (0.59-0.93)	.008
Absence vs presence of LVH§		
Composite	0.58 (0.38-0.86)	.008
CV mortality	0.34 (0.17-0.71)	.004
Myocardial infarction	0.48 (0.24-0.93)	.03
Stroke	0.72 (0.42-1.24)	.24
All-cause mortality	0.36 (0.23-0.59)	<.001

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LV, left ventricular; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.

*LVMI calculated as LV mass in grams divided by body surface area in square meters; 25.3 is 1 SD of the baseline LVMI.

†Adjusted for baseline LVMI, treatment, and blood pressure lowering.

‡Adjusted for baseline LVMI, treatment, blood pressure lowering, age, smoking, diabetes, prior stroke, prior myocardial infarction, and heart failure.

§Adjusted for baseline LVH, treatment, and blood pressure lowering. LVH defined as LVMI >116.0 in men and >104.0 in women.

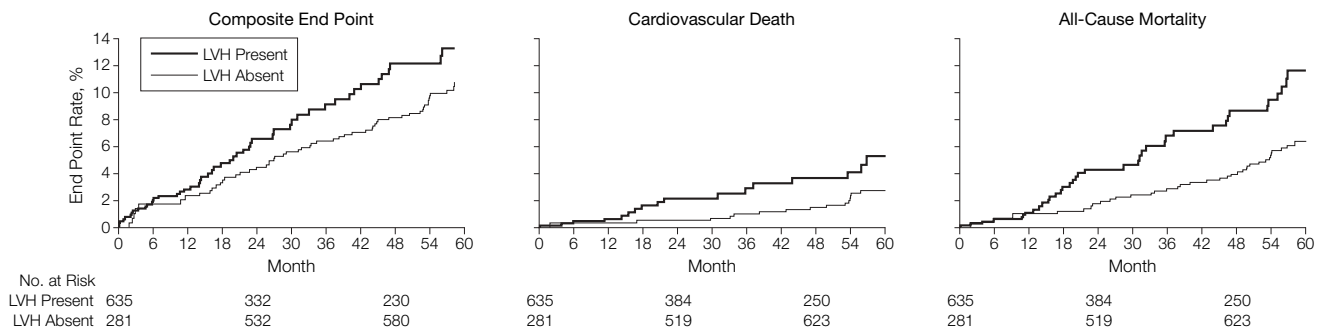
time-varying changes in left ventricular mass as a continuous variable are summarized in TABLE 2. After adjusting for baseline LVMI, study treatment, and degree of BP lowering, reduction in left ventricular mass was strongly associated with reduced risk for the composite end point, CV mortality, stroke, and the secondary end point of all-cause mortality. These reductions largely persisted after further adjusting for age, smoking, diabetes, prior stroke, prior MI, and heart failure.

Cox regression analysis investigating the risk of composite end points after the first year of treatment independent of baseline LVMI, antihypertensive treatment, and BP lowering showed that HRs per 1-SD (25.3) decrease in in-treatment LVMI were 0.74 (95% CI, 0.65-0.91; $P = .003$) for the composite end point and 0.57 (95% CI, 0.45-0.76; $P < .001$) for CV mortality, 0.88 (95% CI, 0.64-1.20; $P = .41$) for MI ($n = 31$), 0.78 (95% CI, 0.59-0.95; $P = .02$) for stroke ($n = 47$), and 0.70 (95% CI, 0.58-0.86; $P < .001$) for all-

cause mortality ($n = 64$). Alternative models using change from baseline in systolic or diastolic BP, pulse pressure, or attainment of BP control ($<140/90$ mm Hg) had little impact on the association of lower in-treatment LVMI with lower rate of the composite end point ($P < .05$ for all) or other clinical outcomes. Addition of the electrocardiographic Cornell voltage-duration product as a time-varying covariate to our primary model had virtually no effect on the risk reduction associated with lower LVMI for the composite end point (HR, 0.79; 95% CI, 0.65-0.96; $P = .02$), CV mortality (HR, 0.58; 95% CI, 0.43-0.77; $P < .001$), stroke (HR, 0.78; 95% CI, 0.60-1.01; $P = .06$), or all-cause mortality (HR, 0.69; 95% CI, 0.56-0.86; $P < .001$).

Additional Cox models substituted the presence or absence of LVH by sex-specific LVMI partition values for ventricular mass as a continuous time-varying covariate; these are also summarized in Table 2 and in the FIGURE. Absence vs presence of LVH

Figure. Composite End Point, Cardiovascular Death, and All-Cause Mortality Stratified by Time-Varying Presence of Echocardiographic Left Ventricular Hypertrophy



Left ventricular hypertrophy (LVH) defined as left ventricular mass index of >116.0 in men and >104.0 in women. Patients with LVH at baseline are counted in the "LVH absent" group at the time at which their LVH regresses.

was associated with lower rates of the composite end point, of CV mortality, and of all-cause mortality (Figure). Compared with results using LVMI as a continuous variable, absence of LVH as a categorical variable was associated more strongly with reduced risk of MI and less strongly with lower rate of stroke (Table 2).

In contrast to the lower end point rates associated with lower in-treatment LVMI, in the model that also considered LVMI and diastolic pressure as time-varying covariates and treatment as a fixed covariate, lower in-treatment systolic pressure was associated with higher rates of the composite end point (HR, 1.19 per SD [14.1 mm Hg] of baseline values; 95% CI, 1.00-1.38; $P=.045$) and CV death (HR, 1.44; 95% CI, 1.09-1.79; $P=.01$), with parallel but nonsignificant trends for other end points. Attainment of BP less than 140/90 mm Hg was associated with a trend toward fewer composite end points (HR, 0.85; 95% CI, 0.55-1.31; $P=.46$).

Outcomes in Subsets of the Population

Associations between lower in-treatment LVMI and lower rate of the composite end point were also seen in women and men (HR, 0.70 [95% CI, 0.52-0.95] and 0.86 [95% CI, 0.67-1.11] per 1-SD LVMI decrease, respectively; $P=.06$), patients older vs younger than 65 years (HR, 0.85 [95% CI, 0.67-

1.08] and 0.75 [95% CI, 0.55-1.03]; $P=.14$), patients with and without diabetes (HR, 0.72 [95% CI, 0.45-1.16] and 0.78 [95% CI, 0.64-0.95]; $P=.91$) and in black and nonblack participants (HR, 0.76 [95% CI, 0.56-1.13] and 0.77 [95% CI, 0.62-0.95]; $P=.44$). The reduction in rate of the composite end point per 1-SD LVMI decrease tended to be nonsignificantly greater in patients assigned to losartan than to atenolol-based treatment (HR, 0.72 [95% CI, 0.56-0.92] vs 0.89 [95% CI, 0.67-1.19]; $P=.12$).

COMMENT

The current study extends previous reports by demonstrating the relevance to prognosis of serial measurements of left ventricular mass during treatment in a prospectively studied cohort of patients with moderate severe essential hypertension as documented by BP level and presence of baseline electrocardiographic LVH. Patients with lower LVMI on annual echocardiograms during treatment were 22% less likely to experience the composite end point of cardiovascular morbidity and mortality during 4.6 years of follow-up for each 1-SD (25.3) decrease in in-treatment LVMI. Dichotomization of patients based on presence or absence of LVH on each echocardiogram revealed a 42% lower rate of subsequent composite end points in patients without LVH on in-treatment echocardiograms. Of note,

the lower mortality and morbidity associated with lower in-treatment left ventricular mass was additive to the predictive value of the baseline levels of left ventricular mass and BP, in-treatment BP changes, randomized assignment to losartan or atenolol, and concomitant electrocardiographic measures of LVH. The study thus shows that regression or prevention of LVH during antihypertensive therapy, compared with persistence or development of hypertrophy, is associated with a reduced rate of major CV events. Our results extend those of previous, less definitive, outcome studies suggesting that reduction of ventricular mass predicts improved prognosis and is thus a desirable outcome of antihypertensive therapy.^{13,14,17-19} These results may facilitate hypertension research because measurement of left ventricular mass may be a useful method to provide initial estimates of prognostic benefits of future treatments of hypertension.³⁷

Our data also demonstrate relations between lower in-treatment LVMI and lower rates of CV and all-cause mortality. These were respectively diminished by means of 38% and 28% per 1-SD reduction of LVMI as a continuous variable and by 66% and 64% associated with absence vs persistence of LVH as a time-varying categorical variable. Lower in-treatment LVMI was also associated with reduced rates of both MI and stroke. However, analyses us-

ing LVMI as a time-varying continuous variable showed greater reduction of the rate of stroke than that of MI (mean, 22% vs 15% per 25.3), whereas analyses using absence of LVH as a categorical variable showed less reduction of stroke than of MI (28% vs 52%). It is uncertain whether the stronger association between LVH and MI using LVH as a categorical variable as opposed to the association between LVMI and MI using as a continuous variable reflects a true biological effect of LVH detected by criteria chosen a priori or is a chance result of small random fluctuation in LVMI values. However, the observed association between in-treatment LVH and the occurrence of MI is in accord with previous clinical and experimental observations.

Our results have potential implications for clinical management of hypertension. This and previous studies support the concept that reduction of left ventricular mass augments the benefit of antihypertensive therapy.¹⁷⁻¹⁹ The study shows that reassessment of LVMI over several years of treatment helps assess the subsequent level of risk in treated patients with hypertension independent of BP control and treatment regimen. The present echocardiographic study of a large population of patients with hypertension shows that hypertensive LVH is reversed in many, but not all, patients by antihypertensive therapy. As we reported elsewhere,^{20,38} losartan was more effective than atenolol in reducing left ventricular mass as well as electrocardiographic measures of hypertrophy in the LIFE trial.

The present study's finding of a strong, independent relation between lower echocardiographic LVMI and reduced rates of CV events is complemented by the report by Okin and colleagues³⁹ in this issue of *JAMA* that lower electrocardiographic measures of LVH were associated with reduced rates of morbidity and mortality in the entire LIFE population. The finding of concordant, strong relations between better outcomes and lower LVH indices during antihypertensive treatment by

2 entirely different techniques—direct anatomical visualization by echocardiography and indirect left ventricular assessment by electrocardiographic measures of QRS voltage and duration—demonstrate the biological robustness of this relationship. Of note, the quantitative reduction of the rate of the LIFE composite end point per SD of baseline values was highest for echocardiographic LVMI (22%) but only modestly lower for electrocardiographic Cornell voltage-duration product and Sokolow-Lyon voltage (15%-20%), demonstrating both a greater ability of direct anatomical measurements and the considerable usefulness of more widely available and less expensive electrocardiographic indices of LVH to predict the reduction of CV events associated with LVH regression.

Some limitations of the study merit consideration. First, patients with the most- and least-severe disease were underrepresented. Patients with recent MI or stroke, known ejection fraction less than 40%, or need for several classes of antihypertensive medication were excluded. Conversely, our patients were at relatively high risk because of moderately elevated BP and presence of LVH on a screening electrocardiogram. Second, the 2% of patients without LVMI at baseline were excluded, slightly reducing the power of the study. Finally, while "regression to the mean" can occur in studies that assess the relation between changes in a parameter over time and outcome,⁴⁰ the consistent results in the analysis that used in-treatment echocardiograms after at least 1 year of randomized therapy, with adjustment for baseline LVMI, as a predictor variable in the present study suggest that the effect of this phenomenon is minimal.

The association we found between lower in-treatment systolic pressure and higher rate of CV events may be due at least in part to an association between worsening left ventricular systolic function and lower systolic and pulse pressures during treatment that we have reported previously.⁴¹

In summary, reduction of left ventricular mass during antihypertensive

treatment is associated with improved prognosis in treated patients with hypertension. Our observations substantially extend previous evidence^{13,14,17-19,35,37} that left ventricular mass reduction is a desirable outcome of hypertension therapy and development or persistence of LVH during treatment is an ominous sign, independent of BP control and treatment modality. Further research is needed to determine whether treatment guided by serial measurements of left ventricular mass to regress hypertensive LVH provides incremental benefit to patients beyond that obtained from BP control.

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