Prognostic Significance of Serial Changes in Left Ventricular Mass in Essential Hypertension

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Background—Increased left ventricular (LV) mass predicts an adverse outcome in patients with essential hypertension. The purpose of this study was to determine the relation between changes in LV mass during antihypertensive treatment and subsequent prognosis.

Methods and Results—Procedures including echocardiography and 24-hour ambulatory blood pressure (BP) monitoring were performed in 430 patients with essential hypertension before therapy and after 1217 patient-years. Months or years after the follow-up visit, 31 patients suffered a first cardiovascular morbid event. The patients with a decrease in LV mass from the baseline to follow-up visit were compared with those with an increase in LV mass. There were 15 events (1.78 per 100 person-years) in the group with a decrease in LV mass and 16 events (3.03 per 100 person-years) in the group with an increase in LV mass (P=.029). In a Cox model, the lesser cardiovascular risk in the group with a decrease in LV mass (hazard ratio [HR], 0.46; 95% CI, 1.03 to 1.10; P=.0008) and baseline LVH at ECG (HR, 3.85; 95% CI, 1.52 to 9.78; P=.012). In that model, baseline LV mass bordered on statistical significance (HR, 1.01; 95% CI, 1.00 to 1.03; P=.06). In the subset with LV mass >125 g/m² at the baseline visit (26% of subjects), the event rate was lower among the subjects who achieved regression of LVH than in those who did not (1.58 versus 6.27 events per 100 person-years; P=.002). This difference held in the multivariate analysis (HR, 0.18; 95% CI, 0.05 to 0.68).

Conclusions—In essential hypertension, a reduction in LV mass during treatment is a favorable prognostic marker that predicts a lesser risk for subsequent cardiovascular morbid events. Such an association is independent of baseline LV mass, baseline clinic and ambulatory BP, and degree of BP reduction. (Circulation. 1998;97:48-54.)

Key Words: hypertension • prognosis • hypertrophy • echocardiography • electrocardiography

Left ventricular hypertrophy detected at echocardiography in a single session predicts an increased risk for cardiovascular disease in patients with essential hypertension. Although the mechanisms of this association are undefined, LV mass is generally considered a biological assay that reflects and integrates the long-term cumulative effect of several risk factors for cardiovascular disease. Antihypertensive therapy may lead to regression of LVH, but the prognostic significance of this finding is still undetermined. In the Framingham Heart Study, the subjects with an increase of a quartile in the sum of the R wave in the aVL lead plus the S wave in the V₃ lead were twice as likely to suffer a cardiovascular morbid event over the subsequent years than those with a decrease by a quartile in the voltage score. However, the ECG is less sensitive than echocardiography for detection of LVH. Some investigations found a link between regression of echocardiographic LVH and cardiovascular disease in essential hypertension, but none of these studies could provide conclusive evidence of an independent predictive effect of serial changes in LV mass, in subjects free of cardiovascular disease, on the subsequent cardiovascular event risk. In the setting of the PIUMA registry, the purpose of the present study was to determine the prognostic significance of serial changes in LV mass in subjects who attended the baseline and follow-up visits free of cardiovascular disease. Because ambulatory BP monitoring was carried out at both visits, we could adjust for the potential confounding effect of ambulatory BP. In fact, the changes in LV mass during treatment correlate more closely with the concomitant changes in ambulatory BP than with the changes in clinic BP and data from our laboratory suggest that the prognostic value of ambulatory BP is superior to that of clinic BP.

Methods

Subjects
We studied 430 hypertensive subjects (54.0% men) 48.2±11 years old (mean±SD) who attended the baseline visit and a follow-up visit in the setting of the PIUMA study, a prospective registry of morbidity.
and mortality in subjects with essential hypertension whose off-therapy initial diagnostic workup included 24-hour noninvasive ambulatory BP monitoring according to a standardized protocol. Details of the PIUMA registry have been reported previously. At entry, all patients had clinic systolic BP 140 mm Hg and/or diastolic BP 90 mm Hg on at least three visits at 1-week intervals and fulfilled all the following inclusion criteria: (1) no previous treatment for hypertension (n=293) or withdrawal from antihypertensive drugs at least 4 weeks before the study (n=137); (2) no clinic or laboratory evidence of heart failure, renal failure, coronary artery disease, valvular defects, or secondary causes of hypertension; and (3) at least one valid BP measurement per hour over the 24 hours.

BP Measurement
Clinic BP was measured with a standard mercury sphygmomanometer with the subject sitting for at least 10 minutes. Clinic heart rate was determined immediately thereafter. Caffeine ingestion and cigarette smoking were not permitted during the previous 2 hours. Ambulatory BP was recorded with SpaceLabs units 90202 and 90207 set to take a reading every 15 minutes throughout the 24 hours. Normal daily activities were allowed, and patients were told to keep their nondominant arm still and relaxed to the side during measurements. The spontaneous day-to-day variability of ambulatory BP was assessed in some of these patients.

Echocardiography
The M-mode echocardiographic study of the LV was performed under cross-sectional control with commercially available machines according to standard laboratory procedures. Echocardiographic examinations were performed by two physicians, and tracings were read by two other investigators. The mean value from at least five measurements of the LV per observer was computed. At the time of the echocardiographic examination, all involved investigators were unaware of all patients’ clinical data, including office BP, ambulatory BP, and cardiovascular complications. LV mass was determined according to the formula introduced by Devereux et al: 0.80×[(septal thickness + LV internal diameter + posterior wall thickness)²−(LV internal diameter)²] + 0.6 g and was normalized by body surface area. In our laboratory, the intraobserver coefficients of variation were 4.50% for septal thickness, 1.65% for LV internal diameter, 4.81% for posterior wall thickness, and 6.33% for LV mass index. Interobserver coefficients of variation are 6.30% for septal thickness, 1.65% for LV internal diameter, 6.73% for posterior wall thickness, and 7.65% for LV mass index.

Electrocardiography
Standard 12-lead ECGs were recorded in all subjects at 25 mm/s and 1-mV/cm calibration. Tracings were coded and interpreted by two investigators without knowledge of other patient data. Interobserver differences occurred in <5% of readings and were resolved by consensus. Complete bundle-branch block and Wolff-Parkinson-White syndrome were exclusion criteria from ECG analysis for LVH. Previous myocardial infarction and atrial fibrillation were exclusion criteria from ECG analysis for LVH. None of the patients had developed a cardiovascular morbid event at the time of the follow-up visit.

Contacts with family doctors of patients and telephone interviews were periodically undertaken to ascertain the incidence of major cardiovascular complications of hypertension. All interviews were conducted without knowledge of the results of echocardiographic studies or ambulatory BP monitoring. Many of the patients continued to be periodically referred to our institution for BP checks and other diagnostic procedures. A major effort was recently undertaken over ~1 month to assess the vital status of all subjects.

End-Point Evaluation
Hospital record forms and other available original source documents were reviewed in conference by the authors of this study for the subjects who developed a cardiovascular morbid event. Cardiovascular events included new-onset coronary artery disease (myocardial infarction, or angina with concomitant ischemic ECG changes), stroke, transient cerebral ischemic attack, symptomatic aortoiliac occlusive disease verified at angiography, thrombotic occlusion of a retinal artery documented at fluorescein angiography, progressive heart failure requiring hospitalization, and renal failure requiring dialysis. Transient ischemic attack was defined by the diagnosis, by a physician, of any sudden focal neurological deficit that cleared completely in <24 hours. Heart failure was defined by the simultaneous presence of at least two major criteria or one major plus two minor criteria as reported in the Framingham Heart Study. The international standard criteria used to diagnose cardiovascular events in the PIUMA study have been described elsewhere.

Data Analysis
Parametric data are reported as mean±SD. Standard descriptive and comparative statistical analyses were undertaken. Cardiovascular event rate is presented as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure. Survival curves were estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated by the Cox semiparametric regression model. In the Cox model, we tested the following covariates: age (years), sex (female, male), diabetes mellitus (no, yes), cardiac death in a parent at ≤55 years of age, baseline clinic systolic and diastolic BPs and their change from baseline to the follow-up visit, average 24-hour systolic and diastolic BPs and their change from baseline to the follow-up visit, smoking habits at the baseline visit (current smokers, previous smokers, never smokers) and failure of quitting smoking (those who continued smoking versus the others), serum cholesterol (mmol/L), body mass index (body weight in kilograms divided by the square of height in meters), ECG LVH defined by a Romhilt-Estes score ≥5 points (no, yes), and baseline LV mass index (grams divided by body surface area). Two groups were defined on the basis of changes in LV mass from baseline to follow-up: decrease in LV mass (group 1) or no change or increase in LV mass (group 2). Echocardiographic LVH was defined by an LV mass >125.0 g/m² because the prognostic value of such definition in uncomplicated subjects with essential hypertension is the most widely documented. We also tested the hypothesis of a different outcome between regressors and nonregressors in the subset with echocardiographic LVH at the baseline visit. The assumption concerning risk linearity for continuous variables was verified by visual inspection.
TABLE 1. Main Clinical Characteristics in the Study Population at the Baseline and Follow-up Visits

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>74.9 (14)</td>
<td>75.6 (14)</td>
<td>.015</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5 (4)</td>
<td>26.7 (3.9)</td>
<td>.016</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>3.0</td>
<td>3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>26.5</td>
<td>20.5</td>
<td>.042</td>
</tr>
<tr>
<td>Clinic BP, mm Hg</td>
<td>153 (17)</td>
<td>145 (17)</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic</td>
<td>98 (10)</td>
<td>91 (9)</td>
<td>.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.0 (10)</td>
<td>72.6 (10)</td>
<td>.013</td>
</tr>
<tr>
<td>Average 24-hour ambulatory BP, mm Hg</td>
<td>136 (14)</td>
<td>128 (12)</td>
<td>.001</td>
</tr>
<tr>
<td>Average 24-hour ambulatory HR, bpm</td>
<td>87 (10)</td>
<td>81 (8)</td>
<td>.001</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>115.2 (2.4)</td>
<td>107.1 (1.9)</td>
<td>.001</td>
</tr>
<tr>
<td>LV internal diameter, mm</td>
<td>49.2 (5.3)</td>
<td>49.5 (5.3)</td>
<td>.031</td>
</tr>
<tr>
<td>PW thickness, mm</td>
<td>10.1 (2.0)</td>
<td>9.6 (1.7)</td>
<td>.001</td>
</tr>
<tr>
<td>LV mass, g/BSA</td>
<td>109 (31)</td>
<td>101 (27)</td>
<td>.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.58 (1.11)</td>
<td>5.69 (1.08)</td>
<td>.027</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.26 (0.32)</td>
<td>1.34 (0.35)</td>
<td>.001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.61 (0.97)</td>
<td>3.62 (0.98)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.62 (1.10)</td>
<td>1.59 (1.05)</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.45 (0.81)</td>
<td>5.52 (1.19)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>85.4 (22)</td>
<td>88.1 (19)</td>
<td>.008</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>141.0 (3)</td>
<td>141.4 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.16 (0.4)</td>
<td>4.19 (0.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HR, heart rate; IVS, Interventricular septum; PW, posterior wall; and BSA, body surface area. Continuous variables are expressed as mean ± SD.

The other comparisons were made by Student’s t test and χ² test when appropriate. In two-tailed tests, values of P < .05 were considered statistically significant. BMDP package release 7 (BMDP Statistical Software) was used to perform the analyses.

Results

Table 1 shows the main characteristics of the whole population at baseline and follow-up visits. Basally, LV mass index was more closely correlated with average 24-hour ambulatory BP \((r=5.40\) systolic and \(r=3.73\) diastolic, both \(P<.001\)) than with clinic BP \((r=.22\) systolic and \(r=1.7\) diastolic, both \(P<.001\)). There was a clinically consistent and statistically significant reduction in BP and LV mass over the follow-up period. There was also a small but significant increase in body weight and body mass index. The changes in LV mass index showed a closer association with the changes in 24-hour ambulatory systolic and diastolic BPs \((r=.41\) and \(r=.34\), respectively, both \(P<.001\)) than with the changes in clinic BP \((r=.34\) and \(r=.34\), respectively, all \(P<.001\)). Among routine laboratory tests, there was a small but statistically significant increase in total and HDL cholesterol and serum creatinine. Table 2 shows some demographic, BP, echocardiographic, and laboratory data in the two groups with reduction or no reduction in LV mass. Age at entry (48.3 versus 48.0 years) and sex distribution (44% versus 49% women) did not differ between the former and the latter groups (both \(P=NS\)).

The proportions of subjects receiving lifestyle measures only, diuretics and/or β-blockers alone or combined, ACE inhibitors and/or calcium channel blockers alone or combined, or various drug associations were 42.1%, 9.1%, 23.9%, and 24.9%, respectively, in the subset with reduction in LV mass and 49.7%, 13.1%, 15.2%, and 22.1% in the subset without any reduction in LV mass (\(P=.09\)).

Cardiovascular Morbidity

Months or years after the follow-up visit, there were 31 nonfatal cardiovascular morbid events. One additional patient died of intestinal cancer and another committed suicide, but there were no cardiovascular deaths. The 430 study subjects contributed 1367 person-years of observation over the entire study period up to the terminating event or censoring (mean, 3.2 years), and the overall event rate was 2.27 per 100 person-years. There were 10 subjects with stroke, 4 with myocardial infarction, 4 with transient ischemic attack, 9 with new-onset coronary artery disease, 1 with heart failure requiring hospitalization, 1 with new-onset aortoiliac occlusive disease, 1 with occlusion of the retinal artery, and 1 with renal failure requiring dialysis.

Distribution of antihypertensive treatments at the follow-up visit did not differ among the subjects with and those without future cardiovascular events (lifestyle measures only, diuretic and/or β-blockers alone or combined, ACE inhibitors and/or calcium channel blockers alone or combined, or various drug associations in 16.1%, 9.7%, 38.7%, and 36.5% in the former versus 39.3%, 9.0%, 23.1%, and 28.6% in the latter, \(P=.06\)).

Only 5 of 162 subjects (3%) who were maintained on lifestyle interventions alone at the follow-up visit suffered morbid events in the future, versus 26 of the 268 subjects (9.7%) who received antihypertensive drugs (\(P=.017\) between the groups [Yates’ correction]). However, the former group had a lower cardiovascular risk profile at the baseline visit than the latter group. In fact, in this group the mean age (45 versus 50 years, \(P<.01\)), office BP (144/94 versus 160/100 mm Hg, both \(P<.01\)), average 24-hour BP (126/81 versus 142/91 mm Hg, both \(P<.01\)), and LV mass (97 versus 116 g/m², \(P<.01\)) were all lower than in the group that was subsequently treated with drugs.

ECG LVH and Cardiovascular Risk

At entry, the Romhilt-Estes score was ≥5 points in 23 subjects (prevalence, 5.3%). Consequently, the prognostic value of serial ECG changes could not be tested because of the small number of subjects with ECG LVH. However, the frequency of cardiovascular events was 26.1% among the subjects with baseline Romhilt-Estes score ≥5 points versus 5.8% among those with a lower score (\(P<.01\)), and the excess risk associated with ECG LVH held in the multivariate analysis (adjusted HR, 3.85; 95% CI, 1.52 to 9.78; \(P=.012\)). Therefore, despite its low prevalence, LVH diagnosed at ECG by the Romhilt-Estes score identified a subset at increased cardiovascular risk.
Echocardiographic LVH and Cardiovascular Risk

**Total Population**

The prevalence of LVH at echocardiography (LV mass >125.0 g/m²) was 26%, and the event rate in this group was higher (3.9 events per 100 person-years) than among subjects with normal LV mass (1.6 events per 100 person-years). Fig 1 shows event-free survival curves in the two groups. There were 15 events (1.78 per 100 person-years) among the 285 subjects with a decrease in LV mass from baseline to follow-up visit and 16 events (3.03 per 100 person-years) in the group with no change or increase in LV mass (P=.029, log-rank test). The different event rates in the two groups are depicted in Fig 2. In a Cox model, the lesser cardiovascular risk in the group with a decrease in LV mass (adjusted HR, 0.46; 95% CI, 0.22 to 0.99) remained significant (P=.04) after adjustment for age (adjusted HR, 1.06; 95% CI, 1.03 to 1.10; P=.0008) and baseline LVH at ECG (adjusted HR, 3.85; 95% CI, 1.52 to 9.78; P=.012). Baseline LV mass bordered on statistical significance (adjusted HR, 1.01; 95% CI, 1.00 to 1.03; P=.06). None of the other covariates (see Data Analysis), including clinic and ambulatory

**TABLE 2. Demographic, Blood Pressure, Echocardiographic, and Biochemical Characteristics in the Study Groups Defined by Changes in LV Mass From Baseline to Follow-up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decrease in LV Mass From Baseline to Follow-up Visit (n=285)</th>
<th>No Change or Increase in LV Mass From Baseline to Follow-up Visit (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Visit</td>
<td>Follow-up Visit</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.5 (13)</td>
<td>75.3 (13)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3 (3)</td>
<td>26.6 (4)</td>
</tr>
<tr>
<td>Clinic systolic BP, mm Hg</td>
<td>155 (17)</td>
<td>143 (15)</td>
</tr>
<tr>
<td>Clinic diastolic BP, mm Hg</td>
<td>99 (10)</td>
<td>90 (9)</td>
</tr>
<tr>
<td>Clinic HR, bpm</td>
<td>74 (10)</td>
<td>72 (9)</td>
</tr>
<tr>
<td>Average 24-hour systolic BP, mm Hg</td>
<td>137 (14)</td>
<td>126 (10)</td>
</tr>
<tr>
<td>Average 24-hour diastolic BP, mm Hg</td>
<td>88 (10)</td>
<td>80 (7)</td>
</tr>
<tr>
<td>Average 24-hour HR, bpm</td>
<td>75 (8)</td>
<td>73 (9)</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>12.0 (2.3)</td>
<td>10.5 (1.7)</td>
</tr>
<tr>
<td>LV internal diameter, mm</td>
<td>49.0 (5.0)</td>
<td>49.1 (5.2)</td>
</tr>
<tr>
<td>PW thickness, mm</td>
<td>10.5 (1.8)</td>
<td>9.4 (1.6)</td>
</tr>
<tr>
<td>LV mass, g/BSA</td>
<td>115 (31)</td>
<td>97 (25)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.55 (1.12)</td>
<td>5.65 (1.05)</td>
</tr>
<tr>
<td>HDL</td>
<td>1.26 (0.33)</td>
<td>1.33 (0.31)</td>
</tr>
<tr>
<td>LDL</td>
<td>3.58 (0.96)</td>
<td>3.61 (0.95)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.57 (1.16)</td>
<td>1.55 (0.93)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.40 (0.74)</td>
<td>5.47 (1.02)</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>85.8 (22)</td>
<td>87.6 (16)</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140.9 (2)</td>
<td>141.5 (3)</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.1 (0.3)</td>
<td>4.0 (0.4)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HR, heart rate; IVS, interventricular septum; PW, posterior wall; and BSA, body surface area.

![Figure 1](http://circ.ahajournals.org/). Event-free survival in the two groups with (thick line) and without (thin line) echocardiographic LVH at the baseline visit. BSA indicates body surface area.

![Figure 2](http://circ.ahajournals.org/). Event rate in the two groups with LV mass reduction (open column) or increase (solid column) from baseline to follow-up visit.

**Verdecchia et al 51**
BPs and their changes from baseline to follow-up visit, attained statistical significance to enter the model. Because highly correlated risk variables, particularly clinic and ambulatory BPs, did not enter the model, collinearity between significant predictors was not a problem in the present study.

Subset With Increased LV Mass

Among the subjects with LV mass >125 g/m² at the baseline visit, the event rate was considerably lower in the subset (n=52; 47%) with regression of LVH (LV mass <125 g/m² at the follow-up visit) than in that with LV mass persistently >125 g/m² (1.58 versus 6.27 events per 100 person-years; P=.002, log-rank test). Fig 3 shows survival curves in the two groups. In a Cox model, the lesser event risk in regressors compared with nonregressors (adjusted HR, 0.18; 95% CI, 0.05 to 0.68; P=.004) held after adjustment for age (adjusted HR, 1.08; 95% CI, 1.02 to 1.14; P=.0001), whereas none of the other covariates attained statistical significance to enter the model. A representative tracing of a patient with regression of echocardiographic LVH is reported in Fig 4.

Discussion

The most important result of this study is that a serial reduction in LV mass in uncomplicated subjects with essential hypertension has a favorable prognostic value by predicting a lesser risk for subsequent cardiovascular disease. This association was independent of baseline LV mass, baseline clinic and ambulatory BPs, and BP changes from baseline to follow-up visit. These results were obtained in a 100% white population and may not be applicable to other racial groups.

Previous Studies

In contrast to previous echocardiographic studies that assessed the prognostic value of baseline LVH, we evaluated the implications of serial changes in LV mass on the subsequent cardiovascular risk. To the best of our knowledge, only three studies examined the relation between changes in LV mass and cardiovascular disease risk in patients with essential hypertension. In one study, available in abstract form, 166 hypertensive patients had echocardiographic examinations before and after an average of 5 years of treatment. Over the subsequent years, there were 18 cardiovascular morbid events, which occurred more frequently in the subjects with an increase (16%) than in those with a decrease (6%) in LV mass.13

In another study, 304 hypertensive men with echocardiographic LVH were followed for 4 years with an echocardiographic check every year, and during this period, LV mass decreased by ~30 g in the subjects without new cardiovascular events, versus an increase of 0.3 g in those with new events. However, LV mass was measured by the Teichholz formula.
which underestimates anatomic LV mass,20 and data analysis did not take into account the potential confounding effect of several associated risk factors. In another study,15 151 white subjects underwent echocardiography before therapy and after 7 to 13 years of follow-up. The frequency of cardiovascular morbid events was higher in the subjects who failed to achieve regression of LVH at follow-up than in those with persistently normal LV mass, whereas the event rate in the group with regression of LVH did not differ from that with persistently normal LV mass.15 However, a limitation of that study was that some of the events occurred before the follow-up echocardiographic study,15 and therefore, apart from a link between changes in LV mass and cardiovascular morbidity, that study could not determine the predictive effect on the subsequent outcome of serial changes in LV mass in subjects still free of cardiovascular disease. In contrast, the present study was carried out in subjects still free of cardiovascular morbid events when they attended the follow-up examination.

Our results are in agreement with a recent report from Framingham based on serial ECG examinations in a general population sample.16 In the present study, we targeted uncomplicated hypertensive subjects to specifically examine LV structural changes secondary to essential hypertension.

**ECG LV Hypertrophy**

The prevalence of LVH was 5.3% by the Romhilt-Estes ECG score and 26% by echocardiographic LV mass. The low prevalence of LVH at the baseline ECG study precluded the prognostic assessment of its regression over time. However, the frequency of cardiovascular events was considerably higher \( (P < .01) \) in the subset with (26.1%) than in that without (5.8%) LVH at the baseline ECG. Hence, despite its low prevalence, ECG LVH allowed identification of a subset at increased cardiovascular risk.

**Echocardiographic LVH**

An important finding in this study was that the favorable prognostic impact of LV mass reduction remained significant in a multivariate analysis that considered baseline LV mass and ECG LVH. In contrast, neither clinic nor ambulatory BP nor the other covariates yielded statistical significance to enter the model. Because the changes in LV mass over time showed a significant association with the changes in ambulatory BP and a weaker association with those in clinic BP, the degree of 24-hour BP control over time may have been important in influencing the degree of LVH regression. However, clinic BP on a single follow-up visit and even ambulatory BP on a single follow-up day might not be adequate to express the degree of BP control over years, and this may explain why the changes in LV mass, as “time-integrated markers of exposure to hypertension,”26 were more potent than the recorded changes in clinic or ambulatory BP for prediction of cardiovascular risk. Moreover, progression of coronary artery lesions27 and other risk factors for LVH and cardiovascular disease2 may have continued to be active in the high-risk subjects who failed to achieve reduction of LV mass or regression of LVH despite a reduction in BP.

An unexpected finding was the lower frequency of subsequent cardiovascular events in the subset maintained on lifestyle intervention alone than in that treated with antihypertensive drugs. Because the former group did show a lower cardiovascular risk profile at the baseline visit, treatment decisions may have selectively turned from nonpharmacological to pharmacological therapy in those patients who were identified on the basis of clinical judgment as being at highest risk of morbid events.

**Limitations of the Study**

A limitation of this study is the lack of fatal cardiovascular end points, which might be accounted for by the relatively young age of the subjects (48.2 years), the low prevalence of diabetes (3.0%), the absence of previous cardiovascular morbid events, and the relatively short duration of follow-up (average, 3.2 years). Consequently, the results of this study need further assessment in large, ongoing observational studies, including the CARDIA Study,27 the Cardiovascular Health Study,28 the Strong Heart Study,29 and the Framingham Heart Study. Furthermore, several outcome trials comparing different antihypertensive regimens include echocardiography among experimental procedures.30–33 These trials have been specifically designed to see whether a particular antihypertensive therapeutic strategy is more advantageous over another in inducing regression of LVH, with subsequent prognostic implications. Compared with the present observational study, these intervention megatrials are also structured to permit a greater control of the time course of BP levels over several visits and long-term adherence to antihypertensive therapy.

**Clinical Implications**

In hypertensive patients, a “limited echocardiographic study” is clinically valuable and cost-effective,34,35 and in this setting, M-mode echocardiography may be cheaper than ECG per case of LVH detected.36 Although limited by the relatively small sample size and by the lack of fatal end points, the present study suggests the clinical usefulness of periodic measurements of LV mass in patients with essential hypertension to improve cardiovascular risk stratification. The patients who fail to achieve reduction in LV mass or regression of LVH should be considered at increased risk for subsequent cardiovascular disease, and a more aggressive therapeutic approach is justified in these subjects.

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**References**


**Verdecchia et al**
54

Regression of Hypertrophy Predicts Prognosis

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