Left Ventricular Hypertrophy Reversal and Prevention of Diabetes
Two Birds With One Stone?

Giuseppe Schillaci, Matteo Pirro, Elmo Mannarino

Left ventricular hypertrophy (LVH) is a strong and independent herald for cardiovascular morbidity and mortality in hypertension. Among the many proposed indexes of hypertensive target-organ damage, LVH stands out as the only available marker of preclinical cardiovascular disease of which the treatment-induced regression has been unequivocally associated to a better prognosis over the few next years, even after accounting for the confounding effect of treatment-induced blood pressure reduction. As summarized in the Table, LVH regression has been shown to have a favorable effect on a wide array of adverse cardiovascular outcomes.

In the present issue of Hypertension, Okin et al. suggest a novel potential benefit of LVH reversal by demonstrating for the first time a relation between time-varying electrocardiographic LVH and the subsequent development of diabetes. In a large cohort of 7998 nondiabetic hypertensive people with hypertensive LVH drawn from the Losartan Intervention for Endpoint Reduction in Hypertension Study, which was examined prospectively for an average of 4.6 years, regression or persistent absence of LVH on the ECG during antihypertensive treatment was associated with a lower rate of new-onset diabetes. This might be considered in part an anticipated finding, given that treatment with losartan had already been shown in the Losartan Intervention for Endpoint Reduction in Hypertension Study to be more effective than atenolol in reducing both LVH and the incidence of new diabetes. Not unexpectedly, adjustment for treatment arm and a number of other confounding variables, including baseline serum glucose concentration, baseline and in-treatment blood pressure levels, Framingham risk score, and body mass index, reduced the size of the favorable effect of LVH reversal on the subsequent risk of developing diabetes. However, regression or persistent absence of LVH remained independently related to a 26% lower risk of incident diabetes also in a fully adjusted multivariate regression model (odds ratio: 0.74; 95% CI: 0.58 to 0.93; P=0.011).

The possibility to prevent the occurrence of diabetes among hypertensive subjects is a topic of considerable epidemiological relevance. The unprecedented worldwide escalation in the prevalence of diabetes and obesity during the past 20 years has been recognized as one of the most significant public health hazards for the near future. Hypertension is frequently accompanied by insulin resistance and represents a condition at particularly high risk of developing type 2 diabetes. Moreover, treatment with some antihypertensive drug classes has been linked to an increased risk of developing diabetes. The importance of the issue is underscored by the high incidence of new-onset diabetes among nondiabetic hypertensive subjects, which was ~1.5 per 100 patient-years in the Losartan Intervention for Endpoint Reduction in Hypertension Study.

A recent analysis of the Valsartan Antihypertensive Long-term Use Evaluation Trial showed that patients who develop diabetes during antihypertensive treatment have cardiac morbidity intermediate between those patients with diabetes at baseline and those who never had diabetes. The results of this large, prospective study confirm that new-onset diabetes should not be regarded as a prognostically irrelevant incidental finding in the course of antihypertensive treatment and underscores the importance of attempts aimed at preventing the occurrence of diabetes in hypertensive patients. The Okin et al. article reports an epidemiological association, but its potential mechanisms remain speculative. Why should treatment-induced regression of LVH decrease the risk of developing diabetes? Among possible explanations, LV mass and its changes might serve as markers of microvascular resistance, which may play a role in determining insulin resistance. Importantly, renin-angiotensin-aldosterone system blockade, which has been associated with left ventricular mass reduction in several trials, improves insulin sensitivity both by reducing vascular resistance in skeletal muscles, thus facilitating glucose and insulin delivery to insulin-sensitive tissues and peripheral glucose use, and by promoting differentiation of preadipocytes into adipocytes as a result of increased adiponectin levels. Adiponectin inhibits hypertrophic signaling in the myocardium, implying that plasma levels of this adipocytokine may represent an important link between left ventricular mass and insulin sensitivity. Also, increased sympathetic activity and its modulation by antihypertensive treatment might be of relevance in explaining the relation between LVH and insulin resistance. Treatment of hypertensive nondiabetic patients with losartan was associated with a 30% increased glucose disposal rate during a euglycemic hyperinsulinemic clamp, whereas plasma norepinephrine decreased by 40%, suggesting that angiotensin-receptor blockers may improve insulin sensitivity in essential
hypothesis also by a sympatholytic effect.\textsuperscript{10} The antihypertensive effects of renin-angiotensin-aldosterone system blocking agents might be involved both in LVH regression and in hampering insulin resistance.

On the other hand, reverse causation cannot be discarded. It has been demonstrated recently in the Losartan Intervention for Endpoint Reduction in Hypertension Study that hypertensive patients with diabetes have less regression of electrocardiographic LVH in response to antihypertensive therapy than patients without diabetes.\textsuperscript{11} Thus, those subjects in whom regression of LVH was not achieved during treatment might already have glucose metabolism abnormalities, which, although not fulfilling the full-blown definition of diabetes, expose those individuals to a high risk of becoming diabetic.

There are a few caveats, however, for this analysis. Okin et al\textsuperscript{9} did not compare the incidence of diabetes in 2 well-defined groups of subjects who had or had not achieved regression of LVH. Instead, a model was used in which LVH was considered as a time-varying covariate. In this model, assignment to LVH category was updated at the time of each ECG based on the Cornell product. Because LVH could be found in some, but not all, of the visits during follow-up in individual patients, patients moved from 1 category (LVH) to another (no LVH) at different times.

Models that treat risk factors as time-varying covariates are particularly suitable to characterize risk associations over time by accounting for the changing levels of risk factors and have the advantage to maximize the number of outcome events and the power of the study. However, this approach is different from comparing 2 well-defined groups that have or have not obtained regression of LVH. For instance, the Kaplan-Meier survival curves displayed in the figure of the article by Okin et al\textsuperscript{9} do not refer to 2 groups with or without LVH regression. Rather, individual patients may be variably included in 1 of the 2 curves at different times during follow-up. Therefore, the study allows us to conclude that in-treatment LVH status is associated with the subsequent rate of developing diabetes and should not be intended as a study aimed at assessing prospectively whether treatment-induced LVH regression may diminish the future incidence of diabetes. As such, this should be considered as a hypothesis-generating study rather than a definite proof of evidence.

Despite the above limitations, the study by Okin et al\textsuperscript{9} extends our knowledge and understanding of the importance of LVH reversal by showing the beneficial metabolic effects of treatment-induced regression of LVH in a large series of patients with hypertensive heart disease. Observations from this trial should help to make way for further studies aimed at exploring the potential of LVH regression in preventing new-onset diabetes and the underlying pathophysiological mechanisms.

### Disclosures

None.

### References


### Table. Beneficial Effects of LVH Regression Induced by Antihypertensive Treatment in Individual Studies or Meta-Analyses of Prospective Studies Carried Out in Hypertensive Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Reference</th>
<th>LVH Detection</th>
<th>Analysis</th>
<th>Risk Reduction (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular morbid events</td>
<td>Verdecchia et al\textsuperscript{2}</td>
<td>Echo</td>
<td>Univariate*</td>
<td>59 (22 to 79) for LVH regression</td>
</tr>
<tr>
<td></td>
<td>Okin et al\textsuperscript{3}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>14 (10 to 18) for 1-SD CP reduction</td>
</tr>
<tr>
<td></td>
<td>Devereux et al\textsuperscript{4}</td>
<td>Echo</td>
<td>Multivariate</td>
<td>22 (6 to 35) for 1-SD LV mass reduction</td>
</tr>
<tr>
<td>Stroke</td>
<td>Okin et al\textsuperscript{3}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>10 (4 to 16) for 1-SD CP reduction</td>
</tr>
<tr>
<td></td>
<td>Devereux et al\textsuperscript{4}</td>
<td>Echo</td>
<td>Multivariate</td>
<td>24 (4 to 40) for 1-SD LV mass reduction</td>
</tr>
<tr>
<td></td>
<td>Verdecchia et al\textsuperscript{5}</td>
<td>Echo</td>
<td>Multivariate</td>
<td>64 (15 to 85) for LVH regression</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Okin et al\textsuperscript{3}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>10 (2 to 18) for 1-SD CP reduction</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>Okin et al\textsuperscript{3}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>22 (17 to 27) for 1-SD CP reduction</td>
</tr>
<tr>
<td></td>
<td>Devereux et al\textsuperscript{4}</td>
<td>Echo</td>
<td>Multivariate</td>
<td>38 (18 to 53) for 1-SD LV mass reduction</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>Wachtell et al\textsuperscript{6}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>19 (10 to 27) for 1-SD CP reduction</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Okin et al\textsuperscript{7}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>23 (17 to 29) for 1-SD CP reduction</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Okin et al\textsuperscript{8}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>12 (3 to 20) for 1-SD CP reduction</td>
</tr>
<tr>
<td>New-onset diabetes mellitus</td>
<td>Okin et al\textsuperscript{9}</td>
<td>EKG</td>
<td>Multivariate</td>
<td>26 (7 to 42) for LVH regression or absence</td>
</tr>
</tbody>
</table>

*Echo indicates echocardiography; EKG, electrocardiography; CP, Cornell product.


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