Left ventricular hypertrophy (LVH), as defined by increased LV mass (LVM) on echocardiography, predicts cardiovascular events in hypertensive patients as well as in the general population. LVH can occur through ventricular dilatation, wall thickening, or combinations thereof. To distinguish between these patterns of hypertrophy, LVH has been subclassified based on relative wall thickness (RWT; wall thickness/LV internal radius). If the ratio is high, the term concentric is applied; if not, the term eccentric hypertrophy is used. Recently, a new 4-group classification system derived by cardiac MRI reclassified participants with eccentric LVH with normal LV end-diastolic volume (EDV) into a subgroup with better LV function and, maybe, better outcome that is not captured with the conventional 2-group classification. The new classification has not yet been related to clinical outcome in hypertensive patients.

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Background—Left ventricular hypertrophy (LVH; high LV mass [LVM]) is traditionally classified as concentric or eccentric based on LV relative wall thickness. We evaluated the prediction of subsequent adverse events in a new 4-group LVH classification based on LV dilatation (high LV end-diastolic volume [EDV] index) and concentricity (mass/end-diastolic volume [M/EDV]^2/3) in hypertensive patients.

Methods and Results—In the Losartan Intervention for Endpoint Reduction (LIFE) echocardiography substudy, 939 hypertensive patients with measurable LVM at baseline were randomized to a mean of 4.8 years of losartan- or atenolol-based treatment. Patients with LVH (LVM/body surface area ≥116 and ≥96 g/m² in men and woman, respectively) were divided into 4 groups—concentric nondilated (increased M/EDV, normal EDV), eccentric dilated (increased EDV, normal M/EDV), concentric dilated (increased M/EDV and EDV), and eccentric nondilated (normal M/EDV and EDV)—and compared with patients with normal LVM. Time-varying LVH classes were tested for association with all-cause and cardiovascular mortality and a composite end point of myocardial infarction, stroke, heart failure, and cardiovascular death in multivariable Cox analyses. At baseline, the LVs were categorized as eccentric nondilated in 12%, eccentric dilated in 20%, concentric nondilated in 29%, concentric dilated in 14%, and normal LVM in 25%. Treatment changed the prevalence of 4 LVH groups to 23%, 4%, 5%, and 7%; 62% had normal LVM after 4 years. In time-varying Cox analyses, compared with normal LVH, those with eccentric dilated and both concentric nondilated and dilated LVH had increased risks of all-cause or cardiovascular mortality or the composite end point, whereas the eccentric nondilated group did not.

Conclusions—Hypertensive patients with relatively mild LVH without either increased LV volume or concentricity have similar risk of all-cause mortality or cardiovascular events because hypertensive patients with normal LVM seem to be a low-risk group.


Key Words: hypertension ■ hypertrophy ■ left ventricular geometry
Methods

Study Design

More than 10% (n=960) of Losartan Intervention for Endpoint Reduction (LIFE) participants aged 55 to 80 years with stage II to III hypertension were enrolled in the prospectively planned LIFE echocardiography substudy in which echocardiography was performed at baseline and annually thereafter for a median of 4.8 months of follow-up. The LIFE inclusion and exclusion criteria and main outcomes have been reported previously.6,7

The Committees of Ethical Science in participating countries accepted this study. Participants provided written informed consent.

Doppler Echocardiography

Echocardiograms were recorded using phased-array echocardiography, following a standardized protocol under which the parasternal window was used to record ≥10 consecutive beats of 2-dimensional and M-mode recordings of LV internal diameter and wall thicknesses just below the mitral leaflet tips in long- and short-axis views.6 LV chamber dimensions and wall thicknesses were measured following American Society of Echocardiography standards.8 RWT was calculated at end-diastole as (2×posterior wall thickness/internal LV diameter in diastole); endocardial shortening as [(diastolic–systolic LV internal diameter)/diastolic LV internal diameter]; LV chamber volumes and ejection fraction by the angiographically validated Teichholz method; and LVM using an anatomically validated formula \( r=0.90 \) versus postmortem LV weight.9–14 LVM showed excellent interstudy reliability in a separate study of 183 patients from the Reading Center.15 Midwall shortening was calculated using a previously validated formula.16 Stroke volume was determined by Doppler echocardiography and used to calculate cardiac output.17 Aortic regurgitation was assessed by color Doppler.18 A description of derived variables has been published previously.5,7,10

Defining LV Geometry

LVH and increased LV EDV/BSA were defined according to guidelines (LVM/BSA: ≥96 g/m\(^2\) [women] and ≥116 g/m\(^2\) [men]; LV EDV/BSA: ≥76 mL/m\(^2\); Figure 1).10,20 To identify wall thickening, we used a modified formula to calculate an LV concentricity index as proposed by Khouri et al.4 The concentricity index is calculated as \( \text{(LVM myocardial volume/LV EDV)}^{2/3} \), as previously described.4 Sex-specific partitions for LVM/LV EDV\(^{2/3} \) (termed concentricity\(^{2/3} \)) were defined as ≥97.5th percentile of the previously described healthy subpopulation used to define LVH in the Dallas Heart Study4 (≥8.1 g/mL\(^{2/3} \) [women] and ≥9.1 g/mL\(^{2/3} \) [men]; Figure 1). Patients with LVH were then divided into 4 groups based on whether concentricity\(^{2/3} \) and LV EDV/BSA were increased or not using the above threshold values. To recapitulate the standard 2-group classification, we classified hypertrophy as concentric when concentricity\(^{2/3} \) exceeded the above sex-specific thresholds, and as eccentric when it was below those values. To test whether the results were dependent on the method of indexation, 2 sensitivity analyses were performed: (1) height\(^{2.7} \) was used to define LVH (LVM/height\(^{2.7} \) ≥45 g/m\(^2.7 \) [women] and ≥49 g/m\(^2.7 \) [men]); and (2) RWT was used to define concentricity (≥0.43).10

The new classification system was tested in an apparently normal population (n=362) from New York.21 This showed overall specificity of 97% for absence of LVH.20

End Points

All LIFE end points were ascertained by systematic surveillance at regular outpatient visits and investigator contact of patients and verified by an end point committee.8,22 Members of the end point committee were blinded to echocardiographic measurements. Because LVH has been shown to be associated with congestive heart failure, we added hospitalized congestive heart failure to the composite end point.23,24 The primary end point in this post hoc study was all-cause mortality, and secondary end points were cardiovascular death and the composite end point of cardiovascular death, myocardial infarction, hospitalized heart failure, or stroke.8,22

Statistical Analysis

Descriptive data are reported as mean±SD, and frequencies as percentages. Continuous variables without normal distribution were log-transformed as appropriate and expressed as median with first and third quartiles. Differences in categorical variables were evaluated using \( \chi^2 \) and continuous variables using 1-way ANOVA. To test whether the 4-group classification system was clinically relevant, both classification systems were analyzed in uni- and multivariable Cox regression with LVH group inserted as a time-varying variable by using the LVH category just before an end point occurred, with patients with normal
LVM as the reference group. Therefore, a patient who had concentric dilated LVH at baseline may have shifted to a different group before dying or having another endpoint. Multivariable Cox models were adjusted for age, sex, race, randomized study treatment, and time-varying systolic and diastolic blood pressure as well as time-varying diabetes mellitus and heart failure. Because heart failure was a part of the composite endpoint, this endpoint was adjusted for history of heart failure instead of time-varying heart failure. Because of limited events, cardiovascular death adjustment was limited to age, sex, and time-varying systolic blood pressure. Proportionality and linearity assumption for all variables in the multivariable models were checked by testing the dependence of their relative risk estimate on time. No interaction was found between the covariates sex, diabetes mellitus, median age (>66 or ≤66 years), and median systolic blood pressure (>162 or ≤162 mm Hg), and each model of the 4-group classification (all P>0.08). In addition, the multivariable Cox models were adjusted for multiple comparisons using Bonferroni correction for the primary end point of all-cause mortality. Finally, we tested whether the new model improved the net reclassification index for all-cause mortality in addition to continuous LVM/BSA, that is, the proportion of individuals correctly reclassified across risk categories minus the proportion of individuals incorrectly reclassified. We used thresholds of <5%, 5% to 10%, and ≥10% because no established thresholds exist for the new classification models’ action about all-cause mortality.

SAS statistical software package version 9.2 for PC (SAS Institute Inc, Cary, NC) was used for all statistical analyses. Two-tailed P<0.05 was regarded as statistically significant.

Results

The present analysis was undertaken in 939 of 960 participants of LIFE echocardiography substudy with measurable LV dimensions at baseline. Using the new 4-group classification system of LVH, 114 of 939 hypertensive patients (12.1%) had eccentric nondilated LVH, 187 (19.9%) had eccentric dilated LVH, 272 (29.0%) had concentric nondilated LVH, 133 (14.2%) had concentric dilated LVH, and 233 (24.8%) had normal LVM at baseline (Figure 1). Only 4% of 939 patients had concentric LV remodeling (defined as normal LVM but increased concentricity).

After a median follow-up of 4.9 (range, 4.6–5.1) years, lowering of blood pressure with losartan and atenolol changed the prevalence of 4 LVH groups to 23%, 4%, 5%, and 7%, respectively, with normal LVM in 62%.

Baseline Cardiac Structure and Function in LVH Groups

There was no difference in age or systolic blood pressure among the LVH groups; however, both nondilated eccentric and nondilated concentric LVH groups had significantly more women; accordingly, sex was used as a covariate in comparisons using the 4-group classification of LVH. There were higher body mass index, BSA, and high-density lipoprotein in the concentric groups without difference in history of diabetes mellitus. In addition, there were higher mean body mass index and BSA in dilated than in nondilated concentric LVH; higher creatinine in the dilated concentric group; higher urine albumin/creatinine, creatinine, and hemoglobin; and lower high-density lipoprotein in both concentric groups compared with the nondilated eccentric group. Among echocardiographic variables, there were lower total peripheral resistance, pulse pressure/stroke index, and LV ejection fraction; higher Doppler stroke volume, cardiac output, larger atrial volume, LV midwall shortening, and LVM index; and higher prevalence of segmental wall motion abnormalities among the dilated groups than in the nondilated groups.

Comparison of Subjects With Eccentric Nondilated Hypertrophy With Those With Normal LVM

By definition, patients with eccentric nondilated LVH had increased LVM index but did not meet the criteria for concentric or dilated LVH. Because there were significantly more women with eccentric nondilated LVH compared with participants with normal LVM, sex was used as a covariate in comparison with these 2 groups. Compared with the group with normal LVM, eccentric nondilated LVH was associated with higher systolic blood pressure, Cornell voltage–duration product, pulse pressure/stroke index, and Doppler stroke volume; lower BSA and heart rate; and fewer were blacks (Tables 1 and 2).

All-Cause Mortality With Respect to the 2 Different Classification Systems of LVH

In analyses that categorized LVH as a time-varying variable, all-cause mortality occurred in 7.9% of study patients: 11% with eccentric and 18% with concentric LVH, and 5% in the group without LVH. When using the 2-group classification system, both eccentric (hazard ratio [HR], 2.3; 95% confidence interval [CI], 1.4–3.8; P=0.002) and concentric LVH (HR, 4.0; 95% CI, 2.2–7.5; P<0.001) predicted all-cause mortality in univariable Cox regression analysis. In multivariable Cox models, both eccentric and concentric LVH predicted all-cause mortality (HR, 2.0; 95% CI, 1.2–3.6; P=0.013, and HR, 3.5; 95% CI, 1.8–6.9; P<0.001, respectively; Figure 2A).

When using the 4-group classification system, all-cause mortality occurred in 7% with eccentric nondilated, 12% with eccentric dilated, 14% with concentric nondilated, and 23% with concentric dilated LVH (Table 3 and Figure 3). Among patients with eccentric LVH, dilated LVH was associated with increased all-cause mortality (HR, 2.6; 95% CI, 1.5–4.4; P<0.001), whereas nondilated LVH was not (P=0.617). Among patients with concentric LVH, both nondilated and dilated LVH predicted higher all-cause mortality (HR, 3.1; 95% CI, 1.4–7.1; P=0.007, and HR, 5.4; 95% CI, 2.5–11.9; P<0.001, respectively). In multivariable Cox models, eccentric nondilated LVH remained insignificant (P=0.54), but eccentric dilated LVH and both concentric nondilated and dilated LVH still predicted all-cause mortality (HR, 2.7; 95% CI, 1.6–4.8; P<0.001; HR, 2.7; 95% CI, 1.1–6.6; P=0.026; and HR, 3.2; 95% CI, 1.4–7.5; P=0.007, respectively; Figure 2B).

When adjusting the multivariable Cox models for multiple comparison using Bonferroni correction, eccentric dilated LVH and concentric dilated LVH still predicted all-cause mortality (P=0.002 and 0.027, respectively). However, concentric nondilated LVH did not (P=0.10).

Cardiovascular Mortality With Respect to the 2- and 4-Group Classification Systems of LVH

During follow-up, cardiovascular mortality occurred in 3.5% patients: 5% in the eccentric, 8% in the concentric, and 2% in the group without LVH. When using the 2-group classification system, both eccentric and concentric LVH as time-varying categorical covariates were associated with higher cardiovascular mortality in multivariable Cox models (HR, 2.6; 95%...
When using the new 4-group classification system, cardiovascular mortality occurred in none of the eccentric nondilated, 7% in the eccentric dilated, 6% in the concentric nondilated, and 11% in the concentric dilated LVH group (Table 3). Both eccentric and concentric dilated LVH were significant predictors of higher cardiovascular mortality in multivariable models compared with patients with normal LVM (HR, 3.1; 95% CI, 1.4–6.8; \( P = 0.007 \), and HR, 5.1; 95% CI, 1.4–18.5; \( P = 0.013 \), respectively), whereas concentric nondilated LVH was not (HR, 2.7; 95% CI, 0.7–10.0; \( P = 0.138 \); Figure 2B).

Composite End Point With Respect to the 2 Different Classification Systems of LVH

The composite end point, defined as the first event of stroke, myocardial infarction, heart failure, or cardiovascular death, occurred in 14% of patients with eccentric LVH, 33% with concentric LVH, and 9% in the group without LVH. When using the 2-group classification system, both eccentric and concentric LVH were associated with the increased rate of composite end point (HR, 1.7; 95% CI, 1.1–2.6; \( P = 0.029 \), and HR, 4.1; 95% CI, 2.5–6.7; \( P < 0.001 \), respectively; Figure 2A).

When using the 4-group classification system, the composite end point occurred in 5% in the eccentric nondilated, 21% in the eccentric dilated, 16% in the concentric nondilated, and 26% in the concentric dilated LVH group (Table 3). In multivariable Cox models, eccentric dilated LVH and both concentric nondilated and dilated LVH predicted the composite end point (HR, 1.8; 95% CI, 1.1–2.9; \( P = 0.017 \), and HR, 4.0; 95% CI, 2.3–7.2; \( P < 0.001 \), and HR, 4.1; 95% CI, 2.1–8.0; \( P < 0.001 \), respectively), whereas nondilated eccentric LVH did not (Figure 2B).

Sensitivity Analyses to Account for the Method of Indexation When Defining LVH or Increased Volume in the 4-Group Classification System

In the first sensitivity analysis using LVM/height\(^2\) to define LVH, 130 (13.8%) were categorized as eccentric nondilated, 181 (19.3%) as eccentric dilated, 273 (29.1%) as

| Table 1. Baseline Characteristics Stratified by the Presence of LVH and Geometric Subpatterns |

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal LV Mass (n=233)</th>
<th>Eccentric (n=301)</th>
<th>Concentric (n=405)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nondilated (n=114)</td>
<td>Dilated (n=187)</td>
<td>Nondilated (n=272)</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.2±7.0†‡,§</td>
<td>66.5±6.8</td>
<td>66.0±7.2</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>171 (73.4)†‡,§</td>
<td>26 (22.8)</td>
<td>129 (69.0)§</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>166.8±18.8†‡,‖,‖,§</td>
<td>174.6±21.1</td>
<td>174.8±20.3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>94.7±11.0</td>
<td>95.3±12.0</td>
<td>93.6±12.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3±4.4</td>
<td>25.7±4.5</td>
<td>26.6±4.4</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.92±0.17§,¶</td>
<td>1.75±0.15</td>
<td>1.88±0.19§</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>25 (10.7)</td>
<td>15 (13.2)</td>
<td>18 (9.6)</td>
</tr>
<tr>
<td>Blacks, n (%)</td>
<td>42 (18.0)**,§‡‡</td>
<td>9 (7.9)</td>
<td>18 (9.6)</td>
</tr>
<tr>
<td>Heart rate per min</td>
<td>74±12**,‡‡</td>
<td>70±10</td>
<td>70±12</td>
</tr>
<tr>
<td>Creatinine, mmol/L‡§‡</td>
<td>88.4 (78.0–105.3)</td>
<td>76.0 (67.0–89.0)</td>
<td>88.0 (75.5–104.5)</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>144±11</td>
<td>142±12</td>
<td>143±11</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.5±0.4</td>
<td>1.7±0.5</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.1±1.1</td>
<td>6.3±1.2</td>
<td>5.9±1.2</td>
</tr>
<tr>
<td>Urine albumine/creatinine ratio, mg/mmol‡§§</td>
<td>8.4 (3.4–20.2)‡,‖‖,§§</td>
<td>9.7 (3.3–21.0)</td>
<td>13.2 (5.0–46.2)</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>21.1±7.7†‡‡,‖‖,§§</td>
<td>21.9±8.8</td>
<td>22.5±9.3</td>
</tr>
<tr>
<td>Cornell voltage duration, mm-ms‡‡</td>
<td>2205 (1701–2668)+,§,‖</td>
<td>2622 (2295–2970)</td>
<td>2550 (2240–3150)</td>
</tr>
<tr>
<td>Sokolov–Lyon voltage</td>
<td>29.5±10.5§,‡‡</td>
<td>33.2±10.1</td>
<td>30.9±10.0</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BSA, body surface area; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LVH, left ventricular (LV) hypertrophy; and SBP, systolic blood pressure.

*For comparison among the 4 subgroups of LVH.
†\( P < 0.01 \) vs eccentric dilated.
‡\( P < 0.001 \) vs concentric nondilated.
§\( P < 0.001 \) vs eccentric nondilated.
‖\( P < 0.01 \) vs eccentric dilated.
¶\( P < 0.05 \) vs eccentric nondilated.
#\( P < 0.05 \) vs eccentric dilated.
**\( P < 0.05 \) vs eccentric nondilated.
‡‡\( P < 0.01 \) vs concentric nondilated.
§§Median and first and third quartiles.
‖‖Based on logarithm-transformed data.
concentric nondilated, 133 (13.2%) as concentric dilated, and 222 (23.6%) with normal LVM. The majority of the key findings described above persisted when defining LVH by indexation for height. Eccentric dilated LVH predicted both the composite end point (HR, 1.5; 95% CI, 1.0–2.4; \( P = 0.05 \)) and all-cause mortality (HR, 2.0; 95% CI, 1.1–3.5; \( P = 0.022 \)). However, eccentric nondilated LVH did not (both \( P \geq 0.62 \)).

In the second sensitivity analysis using RWT instead of LV M/EDV \(^{2/3} \) to define concentricity, 160 (17.0%) were categorized as eccentric nondilated, 306 (32.6%) as eccentric dilated, 226 (24.1%) as concentric nondilated, 10 (1.1%) as concentric dilated, and 233 (24.8%) with normal LVM. Most of the key findings described above with concentricity defined by LV M/EDV \(^{2/3} \) persisted when using RWT to define concentricity.

Table 2. Baseline Echocardiographic Measures Stratified by Presence of LVH and Geometric Subpatterns

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal LV Mass (n=233)</th>
<th>Eccentric (n=301)</th>
<th>Concentric (n=405)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondilated (n=114)</td>
<td>Dilated (n=187)</td>
<td>Nondilated (n=272)</td>
<td>Dilated (n=133)</td>
</tr>
<tr>
<td>Total peripheral resistance†</td>
<td>1911 (1642–2260)</td>
<td>1991 (1685–2359)</td>
<td>1828 (1565–2189)‡</td>
</tr>
<tr>
<td>Total peripheral resistance index by BSA, dynes-s-cm(^{-2})-m(^{-1})††</td>
<td>3552 (3170–4318)#</td>
<td>3499 (2556–4107)</td>
<td>3373 (2914–4129)</td>
</tr>
<tr>
<td>Pulse pressure/stroke index (mm Hg/ml per m(^2))†</td>
<td>0.52 (0.40–0.63)§</td>
<td>0.63 (0.52–0.75)</td>
<td>0.50 (0.39–0.67)¶</td>
</tr>
<tr>
<td>Left atrial dimension, cm²</td>
<td>3.7±0.5‡‡,§§</td>
<td>3.8±0.5</td>
<td>4.1±0.5‡‡</td>
</tr>
<tr>
<td>LV mass/BSA</td>
<td>95.4±15.2‡‡,‡‡,§§</td>
<td>113.9±15.6</td>
<td>129.3±15.0‡‡</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>71.7±13.2‡‡,††</td>
<td>81.0±13.6</td>
<td>94.7±13.1‡‡</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.1±1.2**</td>
<td>4.9±1.2</td>
<td>5.5±1.3†</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>65.1±7.3‡‡</td>
<td>64.4±7.5</td>
<td>57.0±7.2‡‡</td>
</tr>
<tr>
<td>Midwall shortening predicted, %</td>
<td>99.1±11.8‡‡,§§</td>
<td>102.1±9.3</td>
<td>106.4±11.9§</td>
</tr>
<tr>
<td>Segmental wall motion abnormalities, n (%)</td>
<td>4 (1.7)††</td>
<td>4 (3.5)</td>
<td>23 (18.3)‖</td>
</tr>
<tr>
<td>Isovolumic relaxation time</td>
<td>110.9±23.4§</td>
<td>112.6±23.9</td>
<td>113.6±21.4</td>
</tr>
<tr>
<td>Concentricity(^{2/3} ), g/mL</td>
<td>7.9±1.0</td>
<td>9.4±0.5</td>
<td>7.9±0.5</td>
</tr>
<tr>
<td>LV mass/height(^{2.7} )</td>
<td>43.6±5.2</td>
<td>51.1±5.6</td>
<td>59.5±9.9</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; and LVH, left ventricular (LV) hypertrophy.

*For comparison among the 4 subgroups of LVH.
†Median and first and third quartiles.
‡\( P <0.05 \) vs eccentric nondilated.
§\( P <0.01 \) vs eccentric nondilated.
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††\( P <0.01 \) vs eccentric dilated.
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‖‖\( P <0.01 \) vs concentric nondilated.
¶¶\( P <0.01 \) vs concentric nondilated.
\( P = 0.022 \).

Figure 2. Hazard ratio and confidence interval from multivariable Cox models for cardiovascular (CV) mortality, the composite end point (CEP), and all-cause mortality in 2-group (A) and 4-group (B) left ventricular hypertrophy (LVH) classification model.
Eccentric dilated LVH significantly predicted both the composite end point (HR, 2.1; 95% CI, 1.4–3.3; P<0.001) and all-cause mortality (HR, 2.6; 95% CI, 1.5–4.5; P<0.001), but eccentric nondilated LVH did not (both P≥0.18).

**New Classification Model Adjusted to LVM/BSA**

To test the independence of the new classification model from simple measurement of LVM/BSA, LVM/BSA was added to the Cox model as a time-varying continuous variable. Eccentric dilated LVH and concentric dilated LVH still predicted all-cause mortality (HR, 2.1; 95% CI, 1.4–3.3; P=0.017, and HR, 3.2; 95% CI, 1.1–9.7; P=0.039, respectively); concentric nondilated LVH was nearly significantly associated with all-cause mortality (HR, 2.4; 95% CI, 1.0–6.0; P=0.060), whereas eccentric nondilated LVH was not (P=0.65). Compared with LVM/BSA, the new model improved net reclassification by 12% for all-cause mortality (P=0.035; see the Data Supplement).

**Discussion**

For the first time, the new 4-group classification of LVH has been assessed and compared with the established 2-group classification of LVH with respect to its ability to predict all-cause and cardiovascular mortality and cardiovascular events in high-risk hypertensive patients receiving systematic antihypertensive treatment. The subclassification of patients with eccentric LVH into groups with normal or increased LV chamber volume revealed that the latter, but not the former, predicted increased risk of all-cause and cardiovascular mortality and cardiovascular events. In contrast, the subclassification of patients with concentric LVH into groups with normal or increased LV chamber volume revealed the association of both dilated and nondilated concentric LVH with poor outcome. The consistent adverse implications of dilated and nondilated concentric LVH, but only dilated eccentric LVH, provide insight into the worse prognosis associated with concentric than eccentric LVH in most but not all studies. Furthermore, the findings were largely independent of differences in LVM/BSA between the subgroups.

Recently, a new 4-group model has been suggested as an alternative to the established 2-group classification of LVH. This new model was developed using MR measurements in a population-based sample with relatively low burden of cardiovascular disease. A recent analysis using this model in high-risk hypertensive patients enrolled in the LIFE trial revealed significant differences in hemodynamic and renal function patterns among the 4 groups despite lack of significant differences among the groups in baseline blood pressure.

There is consistency in the literature linking concentric LVH with poor outcome, whereas published studies report conflicting results on the association between eccentric LVH and outcome. In the present study, the new 4-group classification system of LVH failed to detect associations of nondilated eccentric LVH with all-cause or cardiovascular mortality or overall cardiovascular events. At the same time, dilated eccentric LVH significantly predicted all 3 end points. The difference in outcomes between patients with dilated and nondilated eccentric LVH may help explain the conflicting results of previous reports examining prognostic implications of eccentric LVH, depending on the proportion of patients with dilated versus nondilated eccentric LVH in different study populations.

In the previous report from the Dallas Heart Study, participants with eccentric nondilated LVH, compared with those with eccentric dilated LVH, had higher ejection fraction and lower troponin-T, N-terminal pro-brain natriuretic peptide, and brain natriuretic peptide levels. Although no outcome data were available in the Dallas Heart Study, the authors argued that the biomarker differences might reflect lower pathological cardiac stress and, therefore, portend a better prognosis. Norton

![Figure 3. Survival by left ventricular (LV) geometric patterns. K-M indicates Kaplan-Meier.](image-url)
et al. showed that LV dilatation predicted heart failure in pressure-overload hypertrophy, which might be caused by failure to compensate for the increased pressure. Compared with the nondilated groups, the dilated groups in the present study had increased cardiac output and stroke volume and, therefore, increased wall stress, as well as more segmental wall motion abnormalities. Supporting this finding, although the numbers were small, cardiovascular mortality seemed to be higher in the dilated versus nondilated groups in the present study.

Our results suggest that more refined subclassification of LVH patterns may enhance the prediction of prognosis from readily available echocardiographic or cardiac MRI measurements. The present study also showed that this was independent of LVM index, suggesting that the refined model adds prognostic information beyond simple measurement of LVM.

Sensitivity Analyses Using RWT, or LVM/Height

To verify that the finding persisted irrespectively of indexation method, we performed 2 sensitivity analyses to account for the method of indexation. Using these 2 alternative methods of indexation did not change the finding that nondilated eccentric LVH was at lower risk than the other groups with dilated or concentric LVH.

Hypertension Treatment on Geometric Pattern

Approximately 5 years of antihypertension treatment greatly reduced the prevalence of both nondilated and dilated concentric LVH, with a smaller reduction in eccentric dilated LVH. That hypertension treatment decreased the numbers in the 2 dilated groups suggests that dilatation is often a reversible condition as is increased concentricity as a myocardial adaptation to increased afterload or neurohormonal activation. Because we have shown that 3 subtypes of LVH—eccentric dilated and both concentric patterns—predict cardiovascular events, and that LVM regression has been shown to prevent cardiovascular morbidity and mortality, sufficient antihypertension treatment seems important to avoid the 3 high-risk subtypes of LVH: eccentric dilated and concentric nondilated and dilated. However, more outcome studies on regression of the 3 high-risk subtypes are warranted.

Limitations

We did not investigate outcomes associated with concentric remodeling, which is not captured in the 4-group classification, despite its association with worse outcome compared with patients with no LVH. In the present study, only 4% of non-LVH patients had concentric LV remodeling using LV M/EDV criteria, limiting power to assess its prognostic implications. Furthermore, only the primary end point of all-cause mortality was adjusted for multiple comparisons because of smaller numbers of events or overlap with all-cause mortality. Therefore, the analyses of the other end points and baseline differences should be considered exploratory. Strengths of this study include its performance in a large population of well-characterized hypertensive patients.

The small number of end points in some of the subgroups limited power to verify incremental prognostic ability of the 4-group method in the 2 concentric groups of LVH, in particular using RWT. However, we were still able to show significant differences in the 2 groups of greatest interest in both sensitivity analyses.

Finally, the present study was undertaken in a population of patients with moderate to severe hypertension and electrocardiographic LVH. Other populations need to be evaluated to determine the generalizability of conclusions about the prognostic significance of the 4-group versus traditional 2-group classification of LVH, before the new, more complex classification can be recommended for clinical use.

Conclusions

Hypertensive patients with LVH based on echocardiographic geometric patterns can be reclassified into 4 groups that are at differing risks of all-cause and cardiovascular mortality and a composite end point of major cardiovascular events. Verification of the enhanced prognostic power of the 4-group classification of LVH in other populations is needed before recommending that this more refined approach replace the established classification of LVH into eccentric and concentric subgroups.

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This work was supported by The Danish Heart Association (grant number 10-04-R78-A2962-22582) and INTERREG IVA, the European Regional Development Fund.

Disclosures

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**CLINICAL PERSPECTIVE**

There is consistency in the literature linking concentric left ventricular hypertrophy (LVH) with poor outcome, whereas published studies report conflicting results on the association of eccentric LVH and outcome. Recently, a new 4-group classification system derived by cardiac MRI has been suggested as an alternative to the established 2-group classification of geometric LVH. For the first time, the new 4-group classification of LVH has been assessed and compared with the established 2-group classification of LVH with respect to its ability to predict all-cause and cardiovascular mortality and cardiovascular events. We showed that the subclassification of hypertensive patients with eccentric LVH into groups with normal or increased LV chamber volume revealed that the latter, but not the former, predicted increased risk of all-cause and cardiovascular mortality and cardiovascular events. In contrast, the subclassification of patients with concentric LVH into groups with normal or increased LV chamber volume revealed the association of both dilated and nondilated concentric LVH with poor outcome. The consistent adverse implications of dilated and nondilated concentric LVH, but only dilated eccentric LVH, provides insight into the worse prognosis associated with concentric than with eccentric LVH in most but not all studies. Our results suggest that a more refined subclassification of LVH patterns may enhance the prediction of prognosis from readily available echocardiographic or cardiac MRI measurements. Therefore, it might be clinically important to locate a low-risk group among patients with eccentric LVH, with similar risk of all-cause mortality or cardiovascular events as patients with normal LV mass.
Four-Group Classification of Left Ventricular Hypertrophy Based on Ventricular Concentricity and Dilatation Identifies a Low-Risk Subset of Eccentric Hypertrophy in Hypertensive Patients

Casper N. Bang, Eva Gerdts, Gerard P. Aurigemma, Kurt Boman, Giovanni de Simone, Björn Dahlöf, Lars Køber, Kristian Wachtell and Richard B. Devereux

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Supplement Table. Risk Classification by Models With and Without the New 4 group Classification System for All-cause Mortality

<table>
<thead>
<tr>
<th>Model With LV mass</th>
<th>Model with 4 group classification</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5%</td>
<td>5% to &lt;10%</td>
<td>≥10%</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>No-event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>167 / 19%</td>
<td>3 / 0%</td>
<td>0 / 0%</td>
<td>170 / 20%</td>
<td></td>
</tr>
<tr>
<td>5% to &lt; 10%</td>
<td>95 / 11%</td>
<td>387 / 45%</td>
<td>63 / 7%</td>
<td>545 / 64%</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>0 / 0%</td>
<td>18 / 2%</td>
<td>132 / 15%</td>
<td>150 / 17%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>262 / 30%</td>
<td>408 / 47%</td>
<td>195 / 23%</td>
<td>865 / 100.0%</td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>5 / 7%</td>
<td>0 / 0%</td>
<td>0 / 0%</td>
<td>5 / 7%</td>
<td></td>
</tr>
<tr>
<td>5% to &lt; 10%</td>
<td>4 / 5%</td>
<td>29 / 39%</td>
<td>11 / 15%</td>
<td>44 / 59%</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>0 / 0%</td>
<td>2 / 3%</td>
<td>23 / 31%</td>
<td>25 / 34%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13 / 18.8%</td>
<td>42 / 58.0%</td>
<td>34 / 46%</td>
<td>74 / 100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Reclassification across risk groups defined as <5%, 5% to <10% and ≥10% for all-cause mortality. Numbers in the cells refer to numbers of observed events during follow-up over the percent of observed events of the total number of individuals in each combination of categories.

The NRI was 6.8% for patients who survived, 5.4% for those who died, and 12.2% overall (P=0.035).