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

Peter M. Okin, Richard B. Devereux, Katherine E. Harris, Sverker Jern, Sverre E. Kjeldsen, Lars H. Lindholm, Björn Dahlof; for the LIFE Study Investigators

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 \( \geq 2440 \text{ mm} \times \text{ms} \). 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 obesity7,8 and affected by age.8 Moreover, hypertension and diabetes frequently coexist10 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 diabetes4,13,14 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. These findings, taken together with the increased long-term CV risk associated with the development of new diabetes in hypertensive patients, 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 hypertension 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, 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. 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 other risk factors for diabetes.

Methods

Subjects

The LIFE trial enrolled hypertensive patients with ECG LVH by Cornell voltage-duration product or Sokolow-Lyon voltage criteria 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, 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 115 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 consent. The 1195 patients with diabetes mellitus at study baseline 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, additional open-label upward titration of hydrochlorothiazide and if necessary institution of therapy with a calcium channel blocker or additional other medications (excluding AT1- or β-blockers or ACE-inhibitors) was added to the double-blind treatment regimen.

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. The product of QRS duration times the Cornell voltage combination (RV5+SV1, with 6 mm added in women) was used with a threshold value of 2440 mm-seconds to identify LVH. In alternative analyses, ECG LVH was defined by Cornell voltage criteria (RV5+SV1 > 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 described on baseline and year-1 ECGs in a subset of 7174 patients. Repolarization abnormalities in leads V5 and 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.

End Point Determination

New-onset diabetes was initially defined according to the 1985 World Health Organization (WHO) criteria as previously described. 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, 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 1985 or 1999 criteria.

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, 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, 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, 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 new diabetes rates over time to Cornell product LVH was illustrated by plotting events rates as functions of the in-treatment resolution or continued absence versus presence of ECG LVH by Cornell product criteria using a modified Kaplan-Meier method. The extended Kaplan-Meier plots were implemented in SAS Release 8.2 on the WIN_PRO platform. Using this method, LVH category is updated at the time of each ECG based on the Cornell product at those times and patients may be variably included in one curve or another at different times during follow-up. As a consequence, sample sizes in a cohort may increase during follow-up, instead of following a monotonic decrease as with fixed cohorts. These modified Kaplan-Meier curves are intended to illustrate the results of time-varying covariate analyses.
Table 1. Demographic and Clinical Characteristics in Relation to the Development of New-Onset Diabetes Mellitus

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Diabetes (n=7436)</th>
<th>New Diabetes (n=562)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.9±7.0</td>
<td>66.4±6.8</td>
<td>0.071</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>54.4</td>
<td>50.7</td>
<td>0.101</td>
</tr>
<tr>
<td>Prior antihypertensive treatment, %</td>
<td>70.3</td>
<td>80.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment with Losartan, %</td>
<td>50.8</td>
<td>43.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Framingham risk score, %</td>
<td>21.0±8.9</td>
<td>23.6±9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5±4.5</td>
<td>30.5±5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.41±0.95</td>
<td>6.50±1.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>86.0±20.0</td>
<td>89.6±20.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.09±1.11</td>
<td>5.91±1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.54±0.44</td>
<td>1.30±0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>328±78</td>
<td>359±73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio, mg/mM</td>
<td>5.8±28.0</td>
<td>7.0±20.3</td>
<td>0.366</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg</td>
<td>174±14</td>
<td>177±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg</td>
<td>98±9</td>
<td>99±9</td>
<td>0.071</td>
</tr>
<tr>
<td>Baseline Cornell product, mm- msec</td>
<td>2801±1032</td>
<td>2957±113</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline Sokolow-Lyon voltage, mm</td>
<td>30.3±10.4</td>
<td>29.0±10.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline Cornell voltage, mm</td>
<td>27.6±7.5</td>
<td>28.7±7.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Δ Systolic BP, baseline to last measured, mm Hg</td>
<td>-29±19</td>
<td>-32±19</td>
<td>0.005</td>
</tr>
<tr>
<td>Δ Diastolic BP, baseline to last measured, mm Hg</td>
<td>-17±10</td>
<td>-19±10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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, at which time it was agreed that the findings would be published by the investigators regardless of the results. The decision to publish the article, the choice of analyses to include, and the drafting of 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,35 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>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<0.001) and significantly lower prevalence of LVH by Sokolow-Lyon voltage criteria (18% versus 22%, P=0.032), but there was no difference in the prevalence of LVH by Cornell voltage (68.2% versus 65.7%, P=0.260) or of the ECG strain pattern (13.2% versus 10.6%, P=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 2 and the Figure. During treatment, there were 19300 patient-years of follow-up after ECGs with Cornell product LVH and 16200 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 (17.1 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,21,35 in treatment resolution or continued absence of LVH by Cornell product was associated with a 38% lower incidence of diabetes compared with in-treatment persistence or development of ECG LVH. Modified Kaplan-Meier curves44 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\(^{35}\) 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. 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,\(^{21,35}\) and independent of blood pressure lowering and of the predictive value of other risk factors for diabetes in the LIFE study.\(^{35}\) 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.

**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 (\mu)mol/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/m(^2)</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>

**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,\(^{21,35}\) and independent of blood pressure lowering and of the predictive value of other risk factors for diabetes in the LIFE study.\(^{35}\) 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,\(^{4,13,14,35}\) although this relationship can be modulated by the types of antihypertensive medications used.\(^{13–21,35}\) Independent of frank diabetes, there is also an association between insulin resistance and blood pressure,\(^{5,9}\) although both obesity\(^{7,8}\) and age\(^{8}\) can affect this relationship. Established diabetes is strongly associated with increased LV mass\(^{22,23}\) which may be, in part, the result of independent effects of insulin resistance on LV growth,\(^{24}\) and diabetes appears to be associated with an increased prevalence and severity of ECG LVH in hypertensive patients.\(^{4,5}\) In previous reports, the association between diabetes and LVH has generally been interpreted as reflecting a causal role of diabetes in simulating
myocardial growth, potentially mediated by diabetes-induced
protein glycation, arterial stiffening and other mecha-
nisms.8,22–25 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.4 Verdecchia and colleagues4
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 presence 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.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,4 suggesting that prevention of new-onset diabetes in
hypertensive patients may decrease future CV risk.

The present study demonstrates that in-treatment regres-
sion 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,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.35 Given the pos-
sible additional impact of treatment with thiazide diuretics
on the incidence of diabetes,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 reflect-
ing the greater obesity in these patients and the known
negative effect of increased body mass index on Sokolow-
Lyon voltage.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,9 whether insulin resistance
predicts the development of hypertension or incident hyper-
tension predicts subsequent development of hyperinsulinemia
remains controversial.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.6–9,46 Previous
studies have demonstrated a strong association of insulin
resistance with increased systolic blood pressure7,8 and mea-
sures of microvascular function.7,46 Sernen et al7 demonstrated
a strong inverse association between systolic pressure and
insulin sensitivity, which in turn was strongly related to
decreased microvascular function. In addition, ACE-inhibi-
tors and angiotensin receptor blockers can improve insulin
sensitivity and reduce or delay the onset of type 2 diabetes,
9,35,46 possibly via renin-angiotensin system–mediated im-
provement in vascular endothelial function. Indeed, in the
ICARUS substudy of LIFE, Olsen et al46 found that losartan
therapy was associated with less peripheral vascular hyper-
trophy 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,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,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 diabetes43
by some investigators during the later part of the LIFE
study35 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 under-
going treatment,8 taken together with the failure of regression
of hypertrophy to predict an improvement in outcome in
hypertensive patients with LVH and established diabetes,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 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.

Sources of Funding

This work was supported in part by grant COZ-368 from Merck & Co., Inc., West Point, Pa.

Disclosures

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. was formerly employed by Merck & Co Inc and may own Merck stock or stock options. S.J. has no disclosures. S.E.K. receives grant support from Merck & Co Inc. L.H.L. receives honoraria for lectures 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.

References


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36. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. J Am Coll Cardiol. 1992;20:1180–1186.


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_Hypertension_. 2007;50:984-990; originally published online September 24, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.096818

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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