Development of Left Ventricular Hypertrophy in Treated Hypertensive Outpatients

The Campania Salute Network

Raffaele Izzo,* Maria-Angela Losi,* Eugenio Stabile, Mai Tone Lönnebakken, Grazia Canciello, Giovanni Esposito, Emanuele Barbato, Nicola De Luca, Bruno Trimarco, Giovanni de Simone

Abstract—There is little information on left ventricular (LV) hypertrophy (LVH) development during antihypertensive treatment. We evaluate incident LVH in a treated hypertensive cohort, the Campania Salute Network registry. We analyzed prospectively 4290 hypertensives (aged 50.3±11.1 years, 40% women) with at least 1-year follow-up, without LVH at baseline. Incident LVH was defined as the first detection of echocardiographic LV mass index ≥47 in women or ≥50 g/m²² in men. During a median 48-month follow-up, 915 patients (21.3%) developed LVH. They were older, more frequently women, and obese (P<0.0001), with initial higher fasting glucose, diastolic and systolic blood pressure, LV mass index, lower heart rate and glomerular filtration rate, longer hypertension history and follow-up, and higher average systolic blood pressure during follow-up (all P<0.05), despite a more frequent treatment with Ca++-channel blockers and diuretics (both P<0.02). At multivariable Cox regression, incident LVH was independently associated with older age, female sex, obesity, higher average systolic blood pressure during follow-up, and initial greater LV mass index (all P<0.02). By categorizing patients according to obesity and sex, obesity independently increased the risk for incident LVH in both sexes (obese versus nonobese men: hazard ratio, 1.34; confidence interval, 1.05–1.72; P=0.019; and obese versus nonobese women: hazard ratio, 1.34; confidence interval, 1.08–1.66; P=0.007). Despite more aggressive antihypertensive therapy, 21% of hypertensive patients develop clear-cut LVH. After adjusting for confounders, risk of incident LVH is particular relevant among women and is further increased by the presence of obesity.

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Key Words: blood pressure ■ echocardiography ■ female ■ hypertension ■ obesity

Left ventricular (LV) hypertrophy (LVH) is a marker of target organ damage in hypertension and helps stratifying cardiovascular risk. The effect of LVH on incident cardiovascular events is independent of conventional risk factors and of coronary artery disease. In selected subsets of nondiabetic patients, LVH also precedes new onset of diabetes mellitus, suggesting that hypertensive target organ damage might be also a marker of complex metabolic changes associated with the evolution of arterial hypertension. Prevention of the development of target organ damage should be, therefore, the main goal of management of arterial hypertension. The most modifiable parameter to achieve this goal is the effective control of blood pressure (BP) using appropriate antihypertensive medications.

There is no information on whether LVH could develop during antihypertensive regimen. However, we recently demonstrated that carotid plaque can develop in a specific patient phenotype, independently of optimal BP control. In that study, we found that risk of incident carotid plaque was higher in older diabetic or smoker patients with chronic renal failure and higher initial intima-media thickness complex, suggesting that earlier antihypertensive management might be more beneficial to reduce and prevent target organ damage.

In the present analysis, we evaluate whether LVH occurs during antihypertensive therapy and whether a specific phenotype can be identified at risk of incident LVH, in a large treated hypertensive population from a regional Italian registry.

Methods

Study Population
Hypertensive patients were selected from the Campania Salute Network (CSN) Registry. The CSN is an open registry collecting information from general practitioners and community hospitals networked with the Hypertension Research Center of the Federico II University, Naples, Italy; and Department of Advanced Biomedical Sciences, University of Bergen, Norway (M.T.L.).

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II University Hospital.13 Signed informed consents were obtained from all participants, to use their anonymized data for scientific purposes. The Ethics Committee of the Federico II University Hospital approved database generation. Detailed characteristics of this population have been previously reported.12–14

Inclusion criteria for the present analysis were no preexisting cardiovascular disease, ultrasound evidence of normal LV mass index (LVMI) at the time of first clinical examination, no secondary forms of hypertension, chronic kidney disease ≤ stage 3 (glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration equation >30 mL/min per 1.73 m²).13

At the time of the present analysis, a total of 14,169 hypertensive patients ≥ 18 years were registered in the CSN. According to the predefined criteria, we sequentially excluded from analysis: patients with prevalent LVH at baseline (n=6303), prevalent cardiovascular disease (n=82), without at least 1 cardiovascular ultrasound examination after 12 months (n=3444), and without chronic kidney disease more than stage 3 (n=50). Thus, the final study population consisted of 4,290 treated hypertensive patients (mean age 50.3±11.1 years and 40% women). The steps for cohort selection were reported in the Figure 1.

Screened preexisting cardiovascular disease included history of previous myocardial infarction, angina, coronary revascularization, stroke, transitory ischemic attack, or congestive heart failure at the time of the admission visit in our outpatient clinic. Preexisting cardiovascular disease was adjudicated by the Committee for Event Adjudication in the Hypertension Research Center and was based on patients’ history, contact with the reference general practitioner, and clinical records documenting the occurrence of the event.

During initial and follow-up visits, BP, heart rate (HR), body mass index, fasting glucose, and lipid profile were measured by standard methods. All hypertensive patients of the network underwent baseline and follow-up echocardiograms in our Hypertension Research Center. Follow-up period was considered from the initial visit to the last available clinical assessment or the time of first evidence of LVH. Because these patients did not present with LVH at baseline, similar to what we reported for carotid ultrasound, the follow-up echocardiographic controls were decided at discretion of their doctors.

The study was approved by the Ethical Committee of the Federico II University of Naples, and all subjects gave written informed consent. In this study adheres to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Measurements and Definitions

Diabetes mellitus was defined according to 1997 American Diabetes Association criteria (fasting plasma glucose >125 mg/dL or antidiabetic treatment).16 Obesity was defined as a body mass index ≥ 30 kg/m². Good BP control was defined as office BP values <140 (systolic) and <90 mm Hg (diastolic).7

Systolic and diastolic BP were measured by standard aneroid sphygmomanometer after 5 minutes rest in the supine position, according to current guidelines. Three BP measurements were obtained in the sitting position at 2-minute intervals. For data analysis, we used both BP measurements taken at the first clinical assessment (baseline) and the average of all BP measurements from follow-up visits (average BP during follow-up).10

Echocardiography

All echocardiograms were performed in the Hypertension Research Center of the Federico II University of Naples; were recorded on digital formats, using commercial machines and a standardized protocol; and were digitally mastered and read offline by 1 expert reader under the supervision of an experienced senior faculty member, using dedicated workstations (MediMatic, Genova, Italy). Measurements were made according to the American Society of Echocardiography/European Association of Echocardiography Recommendations.15

LV mass was calculated from a necropsy-validated formula18 and normalized for height in meters to the power of 2.7 (LVMI).12,19 LVH was defined as LVMI ≥ 47 g/m² in women and ≥ 50 g/m² in men.12 Relative wall thickness, as the index of concentricity, was computed by posterior wall thickness divided by LV radius.

Statistical Analysis

Data were analyzed using IBM-SPSS (version 23.0; IBM, Chicago, IL) and expressed as mean±1 SD. Variables not normally distributed were log transformed and expressed as median and interquartile range. Descriptive baseline comparison between patients with or without evidence of follow-up LVH was performed using / test. Unadjusted prevalence of specific conditions was compared using the χ² distribution and Monte Carlo simulation to generate exact P values.

To account for therapy, single classes of medications, including antiangiotensin system (anti-renin–angiotensin system, ie, ACE inhibitors and AT1 receptor antagonists), calcium channel blockers, β-blockers, and diuretics, were dichotomized according to their overall use during the individual follow-up, based on the frequency of prescriptions during the control visits during the time of follow-up. All medications prescribed for >50% of control visits were given a higher rank in multivariable analyses. This method to account for therapy during the follow-up has been previously reported.6,20

Incident LVH was analyzed by Cox regression analysis, including covariates statistically different at the exploratory analysis, using a stepwise backward building procedure. Thus, incident LVH was analyzed adjusting for age, sex, obesity, duration of hypertension, diabetes mellitus, initial BP and HR, average follow-up systolic BP and HR, LVMI, and glomerular filtration rate. A sex–obesity interaction term was finally forced in the equation model produced by the backward procedure. Similar Cox backward modeling was run, replacing sex and obesity with a 4-group nominal variable: nonobese man, obese man, nonobese woman, and obese woman. Multiple imputation was used to replace missing values. This procedure results in valid statistical inferences that properly reflects the uncertainty because of a missing value.21 The null hypothesis was rejected at a 2-tailed α-value of ≤ 0.05.

Finally, using a similar approach as previously reported,20 we ran a logistic equation providing the 4-year probability of incident LVH according to the value of main independent predictors. Thus, we used categories of age (40 and 60 years), systolic BP control during follow-up (120 and 140 mm Hg), presence or absence of obesity, and the first or last tertile of sex-specific LVMI.

Results

During a median follow-up of 47.5 months (interquartile range 26.8–85.9), LVH was found in 915 patients (21.3%). Patients...
with incident LVH were older, more frequently female, obese, and diabetic and exhibited lower glomerular filtration rate, longer duration of hypertension, higher initial systolic and diastolic BP, lower HR, and a slightly longer follow-up (Table 1).

During follow-up, the mean value of systolic BP collected during the control visits was higher and the mean HR lower in patients who developed LVH (Table 1).

Patients with incident LVH were prescribed more Ca++-channel blockers, diuretics and calcium channel blocker-anti-renin–angiotensin system in combination, resulting in a higher number of antihypertensive medications (Table 2). However, optimal BP control was more frequent in patients maintaining normal LV mass index than in those developing LVH (Table 2). At baseline, 39% of patients without incident LVH and 36% of patients with incident LVH were untreated (p=ns).

Table 1 displays also parameters of LV geometry. Patients developing LVH exhibited greater initial LVM but similar relative wall thickness.

Cox regression analysis revealed that hazard of incident LVH was substantially greater in women and obese individuals, independently of significant effect of older age, higher average systolic BP during follow-up, lower average HR during follow-up, and higher initial LVMi (Table 3; all P<0.005), with negligible influence of duration of hypertension, initial BP, glomerular filtration rate, and diabetes mellitus and no effect of the sex–obesity interaction term.

Table 1. Baseline Characteristics, Initial Markers of Preclinical Cardiovascular Disease and Ultrasound Cardiac Parameters in Patients Who Did or Did Not Develop Incident LVH During Follow-Up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without Incident LVH, n=3375</th>
<th>With Incident LVH, n=915</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49.3±11.2</td>
<td>53.7±10.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>38.2</td>
<td>44.4</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4±3.5</td>
<td>27.4±3.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Obesity, y</td>
<td>14.5</td>
<td>21.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, y</td>
<td>5.9</td>
<td>7.8</td>
<td>0.033</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>95.4±18.8</td>
<td>97.9±20.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>205.5±39.3</td>
<td>207.3±38.2</td>
<td>0.243</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>50.8±12.8</td>
<td>50.7±12.8</td>
<td>0.841</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>130.9±75.1</td>
<td>132.9±70.9</td>
<td>0.461</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.4±0.4</td>
<td>4.4±0.4</td>
<td>0.608</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.1±1.4</td>
<td>5.0±1.4</td>
<td>0.219</td>
</tr>
<tr>
<td>GFR EPI, mL/min per 1.73 m²</td>
<td>92.6±13.5</td>
<td>90.5±12.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>4.8±5.9</td>
<td>6.0±6.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline SBP before therapy prescribed in our center, mmHg</td>
<td>154.3±18.2</td>
<td>156.1±18.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Baseline DBP before therapy prescribed in our center, mmHg</td>
<td>98.7±9.8</td>
<td>99.4±9.3</td>
<td>0.071</td>
</tr>
<tr>
<td>Baseline HR before therapy prescribed in our center, bpm</td>
<td>75.4±11.7</td>
<td>73.9±10.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean SBP during FU, mmHg</td>
<td>134.6±10.8</td>
<td>136.9±11.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean DBP during FU, mmHg</td>
<td>84.5±6.8</td>
<td>84.6±6.6</td>
<td>0.529</td>
</tr>
<tr>
<td>Mean HR during FU, bpm</td>
<td>75.3±11.7</td>
<td>73.8±10.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Follow-up echo study, mo; median (IQR)</td>
<td>48.0 (26.7–86.4)</td>
<td>44.7 (25.7–80.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoke habit, %</td>
<td>29.9</td>
<td>19.5</td>
<td>0.936</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.37±0.03</td>
<td>0.38±0.03</td>
<td>0.126</td>
</tr>
<tr>
<td>LVM, g</td>
<td>171.0±29.7</td>
<td>178.5±29.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVMi, g/m²⁷</td>
<td>40.6±4.8</td>
<td>44.5±3.6</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index, DBP, diastolic blood pressure; FU, follow-up; GFR EPI, glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration equation; HR, heart rate; IQR, interquartile range; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; and SBP, systolic blood pressure.

Table 2. Antihypertensive Drugs Prescribed During the Follow-Up in Patients Who Did or Did Not Develop Incident LVH During Follow-Up

<table>
<thead>
<tr>
<th>Antihypertensive Drugs and BP Control During Follow-Up</th>
<th>Without Incident LVH, n=3375</th>
<th>With Incident LVH, n=915</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-RAS, %</td>
<td>59.5</td>
<td>60.6</td>
<td>0.545</td>
</tr>
<tr>
<td>CCB, %</td>
<td>17.1</td>
<td>23.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>25.0</td>
<td>23.5</td>
<td>0.335</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>34.0</td>
<td>38.2</td>
<td>0.019</td>
</tr>
<tr>
<td>CCB+anti-RAS, %</td>
<td>10.2</td>
<td>14.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Antihypertensive meds, n</td>
<td>1.4±1.0</td>
<td>1.5±1.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Proportion of optimal BP control, %</td>
<td>64.9</td>
<td>57.9</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CCB, calcium channel blocker; LVH, left ventricular hypertrophy; and RAS, renin–angiotensin system.

Table 3. Proportional Hazard for Incident LVH, by Stepwise Backward Procedure With Forced Sex–Obesity Interaction

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Sig.</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.0001</td>
<td>1.03</td>
<td>1.02</td>
</tr>
<tr>
<td>Sex, W</td>
<td>0.0001</td>
<td>2.08</td>
<td>1.74</td>
</tr>
<tr>
<td>Average follow-up systolic BP, ×5 mmHg</td>
<td>0.008</td>
<td>1.04</td>
<td>1.01</td>
</tr>
<tr>
<td>Average follow-up heart rate, bpm</td>
<td>0.015</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Obesity, y</td>
<td>0.003</td>
<td>1.28</td>
<td>1.09</td>
</tr>
<tr>
<td>LV mass index, ×5 g/m²⁷</td>
<td>0.0001</td>
<td>2.23</td>
<td>2.10</td>
</tr>
<tr>
<td>GFR EPI, mL/min×1.73 m²</td>
<td>0.078</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Interaction sex×obesity</td>
<td>0.814</td>
<td>1.04</td>
<td>0.75</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CI, confidence interval; GFR EPI, glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration equation; HR, hazard ratio; LV, left ventricular hypertrophy; and W, women.
Figure 2 makes visually evident the importance of female sex and obesity to explain the incidence of LVH, after adjusting for the variables displayed in Table 3.

The calculated 4-year probability of incident LVH in association with different levels of the main covariates (age, sex, obesity, average follow-up systolic BP, and categories of baseline LV mass) was reported in the Figure 3.

**Discussion**

There is a robust evidence that treatment of hypertension can induce regression of LVH, an evidence gained from randomized clinical trials and corresponding meta-analyses, but there are no data on the risk of development of LVH in treated hypertensive patients in a real-world context.

Our study demonstrated that

1. LVH can develop frequently in patients with hypertension (≈1 of 5), despite pharmacological treatment,
2. obesity, poor BP control during follow-up, and greater values of initial LV mass index characterize the cardiovascular phenotype of patients who will develop LVH, without detectable effect for initial BP, duration of hypertension, and renal function, and
3. risk of incident LVH during antihypertensive therapy is substantially greater in women than in men, irrespective of the presence of obesity and other adverse features.

In our registry of hypertensive patients, LVH developed in the 23% of cases. Data from the CARDIA study (Coronary Artery Risk Development in Young Adults) showed an LVH incidence of 20% in subjects from general population at a follow-up 25 years, and this phenomenon, even if attenuated, is also described in some randomized controlled trial (eg, ONTARGET and TRANSCEND trials). The fact that in our hypertensive patients LVH develops early throughout follow-up confirms that hypertensive patients are at faster and greater risk to develop it.

Our results demonstrate that the treatment of hypertension could reduce, but certainly does not eliminate, the risk of progression to LVH. Interestingly, the hazard of incident LVH is particularly high for the highest values of LV mass index, indicating that the possibility to prevent development of clear-cut LVH is a function of the preexisting involvement. This finding parallels previous evidence that the probability of developing carotid plaques in a population sample from the CSN is strictly related to the magnitude of initial carotid intima-media thickness. Also interesting is that the subsample of CSN participants with true resistant hypertension was also characterized by the highest severity of target organ damage. But even...
excluding resistant hypertension, BP in patients with target organ damage is much more difficult to control,\textsuperscript{2,6} despite a more aggressive therapy.\textsuperscript{25}

Taken altogether, these findings strongly suggest that aggressive antihypertensive management should be adopted as soon as possible to optimally control BP and prevent development of target organ damage\textsuperscript{26} because once hypertensive target organ damage is advanced, slowing down progression might be difficult,\textsuperscript{27} especially in a real-world context, where coexistent risk factors are likely to be present.

Specifically, in our analysis, in addition to the highest level of initial LVMi, paralleled by the suboptimal BP control during the follow-up, female sex and obesity play a significant role in developing LVH, despite antihypertensive therapy and independently of the class of medications, indicating that obesity might be particularly harmful in women.

Cross-sectional studies reported that the prevalence of LVH in hypertensive patients goes from 11.7\% in normal weight subjects to 48.4\% in obese hypertensive patients.\textsuperscript{28} However, longitudinal studies to assess the effect of obesity on development of hypertensive LVH are scarce. In a study of 727 young-to-middle age, untreated subjects screened for stage 1 hypertension and followed up for 8 years, obesity was associated with both incident sustained hypertension and LVH.\textsuperscript{29} There is also scattered evidence that reduction of body mass index has favorable effects on reduction of LVH and that LVH is a distinctive characteristics in metabolic syndrome even in the absence of arterial hypertension.\textsuperscript{32}

In the context of a population of hypertensive patients, obesity is a deleterious condition, substantially increasing the chance to develop LVH. Thus, obesity should be managed contextually to the antihypertensive therapy, especially in women, at least with appropriate intervention on lifestyle.\textsuperscript{33}

Hypertensive women exhibit a risk to develop LVH that is twice the risk in men. Previous studies have reported sex differences in LV adaptation to the increased chronic workload in arterial hypertension.\textsuperscript{34,35} In the LIFE study at the end of follow-up, hypertensive women with initial electrocardiographic LVH exhibit residual LVH more often than men, despite aggressive antihypertensive therapy.\textsuperscript{36} In the cohort of the Strong Heart Study, women exhibit greater LVMi than men, a difference substantially amplified by the copresence of obesity and independent of several confounders.\textsuperscript{37} Not surprisingly, hypertensive women with LVH have an increased risk of incident heart failure with preserved ejection fraction,\textsuperscript{38} and the reduction of risk parallels decrease in electrocardiographic LVH during antihypertensive treatment.\textsuperscript{39} The evidence that in women development of LVH occurs with higher likelihood than in men might potentially help better understanding the progression toward heart failure with preserved ejection fraction, through the identification of an intermediate step (development of LVH) that might help programs of primary prevention.\textsuperscript{40} The possible mechanism of this phenomenon is suggested by Lam et al,\textsuperscript{41} who underline that antihypertensive therapy reduces arterial and ventricular stiffness, enhances ventricular–arterial coupling, reduces cardiac work, and improves LV efficiency, systolic, and diastolic function. The authors conclude that the attenuated response in women and obesity suggests less reversible abnormalities in these groups, which might be linked to the development of heart failure with preserved ejection fraction.

**Perspectives**

Despite efficacious antihypertensive therapy, a relevant number of hypertensive patients develop LVH during follow-up. After adjusting for confounders, including BP control during follow-up, risk of development of LVH is particularly high in women and in obese individuals. Efforts should be addressed to a better integrated approach in terms of treatment and management, including attention to metabolic risk factors, namely obesity, as well as to timing to issue pharmacological therapy, to prove definitively that earlier therapy is a useful strategy.

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**Disclosures**

None.
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### Novelty and Significance

**What Is New?**

- Left ventricular hypertrophy develops in hypertensive patients despite aggressive antihypertensive therapy and good blood pressure control.

**What Is Relevant?**

- Antihypertensive therapy is not sufficient to prevent the development of left ventricular hypertrophy in real-life contexts, when other stimuli co-exist with hypertension. Specifically, female sex and obesity are potent spurs to induce development of left ventricular hypertrophy, in treated hypertensive patients.

**Summary**

Tailoring proper therapy to reduce blood pressure might be not sufficient to prevent target organ damage without controlling obesity, especially in women.
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