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ORIGINAL ARTICLE

Changes in electrocardiographic left ventricular hypertrophy and risk of major cardiovascular events in isolated systolic hypertension: The LIFE study

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The predictive value of changes in the severity of electrocardiographic left ventricular hypertrophy (ECG-LVH) during antihypertensive therapy remains unclear in isolated systolic hypertension (ISH). In a Losartan Intervention For Endpoint reduction in hypertension substudy, we included 1320 patients aged 54–83 years with systolic blood pressure (BP) of 160–200 mm Hg, diastolic BP <90 mm Hg and ECG-LVH by Cornell voltage-duration product and/or Sokolow–Lyon voltage criteria, randomized to losartan- or atenolol-based treatment with a mean follow-up of 4.8 years. The composite end point of cardiovascular death, non-fatal myocardial infarction (MI) or stroke occurred in 179 (13.6%) patients. In Cox regression models controlling for treatment, Framingham risk score, as well as baseline and in-treatment BP, less severe in-treatment ECG-LVH by Cornell product and Sokolow–Lyon voltage was associated with 17 and 25% risk reduction for the composite end point (adjusted hazard ratio (HR) 0.83, 95% confidence interval (95% CI:) 0.75–0.92, $P=0.001$ per 1050 mm × ms (1 s.d.) lower Cornell product; and HR 0.75, 95% CI: 0.65–0.87, $P<0.001$ per 10.5 mm (1 s.d.) lower Sokolow–Lyon voltage). In parallel analyses, lower Cornell product and Sokolow–Lyon voltage were associated with lower risks of cardiovascular mortality and MI, and lower Sokolow–Lyon voltage with lower risk of stroke. Lower Cornell product and Sokolow–Lyon voltage during antihypertensive therapy are associated with lower likelihoods of cardiovascular events in patients with ISH.
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Introduction

Isolated systolic hypertension (ISH), the most common form of hypertension in the elderly, is associated with increased risk of cardiovascular morbidity and mortality compared with isolated diastolic hypertension,[1,2] and antihypertensive treatment is efficacious.[3]

Left ventricular hypertrophy (LVH) detected by 12-lead electrocardiogram (ECG)[4–7] and by echocardiography[8–13] are common manifestations of preclinical cardiovascular disease that strongly predict cardiovascular morbidity and mortality. Antihypertensive therapy targeted at decreasing blood pressure (BP) can produce regression of LVH,[5,12,14–20] and reduce, but do not entirely eliminate, the increased risk of major cardiovascular events.[21–25] Low sensitivity (13–31%) of standard voltage criteria (Sokolow–Lyon voltage) for the detection of anatomical LVH has limited the use of ECG for detection of LVH and for serial evaluation of changes in the left ventricular mass.[26–34] However, the use of Cornell voltage-duration product enhances sensitivity of the ECG to 51%, with a matched specificity of 95%.[26,27,29–31]

As previously described in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study,[35–39] lower in-treatment values of both Cornell voltage-duration product and Sokolow–Lyon voltage during antihypertensive therapy were strongly associated with decreased risk of the composite end point of cardiovascular death, myocardial infarction

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(MI) or stroke and its individual components, independent of treatment effect, baseline Framingham risk score,[40] baseline and in-treatment BP, as well as severity of baseline ECG-LVH. Furthermore, in a comparative report on cardiovascular outcomes in ISH patients with ECG-LVH, a LIFE substudy demonstrated significantly lower rates of stroke and cardiovascular death in patients randomized to losartan- versus atenolol-based antihypertensive therapy.[41]

However, the effect of reducing ECG-LVH during antihypertensive therapy remains unclear in patients with ISH. The aim of this pre-specified substudy of LIFE was to investigate the effect of lower in-treatment ECG-LVH for cardiovascular morbidity and mortality in patients with ISH, and whether this effect was stronger in patients with ISH than in patients with systolic–diastolic hypertension or isolated diastolic hypertension.

Materials and methods

Study design and target population

As described in detail elsewhere,[35–38] the LIFE study enrolled 9193 patients with essential hypertension (mean seated BP in the range of 160–200 mm Hg systolic, 90–115 mm Hg diastolic or both) having ECG-LVH determined by the Cornell voltage-duration product[29,30] and/or the Sokolow–Lyon voltage criteria[32] on a screening ECG in a prospective, double-blind, parallel group study with randomization to losartan- versus atenolol-based therapy. The main outcome was the composite of cardiovascular death, non-fatal stroke and non-fatal MI. Secondary outcome measures included the components of the primary composite end point (cardiovascular death, all strokes and all MIs). Patients were followed up for $\geqslant 4$ years with regular visits and upward titration of medication targeting a BP level of $\leqslant 140/90$ mm Hg.[35]

The data presented in this study were obtained from 1320 patients (14.4%) with ISH, a subgroup pre-specified in the original LIFE data analysis plan as having systolic BP $\geqslant 160$ mm Hg and diastolic BP < 90 mm Hg after 1–2 weeks of receiving placebo. The trial protocol was approved by all ethics committees concerned, in accordance with the Declaration of Helsinki, and was overseen by an independent data and safety monitoring board, and all patients gave written informed consent. All study data reside in a database with the authors.

Electrocardiography

ECGs were obtained at study baseline, at 6 months and at yearly follow-up intervals until study termination or patient death. All ECGs were read at the core laboratory at the Sahlgrenska University Hospital/Östra, Göteborg, Sweden, by experienced readers blinded to clinical information. QRS duration was measured to the nearest 4 ms and the QRS amplitudes to the nearest 0.5 mm (0.05 mV). The product of QRS duration $\times$ the Cornell voltage combination ($R_{aVL} + S_{V3}$, with 8 mm added in women[29,30]) was used with a threshold value of 2440 mm $\times$ ms to identify LVH. The sex adjustment of Cornell voltage was reduced from 8 to 6 mm, and Sokolow–Lyon voltage ($S_{V1} + R_{V5/6}$) > 38 mm was accepted for electrocardiographic eligibility in patients recruited after 30 April 1996 ($n = 7708$ in the LIFE study, including 1003 in the ISH substudy). The rationale for these changes in ECG entry criteria has been described in detail.[36,39]

Statistical analyses

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± s.d. for continuous variables and as proportions for categorical variables. Comparison among annual measurements of mean BP and ECG-LVH was performed using mixed-effects linear models to account for the within-subject correlation. As previously described,[39] possible associations between ECG-LVH voltage during antihypertensive therapy and the risk of developing the LIFE composite end point and its individual components were analyzed according to a pre-specified statistical analysis plan using Cox proportional hazard models[42] and based on the intention-to-treat principle.[37] Baseline and subsequent determinations of Cornell product and Sokolow–Lyon voltage were entered as time-varying covariates in the Cox models. ECGs undertaken after a non-fatal event were excluded from further time-varying analyses regarding the end point in question. Baseline Framingham risk score and a treatment group indicator were included as standard covariates, and baseline and subsequent systolic and diastolic BP measurements were entered as time-varying covariates. The adjusted hazard ratios (HRs) for the incidence of the composite end point and its components for Cornell product and Sokolow–Lyon voltage treated as continuous variables were computed per 1-s.d.-of-the-mean lower values of the ECG criteria as the antilogarithm of the estimated coefficient multiplied by the s.d.[43] The 95% confidence intervals (95% CIs) of HRs were calculated from the estimated coefficients and their s.e.,[44] and Wald χ^2 statistics and probability values were calculated. In coherence with previous analyses, the baseline s.d. for the whole LIFE population was used in the calculations; 1050 mm $\times$ ms for Cornell product and 10.5 mm for Sokolow–Lyon voltage.[39] To test whether the effect of reduced ECG-LVH on the composite end point was stronger in ISH patients compared with non-ISH patients, interaction analyses were performed using Cox proportional hazard models on the entire LIFE cohort and entering ISH status as a categorical covariate and either Sokolow–Lyon criteria or Cornell product as a time-varying covariate and the cross-product of

ISH status and either time-varying Sokolow–Lyon criteria or Cornell product as a continuous covariate. The *P*-value of this interaction cross-product was used to determine whether there was a positive interaction, that is, whether ISH increased the outcome effect of the reduction in the ECG indices. A two-tailed $P<0.05$ was required for statistical significance.

Results

Characteristics of ISH and non-ISH patients are presented in Table 1. ISH patients were aged 54 through 83 years (mean 70 years) and the mean follow-up time was 4.8 ± 0.9 years. The primary end point, a composite of cardiovascular death, non-fatal MI or non-fatal stroke occurred in 179 (13.6%) of 1320 patients with ISH during 6146 patient-years follow-up (Figure 1). Fatal/non-fatal stroke, fatal/non-fatal MI and cardiovascular death occurred in 88 (6.7%), 67 (5.1%) and 79 (6.0%) patients, respectively.

Serial assessment of BP and ECG-LVH

Baseline and follow-up mean systolic and diastolic BP and ECG-LVH by Cornell voltage-duration product and Sokolow–Lyon voltage, are presented in Figures 2a and b. Mean Cornell voltage (mm × ms) values (s.d.) at baseline, and year 1 through year 5, were 2792 (1101), 2700 (1154), 2607 (1106), 2605 (1109), 2613 (1187) and 2632 (1113). Similarly, mean Sokolow–Lyon voltage (mm) values (s.d.) at baseline, and year 1 through year 5, were 31.0 (10.4), 29.1 (9.8), 28.3 (9.9), 27.7 (9.9), 27.3 (9.5) and 26.9 (9.4). As previously reported for the total LIFE population,[39] for ISH patients, there were also

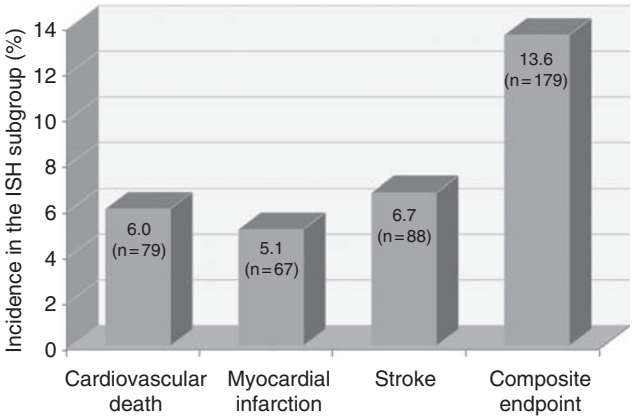

Figure 1 Incidence of cardiovascular morbidity and mortality in patients with isolated systolic hypertension (ISH) over a mean follow-up of 4.8 years.

Table 1 Characteristics of patients with and without isolated systolic hypertension[a]

Characteristics at baseline	*ISH patients (n = 1320)*	*Non-ISH patients (n = 7873)*
Age, years	70.3 (6.3)	66.4 (7.0)
Women, no. (%)	794 (60.2%)	4169 (53.0%)
Ethnicity, no. (%)		
White	1217 (92.2%)	7286 (92.5%)
Black	81 (6.1%)	452 (5.7%)
Hispanic	14 (1.1%)	86 (1.1%)
Asian	6 (0.5%)	37 (0.5%)
Other	2 (0.2%)	12 (0.2%)
Smoking, no. (%)		
Never	661 (50.1%)	3995 (50.7%)
Ex-smoker	464 (35.2%)	2569 (32.6%)
Current smoker	194 (14.7%)	1305 (16.6%)
Blood pressure, mm Hg		
Systolic	174 (11)	174 (15)
Diastolic	83 (6)	100 (6)
Heart rate, beats per min	72 (11)	74 (11)
Body mass index, $kg\,m^{-2}$	27.5 (4.9)	28.1 (4.8)
Framingham risk score, 5-year event rate, %	23.2 (9.95)	22.3 (9.33)
Cornell product, mm × ms	2792 (1101)	2829 (1020)
Sokolow–Lyon voltage, mm	31.0 (10.4)	29.8 (10.3)
Medical history, no. (%)		
Previously untreated hypertension	440 (33.3%)	2116 (26.9%)
Myocardial infarction	116 (8.8%)	453 (5.8%)
Coronary heart disease	295 (22.3%)	1174 (14.9%)
Cerebrovascular disease	156 (11.8%)	572 (7.3%)
Peripheral vascular disease	111 (8.4%)	409 (5.2%)
Diabetes mellitus	234 (17.7%)	961 (12.2%)
Atrial fibrillation	66 (5.0%)	258 (3.3%)

Abbreviation: ISH, isolated systolic hypertension.
[a]Data are presented as mean (s.d.) unless otherwise indicated.

significant decreases ($P<0.001$) in mean systolic and diastolic BP, Cornell product and Sokolow–Lyon voltage during follow-up, as a consequence of protocol-based antihypertensive therapy.

ECG-LVH and cardiovascular events

In Cox regression models controlling only for treatment with atenolol or losartan, lower in-treatment Sokolow–Lyon voltage was significantly associated with lower rates of the composite end point (HR 0.72, 95% CI: 0.63–0.83, $P<0.001$ per 10.5 mm (1 s.d.) lower Sokolow–Lyon voltage) and cardiovascular death (HR 0.67, 95% CI: 0.54–0.83, $P<0.001$ per 1 s.d. lower Sokolow–Lyon voltage), fatal/non-fatal MI (HR 0.77, 95% CI: 0.61–0.97, $P=0.025$ per 1 s.d. lower Sokolow–Lyon voltage) and fatal/non-fatal stroke (HR 0.71, 95% CI: 0.58–0.87, $P=0.001$ per 1 s.d. lower Sokolow–Lyon voltage). In parallel analyses, lower in-treatment Cornell product was associated with lower rates of the composite end point (HR 0.83, 95% CI: 0.74–0.92, $P<0.001$ per 1050 mm × ms (1 s.d.) lower Cornell product), cardiovascular death (HR 0.74, 95% CI: 0.64–0.85, $P<0.001$ per 1 s.d. lower Cornell product) and MI (HR 0.83, 95% CI: 0.70–0.98, $P=0.03$ per 1 s.d. lower Cornell product), but not stroke (HR 0.99, 95% CI: 0.83–1.18, $P=0.91$ per 1 s.d. lower Cornell product). In additional models adjusting for treatment, baseline Framingham risk score, as well as baseline and in-treatment systolic and diastolic BP, the results were largely unaltered (Figure 3). A 1050 mm × ms (1 s.d.) lower Cornell product was associated with a 17% (95% CI: 8–25%) lower risk of the composite cardiovascular end point ($P=0.001$), a 25% (95% CI: 14–35%) lower risk of cardiovascular death ($P<0.001$) and a 17% (95% CI: 2–30%) lower risk of MI ($P=0.028$). A 10.5 mm (1 s.d.) lower Sokolow–Lyon voltage was associated with a 25% (95% CI: 13–35%) lower risk of the composite cardiovascular end point ($P<0.001$), a 28% (95% CI: 11–42%) lower risk of cardiovascular death ($P=0.003$), a 23% (95% CI: 2–39%) lower risk of MI ($P=0.037$) and a 25% (95% CI: 7–39%) lower risk of stroke ($P=0.008$).

The interaction analyses between ISH status (ISH versus non-ISH) and time-varying ECG-LVH, showed a significant interaction between lower time-varying Sokolow–Lyon voltage and lower risk of the

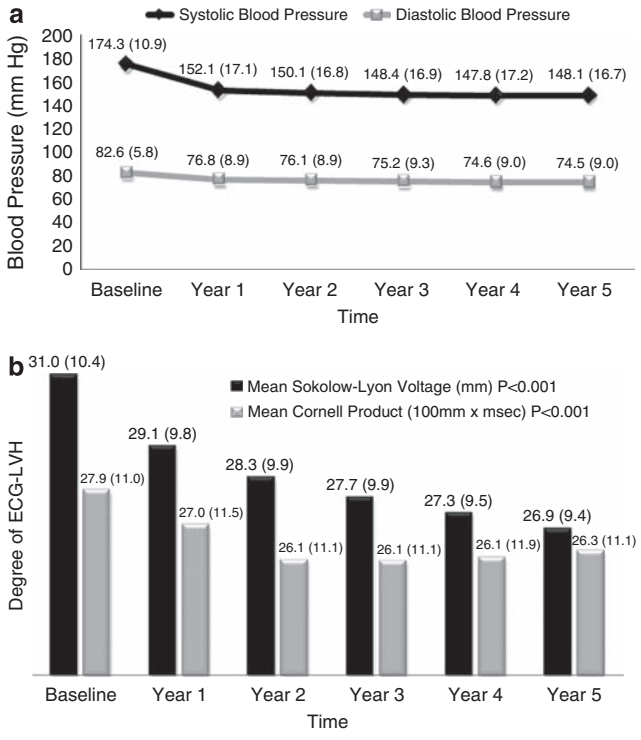

Figure 2 (**a**) Systolic and diastolic blood pressure: significant overall reduction from baseline to year 5 ($P<0.001$). Data are presented as mean (s.d.). (**b**) Electrocardiographic left ventricular hypertrophy was significantly reduced from baseline to year 5. Data are presented as mean (s.d.).

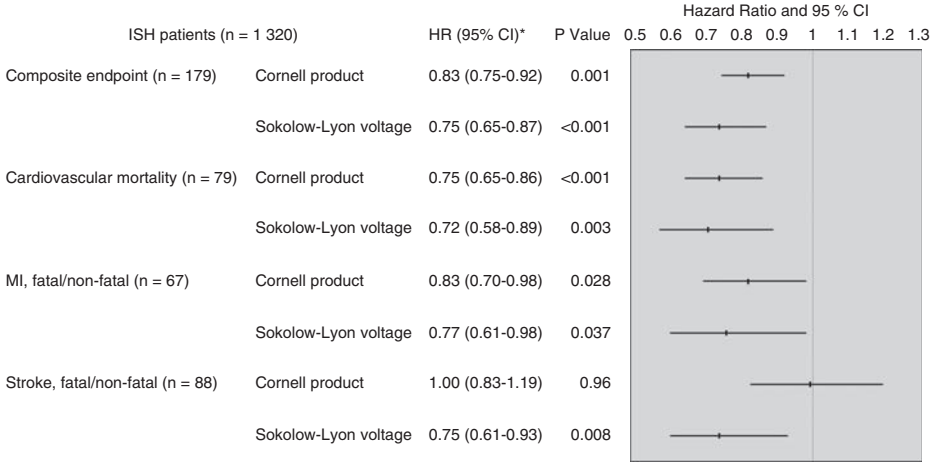

Figure 3 Forest plot: results of Cox proportional hazards models with Cornell product and Sokolow–Lyon voltage as time-varying covariates in examining cardiovascular morbidity and mortality in patients with isolated systolic hypertension. Results were adjusted for treatment effect, baseline Framingham risk score and systolic and diastolic blood pressures at baseline and during treatment. ISH, isolated systolic hypertension; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction. *HRs calculated per 1 s.d. decrease in Cornell product (1050 mm × ms) and Sokolow–Lyon voltage (10.5 mm).

composite end point in ISH versus non-ISH patients ($P=0.048$), that is, ISH patients had an increased outcome effect of reduced time-varying Sokolow–Lyon voltage compared with non-ISH patients. When time-varying systolic BP was added to the model with ISH status and time-varying Sokolow–Lyon criteria, the interaction product of ISH status and time-varying Sokolow–Lyon criteria was borderline significant ($P=0.06$). Not surprisingly, time-varying systolic BP is a strong predictor of the composite end point and a very strong covariate in the above-mentioned regression model. There was no significant interaction between ISH status and the time-varying Cornell product.

Discussion

In this pre-specified prospective substudy in patients with ISH and LVH, we found significant associations between lower in-treatment ECG-LVH by Cornell voltage-duration product or Sokolow–Lyon voltage and reduced risk of the composite end point of cardiovascular death, non-fatal MI or non-fatal stroke. Similarly, we found significant associations between lower in-treatment ECG-LVH and reduced risk of cardiovascular mortality and MI. Furthermore, lower in-treatment Sokolow–Lyon voltage was associated with lower risk of stroke. These results were independent of treatment modality, baseline and in-treatment BP and baseline Framingham risk score. Interaction analyses between ECG-LVH and ISH status identified a significant interaction between lower in-treatment Sokolow–Lyon voltage and lower risk of the composite end point in patients with ISH as compared with those without ISH.

To our knowledge, this is the first study to report a strong, independent association between lower in-treatment ECG-LVH and reduced risk of cardiovascular morbidity and mortality in patients with ISH. LVH demonstrated by ECG and echocardiography is a strong predictor of cardiovascular disease, particularly of cerebrovascular events;[45] and studies have shown that prevention and regression of both indices of LVH are associated with reduced risk of cardiovascular disease.[4,5,19,23,39,46] Predicting the outcome by echocardiography was proven by Levy *et al.*,[9] but to show that regression of LVH translates into improved prognosis, we needed statistical power and a larger number of participants, which was feasible to recruit by ECG only. In particular, this was the case for patients with ISH, which constituted 14.4% of the LIFE population recruited by ECG-LVH. ISH patients were somewhat older than non-ISH patients (Table 1), but the difference was only 3.9 years on average, and overall there is quite minimal overlap between the elderly LIFE participants previously discussed[47] and the ISH subpopulation included in this study. There is a lot of focus on ISH as a particular subgroup of hypertensive patients with stiffer large arteries and worse prognosis, that is, more advanced disease.[3] In LIFE, the ISH subgroup was therefore pre-specified in the data analysis protocol as a group of particular interest,[41] a hypothesis that we pursued in this study. In the main LIFE study, the predictive power of lower in-treatment echo-LVH[46] was similar to the predictive power of lower in-treatment ECG-LVH. Unfortunately, the number of patients with ISH in the echocardiography substudy ($n=145$) was too small to produce any meaningful results for in-treatment echo-LVH.

Our results also suggest superior performance for Sokolow–Lyon voltage LVH compared with Cornell voltage-duration product LVH for prediction of cardiovascular end points in patients with ISH compared with patients without ISH. A possible explanation for this may be that Sokolow–Lyon voltage LVH is strongly associated with systolic BP and therefore ISH, whereas Cornell product LVH is more related to metabolic risk factors.[48] In addition, a possible explanation for the better performance of the Sokolow–Lyon voltage, which is easier to use in clinical practice than the Cornell product, may be sought in the way these criteria were originally developed. It seems that in the Veteran Administration population of hypertensive patients who were investigated for the development of the Sokolow–Lyon ECG-LVH criteria, a majority of patients had quite severe hypertension with a high contribution of patients with ISH.[32] Our data indicate that the regression of ECG-LVH by Cornell voltage-duration product may reach a nadir earlier than the regression of ECG-LVH by Sokolow–Lyon voltage in patients with ISH (Figure 2b). Again, this is possibly explained by the two ECG-LVH criteria characterizing somewhat different LVH populations; Sokolow–Lyon more patients with concentric LVH and Cornell more patients with eccentric LVH;[46] these populations may respond somewhat differently to antihypertensive treatment with respect to regression of LVH. Normalization of the ECG should be sought in all hypertensive patients with ECG-LVH to improve their prognosis, and according to our present data for patients with ISH, this is even more so in the case of having Sokolow–Lyon criteria on ECG.

The association between lower in-treatment LVH and reduced risk of cardiovascular events partly explains our previous report in which treatment with losartan, regardless of similar BP reductions, resulted in lower cardiovascular morbidity and mortality compared with atenolol in patients with ISH, as we found that losartan was more effective in reducing LVH.[41] Furthermore, our data complement a recent report from the LIFE study indicating that there were significantly higher risks for the primary composite end point, stroke and total mortality in the highest versus lowest quartile of baseline pulse pressure with atenolol-based treatment. The risks in the losartan group also increased with increasing pulse pressure quartile, but were lower than those in

the atenolol group, and were not significant.[49] Our study also complements results from the SCOPE (Study on Cognition and Prognosis in the Elderly) substudy including 1518 patients with ISH, in which candersartan-based treatment resulted in a 42% ($P=0.049$) risk reduction for stroke in comparison with other antihypertensive treatment, despite small differences in BP lowering.[50] Finally, data from a substudy of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) trial, indicated that central aortic BP may especially be an important determinant of cardiovascular outcomes,[51] and one could speculate that this effect is even more profound in patients with ISH because of higher arterial stiffness.

In conclusion, lower in-treatment LVH determined by Cornell voltage-duration product and Sokolow–Lyon voltage, was associated with lower likelihoods of cardiovascular morbidity and mortality, independent of BP lowering, baseline Framingham risk score and treatment modality in patients with ISH. These results indicate that targeting antihypertensive treatment at regression or prevention of ECG-LVH, and beyond that of lowering BP, may reduce cardiovascular morbidity and mortality in patients with ISH. This study supports serial measurements of ECG-LVH, and in particular Sokolow–Lyon voltage, for risk stratification in patients with ISH undergoing antihypertensive therapy. However, further investigations may be necessary to evaluate whether treatment should be targeted at regression of ECG-LVH in patients with ISH, and not only at specific BP values.

Limitations

There are several limitations to this study; this is a substudy in patients with ISH in the LIFE study; however, ISH patients were selected *a priori* as being of special interest. Patients evaluated in the LIFE study were predominantly White. Patients included had hypertension and ECG-LVH, and thus represent a patient population with increased risk of cardiovascular events compared with hypertensive subjects without LVH; the results may not extend to ISH patients without LVH. In addition, patients with ISH and ECG-LVH were at an even higher baseline risk than the other hypertensive subjects with LVH. Furthermore, as noted previously by Okin *et al.*,[39] the phenomenon of regression to the mean[52] may affect the current findings, with regard to the use of values of Cornell product and Sokolow–Lyon voltage above threshold levels to select patients for the LIFE study, despite our attempt to minimize this problem by using separate screening and baseline ECGs.[35,36] Owing to this selection process and the intrinsic variability of ECG measurements,[52–55] it is likely that both the degree of ECG-LVH at baseline and the subsequent decrease in LVH during therapy were overestimated in some patients. Despite these limitations, improved outcome was associated with lower ECG-LVH, which would actually bias against our findings, because these overestimations due to statistical fluctuations would lead to a more conservative estimate of the effect of ECG-LVH on outcome. Furthermore, assessment of risk based on ECG-LVH criteria considered as time-varying covariates adjusts for both baseline and subsequent levels of these variables, mitigating the effect of any overestimations.[39] There was no significant association between lower ECG-LVH by Cornell voltage-duration product and stroke ($P=0.96$). This result may represent type II error due to lack of power; the LIFE study was designed for the primary composite end point, and not for its components. As a consequence, the HRs for the single end points cardiovascular mortality, all MIs and all strokes require careful interpretation.

What is known about the topic

- Isolated systolic hypertension is associated with increased risk of cardiovascular morbidity and mortality compared with isolated diastolic hypertension.[1,2]
- Left ventricular hypertrophy strongly predicts cardiovascular morbidity and mortality,[4–13] and antihypertensive therapy can produce regression of LVH.[5,12,14–20] However, no study has been performed to assess the effect of reducing ECG-LVH during antihypertensive therapy in patients with isolated systolic hypertension.

What this study adds

- Lower in-treatment LVH determined by Cornell voltage-duration product and Sokolow–Lyon voltage, was associated with lower likelihoods of cardiovascular morbidity and mortality, independent of BP lowering, baseline Framingham risk score and treatment modality in patients with ISH.
- The results support serial measurements of ECG-LVH, in particular, Sokolow–Lyon voltage, for risk stratification in patients with ISH undergoing antihypertensive therapy and indicate that targeting antihypertensive treatment at regression or prevention of ECG-LVH, and beyond that of lowering BP, may reduce cardiovascular morbidity and mortality in these patients.

Conflict of interest

The LIFE study (Losartan Intervention For Endpoint reduction in hypertension) was originally sponsored by Merck and Co. Inc., Whitehouse Station, NJ, USA. MHO, RBD, SEK and KW were investigators and RBD, HI, SEK and BD were steering committee members for the LIFE Study. BD, RBD and KW have received grant support from Merck and Co. Inc., the sponsor for the LIFE study. All of the authors (except ACKL) receive occasional speaker honoraria from Merck and Co. Inc.

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