Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study)

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Aims Less is known about the relation between in-treatment left ventricular (LV) geometry and risk of cardiovascular events. We assessed LV geometric patterns on baseline and annual echocardiograms as time-varying predictors of the primary composite endpoint (cardiovascular death, stroke, and myocardial infarction) in 937 hypertensive patients with LV hypertrophy during 4.8 years losartan- or atenolol-based treatment in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) echocardiography substudy.

Methods and results LV geometry was determined from LV mass/body surface area and relative wall thickness in combination. At end of the study, 52% of patients with initial LV hypertrophy had normal geometry (P < 0.001). In particular, concentric remodelling was reduced by 82% and concentric LV hypertrophy by 84%. Development of LV hypertrophy was seen in 5%. In Cox regression analyses including LV geometric patterns as time-varying variables and adjusting for treatment, Framingham risk score, race, and time-varying systolic blood pressure, the patterns independently predicted higher risk of primary composite endpoints [HR 2.99 (1.16–7.71) for concentric remodelling, HR 1.79 (1.17–2.73) for eccentric hypertrophy, and HR 2.71 (1.13–6.45) for concentric hypertrophy; all P < 0.05].

Conclusion In hypertensive patients with ECG LV hypertrophy, in-treatment LV geometry by echocardiography adds information on risk of cardiovascular events.

KEYWORDS Hypertension; Left ventricular geometry; Left ventricular hypertrophy; Losartan; Atenolol

Introduction

Left ventricular (LV) hypertrophy is a cardinal manifestation of preclinical cardiovascular disease that strongly predicts cardiovascular events in hypertensive patients as well as in the general population.1,2 Previous publications have suggested that assessment of LV geometry may add prognostic information in hypertensive patients beyond assessment of LV mass alone.1,3,4

Antihypertensive treatment induces individual changes in LV geometry in hypertensive patients. Although lower LV mass during antihypertensive treatment is associated with lower rates of cardiovascular events,5 less is known about the relation between in-treatment LV geometry during aggressive antihypertensive therapy and risk of cardiovascular events. In particular, this has not been addressed prospectively in a large randomized hypertension treatment study.

Thus, the aim of the present analysis was to assess the relation between in-treatment LV geometry and cardiovascular events during randomized losartan- or atenolol-based antihypertensive treatment in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) echocardiography substudy.
Methods

Protocol, patient characteristics, and outcome results in the LIFE echocardiography study and the main LIFE study have been published. The conduct of the LIFE study complied with the Declaration of Helsinki. Approval was obtained from all relevant ethics committees. Patients provided written informed consent.

Patient population

The present analysis was prospectively planned within the LIFE echocardiography study that performed annual echocardiographic follow-up in 960 of the 9149 patients in the parent LIFE trial. The LIFE study randomized hypertensive patients aged 55–80 years with baseline clinic blood pressure 160–200/95–115 mmHg and electrocardiographic LV hypertrophy by Cornell voltage-duration or Sokolow–Lyon voltage criteria to 4.8-year double-blind losartan- or atenolol-based antihypertensive treatment. Among the 960 patients included in the LIFE echocardiography substudy, the present analysis was undertaken within the 937 patients with measurable LV dimensions on the baseline echocardiogram. Compared with patients excluded from the current analysis (n = 23), the present study population had lower body mass index (27.2 ± 4.4 vs. 30.1 ± 6.2 kg/m², P < 0.01), but did not differ in baseline age, blood pressure, gender distribution, race, or prevalence of diabetes mellitus.

Doppler echocardiography

Echocardiograms obtained at baseline and thereafter annually in the LIFE echocardiography study were sent to the Cornell Echocardiography Reading Center for interpretation by an experienced echocardiographer. Reading was performed continuously during the study by readers blinded to study treatment and sequence of the echocardiogram. Left ventricular chamber dimensions and wall thicknesses were measured following the American Society of Echocardiography standards. Relative wall thickness (RWT) was calculated at end-diastole as posterior wall thickness/internal radius, endocardial shortening as the ratio (diastolic–systolic LV internal diameter)/diastolic LV internal diameter, LV ejection fraction by the Teichholz method, and LV mass using an autopsys

Blood pressure, diabetes, and albuminuria

Blood pressure was measured at clinical study visits. Patients were classified as having isolated systolic hypertension if systolic blood pressure was ≥140 and diastolic blood pressure was <90 mmHg, respectively. Baseline Pulse pressure was calculated as the difference between sitting clinic systolic and diastolic blood pressure, and mean blood pressure as sitting diastolic blood pressure plus one-third of pulse pressure. Serum glucose was measured at core laboratories in the USA and Europe from venous blood drawn at clinic visits, with comparability of measurements documented by split-sample determination. Diabetes mellitus was diagnosed by 1985 WHO criteria for fasting and random serum glucose or use of hypoglycaemic medication. Albuminuria was assessed as urinary albumin/creatinine ratio in spot morning urine at baseline and considered present if the ratio exceeded 3.5 mg/mmol.

Statistics

Data management and analysis were performed using SPSS 13.0 (SPSS, Chicago, IL, USA) software. Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Between-group comparisons were made by χ² statistics or unpaired Student’s t-test, as appropriate. In-treatment LV geometry was assessed on annual study echocardiograms until the occurrence of a cardiovascular event in patients who experienced a primary study endpoint, and on all annual study echocardiograms until end of the study in patients who did not experience an endpoint. The pre-specified primary endpoint in the study was a composite endpoint of the first occurrence of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction. Time-varying Cox regression analysis was used to assess the association of baseline and in-treatment LV geometry with the pre-specified composite endpoint of the LIFE study and with individual cardiovascular death, stroke, and myocardial infarction endpoints. The model indicated indicator variables for randomized study treatment and race and baseline LV mass/body surface area, RWT, and Framingham risk score (based on age, gender, diabetes, smoking, and baseline total and high-density lipoprotein cholesterol levels, systolic blood pressure, and LV hypertrophy measured by electrocardiography) as fixed covariates, and in-treatment LV geometric patterns and systolic blood pressure as categorical time-varying covariates. In subsequent models, LV hypertrophy and concentric geometry as time-varying variables or time-varying change in LV mass/body surface area replaced the time-varying LV geometric pattern categories, and time-varying heart rate was added to the covariates. Two-tailed P < 0.05 was considered statistically significant both in univariate and in multivariate analyses.

Results

At baseline, patients in the different LV geometric pattern groups differed significantly in age, systolic blood pressure, and prevalence of albuminuria, whereas gender, race, body mass index, and prevalence of diabetes or isolated systolic hypertension did not differ with LV geometry (Table 1). Aortic regurgitation and history of myocardial infarction or stroke were more prevalent in the groups with LV hypertrophy both at baseline and at end of the study. During 4.8 years of randomized study treatment, LV geometry changed significantly, reducing the prevalences of LV hypertrophy and of concentric remodelling by more than half from baseline to the final study echocardiogram or the last one before an endpoint (Figure 1). Of the 661 patients with eccentric or concentric LV hypertrophy at baseline, 52% had normal geometry at final study echocardiogram (Table 2). In particular, concentric LV hypertrophy was reduced by 84% (Table 2). Furthermore, of the initial 97 patients with concentric remodelling at baseline, 82% had normal geometry. Development of LV hypertrophy was only seen in <5% of patients with initially normal LV mass. Prevalence of LV hypertrophy declined prospectively in both treatment arms, in the Losartan-based group from 72% at baseline and 44% after 1 year to 33% at final event-free study follow-up, and in the Atenolol-based group from...
Normal geometry, concentric LV hypertrophy; E-LVH, eccentric LV hypertrophy; N, antihypertensive treatment. CR, concentric remodelling; C-LVH, concentric LV hypertrophy had significantly higher LV mass/body surface area at final study echocardiogram (P < 0.01) (Table 3).

A total of 105 primary endpoints (combined cardiovascular death, stroke, and myocardial infarction) occurred during the mean 4.8 years of follow-up. Baseline LV geometry did not predict outcome (P > 0.3). To assess the association of in-treatment LV geometry with outcome, time-varying Cox regression models were used. In the first model including concentric geometry and LV hypertrophy together with systolic blood pressure as time-varying covariates and study treatment allocation and Framingham risk score as fixed covariates, in-treatment concentric geometry was associated with higher risk of combined cardiovascular events (HR 2.36 (1.24–4.48), P = 0.031) independent of LV hypertrophy (HR 1.59 (1.06–2.38), P = 0.026) and Framingham risk score (HR 1.05 (1.03–1.07), P = 0.011). In a second model, time-varying LV hypertrophy and concentric geometry were replaced by LV geometric patterns as time-varying categories. In this model, the rate of combined cardiovascular events was three-fold higher with time-varying LV concentric remodelling, 1.8-fold higher with time-varying eccentric LV hypertrophy, and 2.7-fold higher with time-varying concentric LV hypertrophy (all P < 0.05), independent of significant effects of Framingham risk score, race, and time-varying systolic blood pressure (Table 4). Adding history of cardiovascular disease or time-varying heart rate to the variables in the model did not change the results. When evaluating the three individual components of the combined primary endpoint using similar models, risk of stroke was significantly associated with concentric remodelling, whereas risk of cardiovascular death was associated with eccentric LV hypertrophy as well as concentric remodelling, and risk of myocardial infarction with both eccentric and concentric LV hypertrophy, respectively (all P < 0.05) (Table 4). In an additional model, time-varying change in LV mass/body surface area replaced time-varying LV geometry. In this model, larger time-varying reduction in LV mass/body surface area was associated with lower rate of the

Table 1 Characteristics of study population grouped by left ventricular geometric pattern at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal geometry (n = 179)</th>
<th>Concentric remodelling (n = 98)</th>
<th>Eccentric LVH (n = 436)</th>
<th>Concentric LVH (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 7</td>
<td>65 ± 7</td>
<td>66 ± 7*</td>
<td>67 ± 7†</td>
</tr>
<tr>
<td>Women (%)</td>
<td>37</td>
<td>43</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>9</td>
<td>12</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>African American (%)</td>
<td>19</td>
<td>11</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.9 ± 3.7</td>
<td>27.4 ± 4.7</td>
<td>27.4 ± 4.5</td>
<td>27.1 ± 4.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>169 ± 14</td>
<td>169 ± 14</td>
<td>175 ± 15†</td>
<td>177 ± 14†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>97 ± 9</td>
<td>99 ± 9</td>
<td>98 ± 9</td>
<td>99 ± 9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>68 ± 13</td>
<td>70 ± 12</td>
<td>66 ± 12</td>
<td>68 ± 11</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>13</td>
<td>21†</td>
<td>27†</td>
<td>34†</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>123 ± 19</td>
<td>100 ± 14†</td>
<td>161 ± 34†</td>
<td>118 ± 20</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>45 ± 13</td>
<td>34 ± 7†</td>
<td>70 ± 26†</td>
<td>43 ± 14</td>
</tr>
<tr>
<td>LV mass/body surface area (g/m²)</td>
<td>98 ± 11</td>
<td>99 ± 10</td>
<td>134 ± 22</td>
<td>135 ± 24</td>
</tr>
<tr>
<td>RWT</td>
<td>0.38 ± 0.03</td>
<td>0.46 ± 0.03</td>
<td>0.37 ± 0.04</td>
<td>0.49 ± 0.06</td>
</tr>
<tr>
<td>Aortic regurgitation (%)</td>
<td>8</td>
<td>10</td>
<td>16*</td>
<td>17*</td>
</tr>
</tbody>
</table>

LV, left ventricular; LVH, left ventricular hypertrophy; RWT, relative wall thickness.

*P < 0.05; †P < 0.01 vs. normal geometry.
combined primary end-point [HR 0.89 per 10 g/m² reduction in LV mass/body surface area (0.81–0.97), P = 0.009] independent of significant associations with higher baseline LV mass/body surface area and Framingham risk score and lower time-varying systolic blood pressure (all P < 0.01). As illustrated in Figure 2, using findings on the last event-free re-evaluation in individual patients, each pattern of abnormal LV geometry was associated with higher rate of cardiovascular events.

**Discussion**

This study reports on the association of in-treatment LV geometry with cardiovascular events in hypertensive patients participating in a randomized treatment study. The study has several interesting findings adding to previous publications on the prognostic significance of reduction in LV hypertrophy in clinical trials assessed by either serial echocardiograms or electrocardiograms. First, in-treatment LV geometric patterns predict risk of cardiovascular events in hypertensive patients with baseline LV hypertrophy measured by electrocardiography, independent of other potential confounders including age, race, diabetes, total and high-density lipoprotein cholesterol levels, systolic blood pressure, and antihypertensive treatment type. Secondly, in treated hypertensive patients, in-treatment concentric remodelling was significantly associated with cardiovascular mortality and risk of stroke, eccentric LV hypertrophy with cardiovascular mortality and myocardial infarction, and concentric LV hypertrophy with risk of myocardial infarction, respectively.

The finding that in-treatment LV geometric patterns during systematic antihypertensive treatment in the LIFE hypertension treatment study predicted risk of subsequent cardiovascular events is complementary to a previous report by Muiesan et al. In their prospective study of cardiovascular events in a group of 436 hypertensive patients, patients with persistent or new development of concentric LV geometry during follow-up had higher risk of cardiovascular morbidity and mortality. Although the wide confidence limits warrants caution in interpretation of prognostic information by individual in-treatment LV geometric patterns, the present study results, by demonstrating that concentric remodelling as well as eccentric and concentric LV hypertrophy patterns all independently predict risk of combined cardiovascular events (Table 4), adds to previous studies suggesting that evaluation of LV geometry by echocardiography in treated hypertensive patients may add to clinical risk.
Interestingly, as a consequence of higher in-treatment LV mass/body surface area and RWT, in-treatment persistence or development of concentric LV hypertrophy carried a 1.6-fold higher risk for fatal or non-fatal myocardial infarction than the risk associated with eccentric hypertrophy (Table 4). These results are in accordance with previous reports.1,4,29 The particularly high risk of myocardial infarction with concentric LV hypertrophy may be associated with greater myocardial oxygen demand in this geometric group leading to increasing muscle mass-blood supply mismatch and more relative subendocardial ischaemia and lower myocardial contractility in this group, as previously reported.10,31 Furthermore, in hypertensive patients, coronary blood flow reserve has been demonstrated to be particularly low in patients with concentric LV hypertrophy.32–34

The present study also demonstrates that LV geometry changes substantially during aggressive antihypertensive treatment (Figure 1). In particular, the prevalence of the most disadvantageous geometric pattern, concentric LV hypertrophy, was reduced by 82% (Table 3). In fact, already after 1-year treatment, nearly half of the patients with initial abnormal LV geometry had returned to having normal LV geometry. Thus, it is not surprising that LV geometry at baseline did not predict risk of cardiovascular events during ongoing antihypertensive treatment in the present study.

A limitation of the present study is that it was conducted in hypertensive patients complying with the specific inclusion and exclusion criteria used in the main LIFE study.6 In particular, all patients had LV hypertrophy documented on electrocardiograms prior to study enrolment. However, the number of adults who would meet LIFE entry criteria has been estimated at 7.8 million in the first 15 member states of the European Union,35 with nearly as many each in the remainder of Europe and in the USA.

In conclusion, antihypertensive treatment induces major changes of LV geometry in hypertensive patients with electrocardiographic LV hypertrophy, with especially marked reductions in prevalences of concentric LV hypertrophy and remodelling. In the present population, LV geometry at baseline before randomized antihypertensive treatment was started did not independently influence prognosis. In contrast, the presence on in-treatment echocardiograms of each of the three abnormal LV geometric patterns was associated with higher risk of a subsequent combined...
endpoint of cardiovascular death, stroke, and myocardial infarction independent of clinical and demographic confounders of cardiovascular risk in hypertension, including age, gender, race, smoking, blood pressure, and serum cholesterol. One or more of the abnormal LV geometric patterns was also an independent predictor of cardiovascular death, stroke, and myocardial infarction as separate endpoints, despite diminished statistical power due to the smaller number of events in these analyses.

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