In-Treatment Resolution or Absence of Electrocardiographic Left Ventricular Hypertrophy Is Associated With Decreased Incidence of New-Onset Diabetes Mellitus in Hypertensive Patients

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study

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Abstract—Treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy with losartan-based therapy is associated with lower incidence of diabetes mellitus and greater regression of hypertrophy than atenolol-based therapy. However, whether in-treatment resolution or continued absence of electrocardiographic hypertrophy is independently associated with decreased incidence of diabetes is unclear. Electrocardiographic hypertrophy was evaluated over time in 7998 hypertensive patients without diabetes at baseline in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study who were treated with losartan- or atenolol-based regimens and followed with serial electrocardiograms and blood pressure determinations. Electrocardiographic hypertrophy was defined using gender-adjusted Cornell voltage-duration product criteria \( \geq 2440 \text{ mm} / \text{ms} \). During mean follow-up of 4.6±1.2 years, diabetes developed in 562 patients (7.0%). In a Cox model adjusting for treatment assignment, in-treatment resolution or continued absence of Cornell product hypertrophy was associated with a 38% lower risk of new diabetes (HR 0.62, 95% CI 0.50 to 0.78). After adjusting for the association of new diabetes with prior antihypertensive treatment, baseline glucose, and Framingham risk score, baseline and in-treatment systolic and diastolic pressure, HDL, uric acid, and body mass index, and the decreased incidence associated with losartan-based therapy, in-treatment continued absence, or resolution of Cornell product hypertrophy remained associated with a 26% lower risk of new diabetes (HR 0.74, 95% CI 0.58 to 0.93). Thus, compared with presence of hypertrophy by Cornell product criteria during antihypertensive treatment, resolution or continued absence of Cornell product hypertrophy is associated with a lower incidence of diabetes, even after adjusting for the impact of treatment with losartan and other risk factors for diabetes. (Hypertension. 2007;50:984-990.)

Key Words: diabetes mellitus ■ electrocardiography ■ hypertension ■ hypertrophy ■ prognosis

Diabetes mellitus is an established risk factor for cardiovascular (CV) disease and is associated with increased risks of both all-cause and CV mortality.\(^1\)\(^-\)\(^5\) There is a well-established association between blood pressure and insulin resistance,\(^6\)\(^-\)\(^9\) although this relationship is attenuated by obesity\(^7\)\(^8\) and affected by age.\(^8\) Moreover, hypertension and diabetes frequently coexist\(^10\) with the combination associated with a 2- to 3-fold increased risk of CV disease,\(^4\)\(^,\)\(^5\)\(^,\)\(^11\)\(^,\)\(^12\) and hypertensive patients are at an increased risk of developing diabetes\(^4\)\(^,\)\(^13\)\(^,\)\(^14\) that may be modulated by concomitant antihypertensive therapy.\(^13\)\(^-\)\(^21\)

Diabetes is a well-established stimulus for left ventricular hypertrophy (LVH)\(^22\)\(^,\)\(^23\) that may, in part, reflect the independent effects of insulin resistance on LV growth.\(^24\) In addition, there appear to be synergistic effects of hypertension and diabetes on LV structure and function,\(^23\)\(^,\)\(^25\) with a number of studies finding increased prevalence and severity of LVH in hypertensive patients with diabetes than in those without.\(^4\)\(^,\)\(^5\)\(^,\)\(^22\)\(^,\)\(^23\) The presence and severity of LVH are well-established risk factors for CV morbidity and mortality.\(^4\)\(^,\)\(^26\)\(^-\)\(^32\) and regression of LVH has been associated with lower likelihoods of CV morbidity and mortality in the overall Losartan Intervention For Endpoint reduction in hypertension (LIFE) study population.\(^31\)\(^-\)\(^33\) However, despite a greater severity of ECG LVH at baseline, hypertensive patients with established diabetes in the LIFE study had less regression of ECG LVH than patients without diabetes and did not derive...
prognostic benefit from regression of ECG LVH.5 These findings, taken together with the increased long-term CV risk associated with the development of new diabetes in hypertensive patients,4 suggest that prevention of the development of new diabetes in hypertensive patients may be of prognostic benefit.

The relationship of the presence and severity of hypertrophy to the development of new diabetes is less clear. Although Verdecchia et al found a weak univariate association between baseline presence of ECG LVH and subsequent development of new diabetes,4 this relationship was no longer significant in multivariable analyses. In the LIFE study, treatment of hypertensive patients with ECG LVH with losartan-based therapy was associated with a lower incidence of diabetes mellitus and greater regression of ECG LVH than atenolol-based therapy.18,21,32–34 However, whether in-treatment resolution of ECG LVH is independently associated with a decreased incidence of diabetes is unclear. Accordingly, the present study examined whether resolution or continued absence of ECG LVH by Cornell product criteria during antihypertensive therapy is associated with a decreased incidence of new diabetes in the LIFE study, independent of the effects of blood pressure change, treatment type and of other risk factors for diabetes.

Methods

Subjects

The LIFE trial21,31–35 enrolled hypertensive patients with ECG LVH by Cornell voltage-duration product19,32 or Sokolow-Lyon voltage criteria20 on a screening ECG in a prospective double-blind randomized study large enough (n=9193) to have sufficient power (80%) to detect a difference of at least 15% in the incidence of combined CV morbidity and mortality with use of losartan as opposed to atenolol. The study was approved by all ethics committees concerned. As previously described,21,31–35 eligible patients for LIFE were men and women aged 55 to 80 with previously untreated or treated essential hypertension with mean seated blood pressure in the range 160 to 200/95 to 105 mm Hg after 1 and 2 weeks on placebo who had not suffered a myocardial infarction or stroke within 6 months and did not have known LV ejection fraction <40% or require treatment with a β-blocker, angiotensin converting enzyme-(ACE)-inhibitor, or angiotensin receptor-(AT1)-antagonist. All participants gave informed written consent. The 1195 patients with diabetes mellitus at study baseline39 were excluded, leaving 7998 patients who were at risk of developing diabetes to be included in the present study.

Treatment Regimens

Blinded treatment was begun with losartan 50 mg or atenolol 50 mg daily and matching placebo of the other agent, with a target blood pressure of 140/90 mm Hg or lower. During clinic visits at frequent intervals for the first 6 months and at 6-month intervals thereafter, study therapy could be uptitrated by addition of hydrochlorothiazide 12.5 mg, followed by increase in blinded losartan or atenolol to 100 mg daily. In patients whose pressure was still not controlled, ACE-inhibitors) was added to the double-blind treatment regimen.21

Electrocardiography

ECGs were obtained at study baseline, at 6 months, and at yearly follow-up intervals until study termination or patient death. ECGs were interpreted at the Core Laboratory at Sahlgrenska University Hospital/Ostra in Göteborg, Sweden as previously reported in detail.21,31–34 The product of QRS duration times the Cornell voltage combination (RV5+SV1, with 6 mm added in women36,37) was used with a threshold value of 2440 mm²ms to identify LVH.32 In alternative analyses, ECG LVH was defined by Cornell voltage criteria (>20 mm in women and >28 mm in men) or by Sokolow-Lyon voltage criteria (Sv1+RV5 >38 mm). In addition, the presence or absence of ECG strain as a dichotomous variable was visually assessed at Helsinki University Central Hospital as previously described40,41 on baseline and year-1 ECGs in a subset of 7174 patients. Repolarization abnormalities in leads V5 and/or V6 were considered consistent with the presence of typical strain when there was a downsloping convex ST segment with an inverted asymmetrical T-wave with polarity opposite to the main QRS deflection.40,41

End Point Determination

New-onset diabetes was initially defined according to the 1985 World Health Organization (WHO) criteria32 as previously described.43 Because new recommendations for the diagnosis of non–insulin-dependent diabetes mellitus were published by WHO in 1999 while the LIFE study was still in progress,41 it was decided that all patients who were diagnosed with new-onset diabetes would be included in analyses regardless of whether the diagnosis was based on the 198542 or 199943 criteria.35

Statistical Analyses

Data management and analysis were performed by the investigators using SPSS version 12.0. Data are presented as mean±SD for continuous variables and proportions for categorical variables. Differences in mean values between patients with and without new diabetes were compared using unpaired t tests and comparison of proportions between groups was performed using chi-square tests.

To evaluate the relationship of changing values of LVH by Cornell product, Cornell voltage, Sokolow-Lyon voltage, and ECG strain during antihypertensive therapy to the development of new diabetes, the relation of in-treatment resolution or continued absence of ECG LVH by these criteria over time versus presence of ECG LVH by these criteria to the risk of new diabetes was assessed using Cox proportional hazards models,25 with baseline and subsequent determinations of ECG LVH entered as time-varying categorical covariates. History of prior antihypertensive treatment, baseline Framingham risk score, and serum glucose, and a treatment group indicator, were included as standard covariates based on their previously demonstrated predictive value for new diabetes in this population.35 With baseline and subsequent systolic and diastolic blood pressure, HDL cholesterol, uric acid, and body mass index measurements entered as time-varying covariates. Because patients were enrolled in LIFE based on having LVH on a screening ECG,21 presence of ECG LVH was used as the reference category to which the association of resolution or continued absence of LVH as a time-varying covariate with new-onset diabetes was compared in Cox models. Adjusted hazard ratios for incident diabetes associated with in-treatment resolution or continued absence of ECG LVH were calculated from the antilog of the estimated coefficient. The 95% CI of each relative risk was calculated from the estimated coefficients and their standard errors, and Wald χ² statistics and probability values were calculated. For all tests, two-tailed P<0.05 was required for statistical significance.

The relationship of the presence and severity of hypertrophy to the increase of diastolic pressure, or the presence of diabetes is unclear. Accordingly, the present study examined whether resolution or continued absence of ECG LVH by Cornell product criteria during antihypertensive therapy is associated with a decreased incidence of new diabetes in the LIFE study, independent of the effects of blood pressure change, treatment type and of other risk factors for diabetes.
Role of the Sponsor
Merck and Co Inc provided the study authors with free access to all of the data; the authors were free to interpret data and write the article. The sponsor agreed to support the performance of the study, of the data; the authors were free to interpret data and write the manuscript were wholly controlled by P.M.O. and coauthors.

Results
During a mean follow-up of 4.6±1.2 years, new-onset diabetes mellitus developed in 562 patients (7%). Demographic and clinical characteristics of the patients in relationship to the development of new diabetes are compared in Table 1. As previously reported, patients who developed new diabetes were more likely to have had prior antihypertensive treatment, were less likely to have been randomized to losartan-based therapy, were more obese, had higher Framingham risk scores, serum glucose, creatinine and uric acid levels, and lower total and HDL cholesterol levels. The groups were similar with respect to age, gender, race, history of ischemic heart disease, congestive heart failure, myocardial infarction, stroke and peripheral vascular disease, and albuminuria (all \( P \)\textgreater 0.40). Patients who developed diabetes had slightly higher baseline systolic and diastolic blood pressures, significantly higher mean Cornell product and Cornell voltage LVH, but lower mean Sokolow-Lyon voltage. Patients who developed new diabetes had a higher baseline prevalence of LVH by Cornell product criteria (72% versus 66%, \( P \textless 0.001 \)) and significantly lower prevalence of LVH by Sokolow-Lyon voltage criteria (18% versus 22%, \( P \textless 0.032 \)), but there was no difference in the prevalence of LVH by Cornell voltage (68.2% versus 65.7%, \( P \textless 0.260 \)) or of the ECG strain pattern (13.2% versus 10.6%, \( P \textless 0.081 \)).

During follow-up, patients who developed diabetes had significantly greater reductions in systolic and diastolic blood pressure.

The relationship of in-treatment Cornell product LVH to the development of new-onset diabetes is examined in Table 1 and the Figure. During treatment, there were 19 300 patient-years of follow-up after ECGs with Cornell product LVH and 16 200 patient-years of follow-up after ECGs with resolution or continued absence of LVH. New-onset diabetes mellitus developed in 330 patients with persistent LVH during treatment (14.3 per 1000 patient-years) and in 232 with resolution or continued absence of Cornell product LVH (14.3 per 1000 patient-years). In Cox analyses which adjusted for the known effect of losartan versus atenolol treatment on diabetes incidence in LIFE,\textsuperscript{21,35} in treatment resolution or continued absence of LVH by Cornell product was associated with a 38% lower incidence of diabetes compared with continued absence of LVH by Cornell product LVH and 16 200 patient-years of follow-up after ECGs with resolution or continued absence of LVH.

Modified Kaplan-Meier curves\textsuperscript{44} comparing the rate of new diabetes according to the resolution or continued absence of Cornell product LVH on ECGs over the time course of the study (Figure) demonstrate that resolution or continued absence of ECG LVH was associated with an estimated 1.6% lower absolute risk of developing diabetes after 4 years of follow-up as compared with persistence or development of
ECG LVH during treatment. Of note, there was no significant interaction of treatment modality with either in-treatment regression of Cornell product LVH (P=0.146) or continued absence of LVH (P=0.843) in Cox analyses of the predictors of new-onset diabetes.

Because patients who developed diabetes differed significantly from those who did not with respect to demographic and clinical variables which could affect outcome (Table 1), the independent relation of new-onset diabetes to in-treatment Cornell product was examined after adjusting for the possible effects of treatment with losartan versus atenolol, history of prior antihypertensive treatment, baseline Framingham risk score and serum glucose and for baseline and subsequent in-treatment systolic and diastolic blood pressure, HDL cholesterol, uric acid, and body mass index measurements entered as time-varying covariates (Table 2). After adjusting for these factors, in-treatment resolution or continued absence of LVH by Cornell product criteria remained associated with a 26% lower incidence of new diabetes.

In parallel univariate Cox analyses, we found no significant relationship of new diabetes to time-varying presence or absence of Sokolow-Lyon voltage (HR 1.06, 95% CI 0.82 to 1.37, p=ns) or Cornell voltage (HR0.86, 95% CI 0.73 to 1.01, P=0.073). In contrast, although the absence or resolution of ECG strain between baseline and year-1 was a significant univariate predictor of a decreased risk of new diabetes (HR 0.75, 95% CI 0.58 to 0.96, P=0.025), in-treatment ECG strain was no longer a significant predictor after adjusting for other possible predictors of new diabetes in a multivariable Cox model that did not include any other ECG LVH variable (HR 1.02, 95% CI 0.78 to 1.34, P=0.901).

**Discussion**

These findings demonstrate that resolution or continued absence of Cornell product LVH during antihypertensive therapy is associated with a lower likelihood of new-onset diabetes, independent of the previously observed impact of treatment with losartan versus atenolol, and independent of blood pressure lowering and of the predictive value of other risk factors for diabetes in the LIFE study. In contrast, high values of Cornell product LVH during treatment are associated with higher rates of new diabetes. These findings support the value of serial measurement of Cornell product criteria for assessing the risk of developing diabetes in hypertensive patients and suggest that antihypertensive therapy targeted at resolution or prevention of the development of ECG LVH may reduce the incidence of new diabetes.

**Relationship of Diabetes to Left Ventricular Hypertrophy**

The incidence of diabetes is increased in hypertensive patients and is significantly related to blood pressure, although this relationship can be modulated by the types of antihypertensive medications used. Independent of frank diabetes, there is a also an association between insulin resistance and blood pressure, although both obesity and age can affect this relationship. Established diabetes is strongly associated with increased LV mass which may be, in part, the result of independent effects of insulin resistance on LV growth, and diabetes appears to be associated with an increased prevalence and severity of ECG LVH in hypertensive patients. In previous reports, the association between diabetes and LVH has generally been interpreted as reflecting a causal role of diabetes in simulating...

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**Table 2. Treatment-Adjusted and Multivariable Cox Proportional Hazards Models for the Prediction of New-Onset Diabetes Mellitus Comparing Regression and Continued Absence Vs Persistence of Cornell Voltage-Duration Product Left Ventricular Hypertrophy as a Time-Dependent Covariate**

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-adjusted Cox model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-treatment absence of Cornell product LVH</td>
<td>0.62</td>
<td>0.50–0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment with losartan</td>
<td>0.76</td>
<td>0.65–0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariable Cox model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-treatment absence of Cornell product LVH</td>
<td>0.74</td>
<td>0.58–0.93</td>
<td>0.011</td>
</tr>
<tr>
<td>Treatment with losartan vs atenolol</td>
<td>0.76</td>
<td>0.64–0.91</td>
<td>0.003</td>
</tr>
<tr>
<td>Time-varying systolic blood pressure, per 10 mm Hg</td>
<td>1.21</td>
<td>1.15–1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-varying diastolic blood pressure, per 10 mm Hg</td>
<td>1.27</td>
<td>1.15–1.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-varying HDL, per 0.1 mmol/L</td>
<td>0.75</td>
<td>0.71–0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-varying uric acid, per 10 µmol/L</td>
<td>0.98</td>
<td>0.96–0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-varying body mass index, per kg/m²</td>
<td>1.06</td>
<td>1.03–1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline serum glucose, per mmol/L</td>
<td>1.69</td>
<td>1.61–1.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior antihypertensive treatment</td>
<td>1.37</td>
<td>1.10–1.70</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Figure. Rates of new-onset diabetes by in-treatment time-varying presence or absence of left ventricular hypertrophy (LVH) by Cornell voltage-duration product criteria using a threshold value of 2440 mm-ms. (Patients are assigned to each group on the basis of their Cornell product LVH on the baseline and subsequent in-treatment ECGs and may be variably included in one curve or another at different times during follow-up, illustrating the behavior of time-varying categorical LVH as a predictor of new diabetes).**
myocardial growth, potentially mediated by diabetes-induced protein glycation, arterial stiffening and other mechanisms.\textsuperscript{5,22–25} Although the diabetes to LVH sequence is well-supported by experimental observations, the present results identify a more complex relationship, in which LVH may also precede diabetes.

Precedent for our findings is provided by results from the PIUMA study, an observational cohort study of initially untreated hypertensive patients.\textsuperscript{4} Verdecchia and colleagues\textsuperscript{4} found an increased prevalence of ECG LVH by the Perugia score in 43 patients who went on to develop diabetes compared with the 700 patients who did not (23.8 versus 15.5%, \( P<0.05 \)). Although baseline prevalence of ECG LVH was a significant predictor of future CV events in this population, LVH by the Perugia score was not an independent predictor of new-onset diabetes after taking into account other risk factors for diabetes.\textsuperscript{4} However, this study did not assess changing levels of ECG LVH during a follow-up period that ranged from 1 to 16 years (median 6), but importantly did demonstrate that new-onset diabetes was independently associated with an increased risk of CV events,\textsuperscript{4} suggesting that prevention of new-onset diabetes in hypertensive patients may decrease future CV risk.

The present study demonstrates that in-treatment regression of Cornell product LVH was associated with a decreased incidence of new-onset diabetes during 4 to 5 years of antihypertensive therapy. The predictive value of regression of ECG LVH for new diabetes was independent of the previously established decreased incidence of diabetes with losartan therapy in this population,\textsuperscript{21,35} of in-treatment levels of systolic and diastolic blood pressure, and of the predictive value of other risk factors for new diabetes in this population, including prior antihypertensive treatment.\textsuperscript{35} Given the possible additional impact of treatment with thiazide diuretics on the incidence of diabetes,\textsuperscript{13,14,17,20} it is of note that further adjustment for in-treatment hydrochlorothiazide use did not impact on the lower rate of incident diabetes with regression of Cornell product LVH. Also of importance, not all ECG criteria for LVH may have a positive association with new diabetes incidence. Indeed, in the current study, baseline Sokolow-Lyon voltage was actually lower in patients who went on to develop new diabetes (Table 1), possibly reflecting the greater obesity in these patients and the known negative effect of increased body mass index on Sokolow-Lyon voltage.\textsuperscript{45} In addition, neither Sokolow-Lyon voltage LVH nor simple Cornell voltage LVH examined over time were significant predictors of new-onset diabetes in univariate analyses and the univariate association between in-treatment resolution of ECG strain and new diabetes disappeared after adjusting for other potential predictors of new-onset diabetes.

Although the relationship between insulin resistance and hypertension is well established,\textsuperscript{9} whether insulin resistance predicts the development of hypertension or incident hypertension predicts subsequent development of hyperinsulinemia remains controversial.\textsuperscript{9} The observed association of LVH regression with a reduced incidence of new diabetes may be explained in part by the relationships between blood pressure, insulin resistance and microvascular function.\textsuperscript{6–9,46} Previous studies have demonstrated a strong association of insulin resistance with increased systolic blood pressure\textsuperscript{7,8} and measures of microvascular function.\textsuperscript{7,46} Semé et al\textsuperscript{7} demonstrated a strong inverse association between systolic pressure and insulin sensitivity, which in turn was strongly related to decreased microvascular function. In addition, ACE-inhibitors and angiotensin receptor blockers can improve insulin sensitivity and reduce or delay the onset of type 2 diabetes,\textsuperscript{9,35,46} possibly via renin-angiotensin system–mediated improvement in vascular endothelial function. Indeed, in the ICARUS substudy of LIFE, Olsen et al\textsuperscript{46} found that losartan therapy was associated with less peripheral vascular hypertrophy and higher insulin sensitivity than atenolol after 3 years of treatment. These findings, taken together with the greater regression of LVH with losartan therapy in LIFE,\textsuperscript{34} suggest that the lower incidence of diabetes associated with regression of ECG LVH may in part reflect an association between regression of LVH and lesser increases or actual decreases in microvascular resistance with their consequent effects on insulin resistance,\textsuperscript{7,46} with the decreasing LVH functioning as a biomarker of the changes in microvascular function. Further study examining incident diabetes rates in relation to changing levels of microvascular function and LVH over time will be necessary to more clearly elucidate this relationship.

**Limitations**

Several limitations of the current study deserve attention. First, the study population was predominantly White and was derived from a high-risk population of hypertensive patients with ECG LVH on a screening ECG performed before study enrollment, potentially limiting the generalizability of these findings to lower risk populations. Second, the favorable association between LVH resolution and reduced incidence of diabetes was attenuated after multivariable adjustment for other risk factors and the LIFE study was not designed to test whether treatment specifically aimed at producing regression of ECG LVH will decrease the incidence of diabetes. As a consequence, these findings reflect a potentially important association but do not establish causality between resolution of hypertrophy and diabetes incidence. Third, the absence of insulin levels in the overall study population precludes evaluation of the potential interaction of ECG LVH and insulin levels on incident diabetes. Finally, the adoption of a 1999 WHO recommendation for diagnosing type 2 diabetes\textsuperscript{43} by some investigators during the later part of the LIFE study\textsuperscript{35} led the Steering Committee to accept patients with diabetes diagnosed according to both the 1999 and 1985 recommendations.

**Perspectives**

These current findings have potentially important clinical implications. The increased CV risk associated with diabetes and, in particular, the increased risk associated with the development of new diabetes in hypertensive patients undergoing treatment,\textsuperscript{9} taken together with the failure of regression of hypertrophy to predict an improvement in outcome in hypertensive patients with LVH and established diabetes,\textsuperscript{5} make prevention of the development of new diabetes a clinical priority to reduce risk. These results and previous
findings with ACE-inhibitor and angiotensin receptor blocker therapy suggest that antihypertensive therapies with drugs that effectively reduce blood pressure, independently reduce the incidence of diabetes, and moreover can independently produce regression of LVH. They may provide the greatest long-term prognostic benefit by reducing the future burden of CV morbidity and mortality at least in part by preventing new-onset diabetes. Further study will be necessary to determine whether regression of hypertrophy will become a valid independent target for therapeutic intervention in hypertensive patients to prevent the development of diabetes and other adverse CV outcomes associated with ECG LVH.

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P.M.O. receives grant support from Merck & Co Inc. R.B.D. receives grant support and honoraria from Merck & Co Inc and serves on an advisory board for Merck & Co Inc. K.E.H. receives honoraria from Merck & Co Inc. B.D. serves on a speaker’s bureau and receives honoraria from Merck & Co Inc. Novartis, Boehringer Ingelheim, Pfizer, and Servier and is a consultant to Merck & Co Inc, Novartis, Pfizer, and Boehringer Ingelheim.

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