Impact of Diabetes Mellitus on Regression of Electrocardiographic Left Ventricular Hypertrophy and the Prediction of Outcome During Antihypertensive Therapy

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

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Background—Diabetes mellitus is associated with increased cardiovascular (CV) morbidity and mortality and with greater ECG left ventricular hypertrophy (LVH); however, it is unclear whether diabetes attenuates regression of hypertensive LVH and whether regression of ECG LVH has similar prognostic value in diabetic and nondiabetic hypertensive individuals.

Methods and Results—A total of 9193 hypertensive patients (1195 with diabetes) in the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study were treated with losartan- or atenolol-based regimens and followed up with serial ECG and blood pressure determinations at baseline and 6 months and then yearly until death or study end. ECG LVH was defined with gender-adjusted Cornell voltage-duration product (CP) criteria /H11022/2440 mm · ms. After a mean follow-up of 4.8±0.9 years, patients with diabetes had less regression of CP LVH (/H11002/138±866 versus /H11002/204±854 mm · ms, /H11021/P<0.001), remained more likely to have LVH by CP (56.0% versus 48.1%, /H11021/P<0.001), and had higher rates of CV death, myocardial infarction, stroke, and all-cause mortality and of the LIFE composite end point of CV death, myocardial infarction, or stroke. In multivariable Cox proportional hazards models, in-treatment regression or absence of ECG LVH by CP was associated with between 17% and 35% reductions in event rates in patients without diabetes but did not significantly predict outcome in patients with diabetes.

Conclusions—Hypertensive patients with diabetes have less regression of CP LVH in response to antihypertensive therapy than patients without diabetes, and regression of ECG LVH is less useful as a surrogate marker of outcomes in hypertensive patients with diabetes. These findings may in part explain the higher CV morbidity and mortality in hypertensive patients with diabetes, and the absence of a demonstrable improvement in prognosis in diabetic patients in response to regression of ECG LVH suggests a more complex interrelation between underlying LV structural and functional abnormalities and outcome in these patients. (Circulation. 2006;113:1588-1596.)

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.1-4 The increasing prevalence of type 2 diabetes mellitus, the earlier onset of diabetes, and the aging of the population have led to increasing prevalences of diabetes-induced CV disease and its complications,3,5 which suggests that accurate noninvasive identification of high-risk patients with diabetes may contribute to the development of more effective preventive strategies for decreasing diabetes-related risks.4

Clinical Perspective p 1596

The presence and severity of left ventricular hypertrophy (LVH) detected by 12-lead ECG9-10 or by echocardiography11-15 strongly predict CV morbidity and mortality. Among hypertensive patients with ECG LVH at baseline in the

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The online-only Data Supplement can be found with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.574822/DC1.
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Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study, regression of ECG LVH by Cornell product and/or Sokolow-Lyon voltage criteria during antihypertensive therapy was associated with a lower likelihood of CV morbidity and mortality, independent of treatment modality and of decreases in blood pressure.10

Hypertensive patients with diabetes have higher prevalence and greater severity of LVH than those without diabetes,16,17 and among hypertensive patients with diabetes in the LIFE study,18 losartan-based therapy was more effective than atenolol-based therapy in reducing CV morbidity and mortality and was associated with greater reductions in ECG LVH by Cornell product criteria. However, whether diabetes per se attenuates regression of hypertensive LVH is unclear, and whether regression of ECG LVH has similar prognostic value in patients with and without diabetes has not been examined. Therefore, the present study was conducted to examine differences in regression of ECG LVH by Cornell product criteria in the prespecified subgroups of patients with and without diabetes in the LIFE study and to determine whether patients with and without diabetes have different outcomes in response to regression of ECG LVH that may contribute to the increased CV morbidity and mortality and all-cause mortality in LIFE participants with diabetes.

Methods

Subjects

The LIFE trial10,15,18–21 enrolled hypertensive patients with ECG LVH by Cornell voltage-duration product22,23 and/or Sokolow-Lyon voltage criteria24 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.19 The study was approved by all ethics committees concerned. As described previously,18–21 eligible patients for LIFE were men and women aged 55 to 80 years with previously untreated or treated essential hypertension with mean seated blood pressure in the range of 160 to 200 mm Hg systolic/95 to 115 mm Hg diastolic after 1 and 2 weeks of placebo administration. Diabetes mellitus (primarily type 2) was present in 1195 patients (13%) at study baseline.18

Treatment Regimens

See the online-only Data Supplement.

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.10,19,20 The product of QRS duration times the Cornell voltage combination (R_{SV1}+S_{V5}, with 6 mm added in women22,23) was used with a threshold value of 2440 mm·ms to identify LVH.10

End-Point Determination

See the online-only Data Supplement.

Statistical Analyses

Data management and analysis were performed by the Clinical Biostatistics Department of Merck Research Laboratories with SAS version 8 (SAS Institute Inc, Cary, NC) and by investigators using SPSS version 12.0 (SPSS Inc, Chicago, Ill). Data are presented as mean±SD for continuous variables and proportions for categorical variables.

The relationships of regression or continued absence of ECG LVH by Cornell product criteria over time versus the development or persistence of ECG LVH by Cornell product criteria to the risk of clinical end points were assessed with Cox proportional hazards models,25 with baseline and subsequent determinations of ECG LVH by Cornell product entered as time-varying categorical covariates. Adjusted hazard ratios for the incidence of each end point for the absence or regression of Cornell product LVH versus development or persistence of LVH by Cornell product criteria were calculated from the antilog of the estimated coefficient.26 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, 2-tailed P<0.05 was required for statistical significance.

The relationship of event rates over time to Cornell product LVH in patients with and without diabetes was illustrated by plotting events rates as functions of the presence or absence of ECG LVH by Cornell product criteria with a modified Kaplan-Meier method,27 with assignment to LVH category updated at the time of each ECG, based on the Cornell product at those times. These modified Kaplan-Meier curves are intended to illustrate the results of time-varying covariate analyses. Additional information on the complete statistical methods employed is available in the online Data Supplement.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Diabetes mellitus was present in 1195 patients (13%) at study baseline, including 185 with type 1 diabetes and 1010 with type 2 diabetes. As previously reported,18 antidiabetic drugs, insulin, or both had been given to 669 patients (56%) at baseline, of whom 526 received oral drugs (sulfonylureas, biguanides, or both) and 186 received insulin. An additional 275 patients (23%) started taking antidiabetic drugs during the study, and 251 (21%) did not receive antidiabetic drugs during the trial.

Demographic and clinical characteristics of the patients with and without diabetes are compared in Table 1. At study baseline, patients with diabetes were older; more likely to be black; were more likely to have a history of ischemic heart disease, congestive heart failure, stroke, or peripheral vascular disease; were more obese; and had higher serum glucose and creatinine levels, lower total and HDL cholesterol levels, and greater albuminuria. Patients with diabetes had slightly but significantly higher baseline systolic and lower baseline diastolic blood pressures but had significantly higher mean Cornell product and a higher prevalence of LVH by Cornell product criteria (72% versus 66%, P<0.001; Figure 1). After mean follow-up of 4.8±0.9 years, patients with diabetes had slightly greater reductions in systolic and diastolic blood pressure. Of note, there was only a weak, although statistically significant, degree of correlation between Cornell product and body mass index in the present study population (r=0.075, P<0.001).

Regression of ECG LVH in Relation to Diabetes

Mean values at baseline, subsequent in-study measurements, and change between baseline and follow-up measurements for Cornell product in patients with and without diabetes are
compared in Table 2. Because differences in changes in Cornell product could be related to baseline levels of Cornell product and could be affected by in-treatment differences in systolic and diastolic pressures and their changes, differences in Cornell product between patients with and without diabetes were assessed with adjustment for these differences. As expected, according to LIFE entry criteria, mean Cornell product was elevated at baseline in both groups but was significantly higher in those with diabetes (Table 1). Mean Cornell product decreased substantially in both groups during the first 6 months, concomitant with the institution of protocol-based antihypertensive therapy. Greater regression of Cornell product LVH in patients without diabetes became apparent after 1 year of blinded therapy, as confirmed by a significant interaction term between group (diabetes versus no diabetes) and visit ($P=0.019$). The difference in change in Cornell product between groups continued to increase until year 3 of follow-up, thereafter remaining relatively constant and significant until the final in-study ECG. Regression of LVH did not differ between patients with type 1 and type 2 diabetes mellitus (data not shown).

Prevalence of ECG LVH by Cornell product criteria at study baseline and subsequent in-study measurements in patients with and without diabetes are compared in Figure 1. Prevalence of Cornell product LVH in both groups was highest at study baseline and declined in both groups in a pattern similar to the decreases in mean values shown in Table 2. The prevalence of ECG LVH by Cornell product was significantly higher by 6% in patients with diabetes at study baseline and was up to 8% higher throughout the study period. Univariate logistic regression analysis demonstrated that diabetes was associated with a 1.37-fold increased risk of having ECG LVH by Cornell product at last in-study measurement (95% CI 1.21 to 1.55, $P<0.0001$). Additional adjustment for differences between patients with and without diabetes had only minor effects on the relationship between diabetes and LVH: after adjustment for baseline and in-study differences between patients with and without diabetes by multivariable logistic regression analysis, diabetes remained associated with a 1.31-fold increased risk of having ECG LVH at last in-study measurement (95% CI 1.12 to 1.52, $P<0.001$) and was a significant predictor of the presence of Cornell product LVH at each measurement point in the study (adjusted hazard ratios between 1.25 and 1.44, all $P<0.001$).
Outcomes in Relation to Diabetes Mellitus and Regression of ECG LVH

The relationship of the LIFE composite end point, CV death, stroke, or myocardial infarction as separate end points, and all-cause mortality to the presence or absence of diabetes at study baseline is examined in Table 3. After a mean follow-up of 4.8±0.9 years, patients with diabetes had significantly higher rates of the LIFE composite end point, CV death, stroke, myocardial infarction, and total mortality. In univariate Cox models performed in the overall study population, diabetes was associated with a 1.8- to 2.2-fold increased risk of these end points. In multivariable analyses that adjusted for treatment effect, baseline risk factors, baseline and in-treatment systolic and diastolic blood pressure, baseline severity of ECG LVH by Cornell product and Sokolow-Lyon voltage, and in-treatment presence or absence of LVH by Cornell product and that included an interaction term between diabetes and time-varying Cornell product LVH, diabetes remained associated with increased risks of all outcomes.

The relationship of outcomes to changing prevalence of Cornell product LVH is compared between patients with and without diabetes in Table 4 and Figure 2. In both univariate and multivariable Cox models performed in the overall population, interaction terms between diabetes and time-varying LVH by Cornell product were significant for all outcomes other than myocardial infarction, demonstrating statistically different associations between changing Cornell product and outcome in patients with and without diabetes. As a result, Cox analyses to examine the relationship of outcomes to time-varying Cornell product LVH were performed separately in these groups.

In separate univariate Cox analyses, in-treatment regression or continued absence of LVH by Cornell product criteria strongly predicted improved outcome among patients without diabetes compared with persistence of development of LVH by Cornell product criteria. In these patients, regression of Cornell product LVH was associated with between 35% and 45% reductions in the risk of CV death, stroke, or myocardial infarction, a 37% reduction in the LIFE composite end point, and a 28% lower risk of all-cause mortality. In contrast, regression or continued absence of Cornell product LVH was not a significant univariate predictor of these outcomes in

### TABLE 2. Cornell Voltage-Duration Product Measurements and Change in Measurements in Patients With and Without Diabetes

<table>
<thead>
<tr>
<th>Time</th>
<th>Diabetes (n=1195)</th>
<th>No Diabetes (n=7998*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Cornell</td>
<td>Follow-Up Visit</td>
</tr>
<tr>
<td></td>
<td>Product, mm·ms</td>
<td>Product, mm·ms</td>
</tr>
<tr>
<td></td>
<td>Change, mm·ms</td>
<td>n</td>
</tr>
<tr>
<td>Month 6</td>
<td>2900±963</td>
<td>2800±991</td>
</tr>
<tr>
<td>Year 1</td>
<td>2899±981</td>
<td>2773±1052</td>
</tr>
<tr>
<td>Year 2</td>
<td>2883±955</td>
<td>2700±1001</td>
</tr>
<tr>
<td>Year 3</td>
<td>2888±941</td>
<td>2732±1119</td>
</tr>
<tr>
<td>Year 4</td>
<td>2876±944</td>
<td>2715±1121</td>
</tr>
<tr>
<td>Year 5</td>
<td>2854±878</td>
<td>2680±1033</td>
</tr>
<tr>
<td>Last visit</td>
<td>2900±981</td>
<td>2762±1142</td>
</tr>
</tbody>
</table>

*P=0.012 for comparison of changes between patients with and without diabetes, with P=0.019 for the interaction between group (diabetes vs no diabetes) and testing visit, confirming the different trends in changes in Cornell products over time in the 2 groups, from repeated-measures ANCOVA comparing changes in patient groups with and without diabetes, with adjustment for treatment with losartan vs atenolol, baseline Cornell product, and baseline and in-treatment systolic and diastolic blood pressures.

Mean values for baseline at each time point are for the participants who attended each examination.

### TABLE 3. Event Rates and Cox Proportional Hazards Models for the Prediction of Primary CV End Points and All-Cause Mortality in Hypertensive Patients With vs Those Without Diabetes

<table>
<thead>
<tr>
<th>End Point</th>
<th>Event Rate, %</th>
<th>Univariate</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes (n=1195)</td>
<td>No Diabetes (n=7998*)</td>
<td>Hazard Ratio† 95% CI</td>
</tr>
<tr>
<td>CV mortality</td>
<td>8.3</td>
<td>4.2</td>
<td>1.98</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.7</td>
<td>5.3</td>
<td>1.87</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7.6</td>
<td>3.7</td>
<td>2.17</td>
</tr>
<tr>
<td>Composite end point</td>
<td>20.3</td>
<td>10.7</td>
<td>2.00</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>14.0</td>
<td>8.1</td>
<td>1.77</td>
</tr>
</tbody>
</table>

*P<0.001 for all comparisons.
†Adjusted for age, sex, smoking status (current vs not); history of myocardial infarction, stroke, heart failure, and peripheral vascular disease; baseline body mass index; total and HDL cholesterol; fasting glucose; baseline and in-treatment systolic and diastolic pressure; baseline Cornell voltage-duration product and Sokolow-Lyon voltage; and treatment with losartan vs atenolol.
‡Patients with vs without diabetes mellitus.
Diabetes and LVH

Diabetes is a well-recognized stimulus for hypertrophy\cite{16,17} that may be, in part, the result of independent effects of insulin resistance on left ventricle (LV) growth.\cite{29} In addition, there appear to be synergistic effects of diabetes and hypertension on LV structure and function,\cite{17,30} with the combination of the 2 conditions associated with greater prevalences of LVH and subnormal LV function than either alone.\cite{17} However, previous studies have demonstrated conflicting results with respect to the prevalence of ECG LVH in patients with versus without diabetes.

In an observational study of 795 hypertensive patients, of whom 6.5% had type 2 diabetes mellitus at baseline, Verdecchia et al\cite{31} found a significantly higher prevalence of ECG LVH.

Discussion

This study demonstrates that hypertensive patients with diabetes mellitus have greater baseline and in-treatment prevalence and severity of Cornell product LVH and less regression of ECG LVH by Cornell product criteria in response to antihypertensive therapy than patients without diabetes. The lesser regression of ECG LVH and the lack of detectable impact on outcomes in patients with diabetes are independent of baseline differences in severity of ECG LVH and blood pressure and of the slightly greater reductions in systolic and diastolic pressure in diabetic patients. These findings suggest that hypertensive patients with diabetes may not derive the same prognostic benefit from regression of Cornell product LVH as patients without diabetes and may in part explain the higher CV morbidity and mortality in patients with diabetes. These findings raise intriguing questions as to whether therapies aimed at more aggressive reduction of LVH in hypertensive patients with diabetes will provide prognostic benefit in these patients.\cite{28}
by the Perugia score in hypertensive patients than in those without diabetes (27.1% versus 15.5%, \( P < 0.05 \)), but they did not examine the severity of LVH in relation to diabetes and did not take into account possible confounding factors. In contrast, Lonn et al.\(^3\) found no difference in the baseline prevalence of diabetes among high-risk patients with and without ECG LVH by Sokolow-Lyon voltage criteria enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial (39.1% versus 38.1%). The present study demonstrates that diabetes is associated with an increased prevalence and severity of ECG LVH by Cornell product criteria and that this association is independent of clinical conditions.
and demographic differences between patients with and without diabetes.

Previous studies in hypertensive patients with diabetes have demonstrated greater regression of Cornell voltage LVH in response to enalapril and of Sokolow-Lyon voltage and Cornell product LVH in response to losartan-based therapy. However, whether diabetes per se is associated with less regression of LVH in response to antihypertensive therapy had not been addressed previously. Although hypertensive patients with diabetes undergoing community-based therapy appeared to have less regression of ECG LVH by Perugia score than those without diabetes (2.1% versus 4.6%), no statistical test was performed. The present study is the first to demonstrate that hypertensive patients with diabetes have less regression of ECG LVH than patients without diabetes in response to antihypertensive therapy. The lesser regression of Cornell product LVH in patients with diabetes was independent of baseline differences in severity of ECG LVH and hypertension and of any differences in changes in blood pressure between groups. The independent association of concomitant diabetes with attenuated regression of LV mass in the echocardiographic substudy of LIFE further supports these findings. Mechanistically, it is intriguing to postulate that increased formation of advanced glycation end products (AGEs) and their cross-linking with collagen could play a role in the decreased regression of LVH in diabetes. In support of this hypothesis, treatment with the cross-link breaker 3-phenacyl-4,5-dimethylthiazolium chloride restored LV collagen solubility and blunted increases in AGEs and LV mass in diabetic Sprague-Dawley rats. Results of pending phase II clinical trials of this agent in hypertensive patients with and without LVH will hopefully shed more light on the potential clinical role of this pathway in explaining decreased regression of LVH in patients with diabetes.

Regression of ECG LVH and Prognosis

A number of previous studies have demonstrated that regression of ECG LVH and prevention of progression to LVH are associated with a reduced risk of CV morbidity, with recent findings in the overall LIFE study population establishing a strong correlation between changes in ECG LVH and long-term CV outcome during hypertensive treatment. However, only limited data exist on the relation of regression of ECG LVH to outcome in hypertensive patients with diabetes. In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, change in an index of Cornell voltage adjusted for age and body mass index remained a modest predictor of CV events in 468 hypertensive patients with type 2 diabetes mellitus after adjustment for treatment with enalapril versus nisoldipine, history of coronary disease, and duration of diabetes. However, the patients in the ABCD trial were 9 years younger than the patients enrolled in LIFE. In contrast, the present findings do not support the value of ECG LVH regression in improving prognosis in hypertensive patients with diabetes. In-treatment regression or continued absence of ECG LVH by Cornell product criteria was not associated with reduced risk of adverse CV outcomes or of death due to any cause in patients with diabetes, either when examined in simple univariate analyses or in multivariable analyses that controlled for other variables that could affect outcome, including baseline severity of LVH and in-treatment systolic and diastolic pressure. Importantly, similar results were obtained if Cox analyses were performed with continuous measures of Cornell product as the time-dependent covariate of interest or when regression and continued absence of LVH were examined separately in the Cox models, with no significant relation of in-treatment Cornell product to outcomes among diabetic patients. In contrast, regression of Cornell product LVH was a strong predictor of improved outcomes in patients without diabetes in the LIFE study, whether LVH was examined as a categorical or a continuous variable.

Lack of an association between regression of ECG LVH and outcome among patients with diabetes could in part reflect the possible relation of increased interstitial myocardial collagen and AGE formation to increased myocardial stiffness and dysfunction. Failure to improve prognosis in response to LVH regression may also reflect both the lower ejection fraction at baseline and the lesser improvement in LV systolic function in response to blood pressure lowering among hypertensive patients with diabetes in the LIFE study, with these patients being more likely to have reduced LV ejection fraction after 4 years of therapy. The nonsignificant trend toward an increased risk of stroke among patients with diabetes and regression or continued absence of LVH in this study is not an artifact of the Cox models but reflects a higher absolute stroke rate in these patients at the different intervals and may in part reflect a subtle underestimation of the rate of persistent LVH just before these events due to a clustering of Cornell product values just below the threshold value for LVH at these time points in patients with diabetes who had these events (data not shown). As a consequence, small increases in these values would have resulted in reclassification of these patients as having persistent LVH, which would change the results so that there were slightly but not significantly higher stroke and mortality rates among patients with diabetes and persistent LVH.

Study Limitations

Several limitations of the present study deserve attention. First, the study population was predominantly white and was derived from a high-risk population of hypertensive patients with ECG LVH. Second, the smaller number of patients with diabetes coupled with their lesser regression of LVH decreases the power to detect a significant relationship between changing Cornell product LVH and outcomes among patients with diabetes. As a consequence, the present findings may underestimate the predictive value of in-treatment LVH among hypertensive patients with diabetes.

Implications

These findings provide new insights into the relationships between diabetes and LVH. The lesser regression of Cornell product LVH in response to blood pressure lowering in diabetic patients in combination with their greater severity of ECG LVH may in part explain the higher event rates in hypertensive patients with diabetes. However, the absence of
a demonstrable improvement in prognosis in diabetics in response to regression of ECG LVH suggests a more complex interrelation between underlying LV structural and functional abnormalities and outcome in these patients. It is intriguing to postulate that additional antihypertensive and potentially novel therapies targeted at greater regression or prevention of ECG LVH may improve outcome in these patients. Further study will be required to determine whether regression of hypertrophy will become a valid, independent target for therapeutic intervention in hypertensive patients with diabetes.

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Disclosures

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CLINICAL PERSPECTIVE

This study demonstrates that hypertensive patients with diabetes have greater baseline and in-treatment prevalence and severity of Cornell product (CP) left ventricular hypertrophy (LVH) and less regression of ECG LVH by Cornell product criteria in response to antihypertensive therapy than patients without diabetes. In addition, in-treatment regression or absence of ECG LVH by CP was associated with between 17% and 35% reductions in event rates in patients without diabetes, but did not significantly predict outcome in patients with diabetes. The lesser regression of ECG LVH and the lack of detectable impact on outcomes in patients with diabetes are independent of baseline differences in severity of ECG LVH and blood pressure and of the slightly greater reductions in systolic and diastolic pressure in diabetic patients. These findings provide new insights into the relationships between diabetes and LVH and suggest that regression of ECG LVH is less useful as a surrogate marker of outcomes in hypertensive patients with diabetes and may in part explain the higher cardiovascular morbidity and mortality in hypertensive patients with diabetes. However, the absence of a demonstrable improvement in prognosis in diabetics in response to regression of ECG LVH suggests a more complex interrelation between underlying LV structural and functional abnormalities and outcome in these patients.
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