ORIGINAL ARTICLE

Electrocardiographic Left Ventricular Hypertrophy Predicts Cardiovascular Morbidity and Mortality in Hypertensive Patients: The ALLHAT Study

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BACKGROUND
Electrocardiographic (ECG) left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular (CV) morbidity and mortality. However, the predictive value of ECG LVH in treated hypertensive patients remains unclear.

METHODS
A total of 33,357 patients (aged ≥ 55 years) with hypertension and at least 1 other coronary heart disease (CHD) risk factor were randomized to chlorthalidone, amlodipine, or lisinopril. The outcome of the present study was all-cause mortality; and secondary endpoints were CHD, nonfatal myocardial infarction (MI), stroke, angina, heart failure (HF), and peripheral arterial disease. Cornell voltage criteria (S in V_3 + R in aVL > 28 [men] or >22 mm [women]) defined ECG LVH.

RESULTS
ECGs were available at baseline in 26,384 patients. Baseline Cornell voltage LVH was present in 1,741 (7%) patients, who were older (67.4 vs. 66.6 years, $P < 0.001$), more likely to be female (74 vs. 44%, $P < 0001$) with a higher systolic blood pressure (151 vs. 146 mm Hg, $P < 0.001$) than patients without ECG LVH. During 5.0 ± 1.4 years mean follow-up, baseline and in-study ECG LVH was significantly associated with 29 to 98% increased risks of all-cause mortality, MI, CHD, stroke, and HF in multivariable Cox analyses.

CONCLUSIONS
Baseline Cornell voltage LVH is associated with increased CV morbidity and all-cause mortality in treated hypertensive patients independent of treatment modality and other CV risk factors.

CLINICAL TRIALS REGISTRATION
Trial Number NCT00000542.

Keywords: blood pressure; Cornell voltage; electrocardiographic left ventricular hypertrophy; hypertension.

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Several studies have shown that left ventricular hypertrophy (LVH), detected by echocardiography[1] or the 12-lead electrocardiogram (ECG),[2] is not only a cardinal adaptation to increased hemodynamic load in hypertension, but also a common manifestation of preclinical cardiovascular (CV) disease that strongly predicts CV morbidity and mortality.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study[3,4] has previously shown that higher values of ECG LVH by Cornell product and/or Sokolow-Lyon voltage criteria during antihypertensive therapy were associated with higher rates of CV morbidity and mortality, independent of treatment modality and of decreases in blood pressure (BP) in a prospectively studied population of patients with hypertension selected to be at increased risk of CV events based on the presence of LVH on a screening ECG.[5] However, the relation of baseline and in-study ECG LVH to death and CV events in less-selected, lower risk hypertensive patients with average or low prevalence of ECG LVH has not yet been evaluated. Accordingly, the present study was undertaken to determine the predictive value of baseline or development of ECG LVH in hypertensive patients enrolled in the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Study (ALLHAT).

METHODS

Study design

The ALLHAT rationale and design have been reported previously.[6,7] Briefly, participants were men and women aged ≥55 years who had stage 1 or 2 hypertension plus an

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additional risk factor for coronary heart disease (CHD). Individuals with a history of hospitalized or treated symptomatic heart failure (HF) or known left ventricular ejection fraction <35% were excluded. Participants (n = 33,357) were randomly assigned to chlorthalidone, amlodipine, or lisinopril and pairwise comparisons of the latter 2 agents to the diuretic were to be undertaken to assess the incidence of outcomes.

All participants gave written informed consent, and all centers obtained institutional review board approval. Follow-up visits were at 1, 3, 6, 9, and 12 months and quarterly thereafter. Goal BP of <140/90 mm Hg was to be achieved by titration of the assigned study drug (step 1) and addition of open-label agents (step 2 or 3) when necessary. Step 1 drugs were encapsulated and identical in appearance. Dosages were 12.5–25 mg/day for chlorthalidone, 2.5–10 mg/day for amlodipine, and 10–40 mg/day for lisinopril. The choice of step 2 drugs was at the clinician's discretion. Study-supplied open-label drugs were atenolol, reserpine, and clonidine for step 2 and hydralazine for step 3. Other open-label drugs were permitted if clinically indicated.

For the present *post-hoc* analysis, patients with pacemaker or left or right ventricular branch block were excluded.

Electrocardiography

ECGs were recorded at clinical sites using standardized procedures at baseline and biannually thereafter until study termination or patient death. Individual ECG tracings were forwarded to the core ECG Reading Center (University of Minnesota, Minneapolis), where cross-sectional and serial coding of multiple variables was performed manually by reviewers blinded to treatment assignment. These readings were obtained from 1994 to 2002. Patients were excluded if they had baseline complete left bundle branch block, complete right bundle branch block, nonspecific intraventricular conduction delay QRS ≥120 ms or pacemaker.[8] Cornell voltage, the sum of R wave amplitude in aVL and S wave amplitude in V_3, >22 mm in women and >28 mm in men was used to identify LVH.[9]

Endpoints

Follow-up procedures, study endpoints, and ascertainment of events have been described previously.[7,10] The primary endpoint of the present study was all-cause mortality; and secondary endpoints were CHD, nonfatal myocardial infarction (NFMI), stroke, angina, HF, and peripheral arterial disease.

Statistical analyses

Data are expressed as mean (SD) or as proportions. Differences between groups with and without LVH were assessed by independent samples t tests and contingency tables. To test the hypothesis that LVH during antihypertensive therapy results in more clinical events, independent of antihypertensive treatment type and degree of BP lowering, the effect of baseline ECG LVH on risk of clinical endpoints was analyzed, following all randomized patients with baseline ECG LVH values for endpoints for the entire duration of the study, regardless of protocol violations or discontinuation of study medication. The effect of baseline ECG LVH on the risk of clinical endpoints, expressed as the hazard ratio and its 95% confidence interval was analyzed using multivariable Cox regression models. In these models, Cornell voltage was examined using four separate approaches: as a dichotomous variable for the presence or absence of LVH; as a continuous variable; as quartiles of increasing voltage; and as a dichotomous variable comparing the upper quartile with the lower 3 quartiles. The relationship of clinical outcomes to changing levels of ECG LVH during treatment was assessed using Cox models in which ECG LVH measured during the study was entered as a time-varying covariate. The multivariable models were adjusted to standard baseline covariates of age, treatment group, race, ethnicity; history of diabetes, CHD, smoking, and aspirin use; and measured values of heart rate, body mass index, systolic and diastolic BP, potassium, glucose, (estimated) glomerular filtration rate, total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, and triglycerides in a stepwise fashion. Data management and analyses were performed by the ALLHAT study group.

RESULTS

Patient characteristics

Detailed baseline characteristics of ALLHAT participants have been reported previously. Briefly, mean age was 67 years, 53% were male, 25% had a history of CHD, and 36% had a history of diabetes mellitus.

Baseline characteristics of patients with and without baseline ECG LVH are shown in Table 1. Patients with ECG LVH were older; were more likely to be female, Black, nonsmoker; had a higher systolic and diastolic BP, higher heart rate, higher glucose, higher total, low-density lipoprotein and high-density lipoprotein cholesterol; but had less aspirin use, slightly lower kidney function, potassium, and triglyceride levels.

Changes in ECG LVH

Number of individuals with consecutive ECGs at follow-up is shown in Table 2. Cornell voltage characteristics at baseline and years 2, 4, and 6 of the study are presented in Table 3. At baseline, 1,741 patients had ECG LVH. During the study, there was a progression of Cornell voltage in patients with Cornell voltage LVH and a small decrease in Cornell voltage in patients without Cornell voltage LVH (Table 3).

Clinical end points

The primary outcome of all-cause mortality occurred in 3,561 patients during 6 years of follow-up; 69.9/1,000 patient-years in patients with LVH and 46.1/1,000 patient-years in patients without LVH. CHD occurred in 2,290

Table 1. Baseline characteristics by Cornell voltage left ventricular hypertrophy at baseline for subjects with baseline electrocardiogram

	Total	Cornell voltage LVH No	Cornell voltage LVH Yes	*P*
N[a]	26,384	24,643	1,741	
Age—mean (SD) years	66.7 (7.6)	66.6 (7.5)	67.4 (8.4)	<0.001
Female—*n* (%)	12,207 (46.3)	10,920 (44.3)	1,287 (73.9)	<0.001
Black—*n* (%)	9,020 (34.2)	8,020 (32.5)	1,000 (57.4)	<0.001
Hispanic—*n* (%)	4,515 (17.1)	4,218 (17.1)	297 (17.1)	0.951
Systolic blood pressure—mean (SD) mm Hg	146 (16)	146 (16)	151 (15)	<0.001
Diastolic blood pressure—mean (SD) mm Hg	84 (10)	84 (10)	86 (11)	<0.001
Heart rate—mean (SD) beats/min	73 (11)	73 (11)	74 (11)	<0.001
Body mass index	29.7 (6.1)	29.7 (6.1)	29.9 (6.3)	0.232
Current smoker—*n* (%)	5,868 (22.2)	5,534 (22.5)	334 (19.2)	0.002
Atherosclerotic coronary vascular disease—*n* (%)	13,483 (51.1)	12,617 (51.2)	866 (49.7)	0.240
Type II diabetes—*n* (%)	9,257 (35.1)	8,627 (35.0)	630 (36.2)	0.319
History of coronary heart disease—*n* (%)	6,571 (25.1)	6,198 (25.4)	373 (21.6)	0.001
Aspirin use—*n* (%)	9,623 (36.5)	9,122 (37.0)	501 (28.8)	<0.001
Assigned antihypertensive treatment group				0.750
Chlorthalidone—*n* (%)	12,106 (45.9)	11,322 (45.9)	784 (45.0)	
Amlodipine—*n* (%)	7,152 (27.1)	6,670 (27.1)	482 (27.7)	
Lisinopril—*n* (%)	7,126 (27.0)	6,651 (27.0)	475 (27.3)	
Potassium—mean (SD) mEq/l	4.3 (0.5)	4.3 (0.5)	4.2 (0.5)	<0.001
Glucose—mean (SD) mg/dl	123.5 (59.6)	123.3 (59.3)	126.4 (63.6)	0.041
Estimated glomerular filtration rate—mean (SD) ml/min per 1.73 m^2[†,b]	77.8 (19.4)	77.9 (19.3)	76.2 (21.5)	0.001
Cholesterol—mean (SD) mg/dl	216.3 (43.2)	215.7 (43.0)	223.7 (45.9)	<0.001
LDL—mean (SD) mg/dl	136.0 (36.9)	135.6 (36.8)	141.2 (38.6)	<0.001
HDL—mean (SD) mg/dl	46.8 (14.8)	46.5 (14.7)	50.8 (16.0)	<0.001
Triglycerides mean (SD) mg/dl	176.8 (136.6)	177.6 (135.1)	165.4 (155.6)	<0.001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy.
[a]Years to death, mean (SD): Total = 5.0 (1.4); Cornell voltage LVH No = 5.0 (1.3), Yes = 4.9 (1.5); $P < 0.001$.
[b]Simplified 4-variable Modification of Diet in Renal Disease Study Formula.

Table 2. Number of individuals with consecutive electrocardiograms at follow-up (of 31,189 baseline electrocardiograms for 33,357 randomized subjects)

	N	%
Baseline	26,384	84.6
Baseline and one other electrocardiogram (any year)	20,676	66.3
Baseline and year 2	18,751	60.1
Baseline and years 2 and 4	14,227	45.6
Baseline and years 2, 4, and 6	4,069	13.1

patients, NFMI in 1,084, stroke in 1,168, angina in 2,780, HF in 1,575, and peripheral arterial disease in 841 patients. No outcomes had significant study treatment and Cornell voltage interactions; the test for interaction between study treatment and Cornell voltage on the primary endpoint of mortality was amlodipine/chlorthalidone $P = 0.189$, lisinopril/chlorthalidone = 0.754.

All-cause mortality. The results of multivariable Cox proportional hazards analyses considering baseline Cornell voltage are summarized in Table 4. In multivariable analysis adjusting for baseline characteristics, higher baseline Cornell voltage examined as a continuous variable and ECG LVH presence were strongly associated with higher risk of death (Figure 1). Furthermore, having a Cornell voltage in the 4th quartile or the 75th percentile were associated with higher risk of death compared to the 1st quartile and the lower than 75th percentile, respectively. Similar relationships to all-cause mortality were seen when baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables, with statistically significant associations with all-cause mortality (Table 5).

Coronary heart disease. In multivariable Cox analyses (Table 4), higher baseline Cornell voltage, baseline ECG LVH presence, Cornell voltage in the 4th quartile and the 75th percentile were associated with higher risk of CHD (Table 4).

Table 3. Cornell voltage characteristics

	Total		
	N	Mean (SD)	Range
Baseline	26,384	14.74 (6.53)	
Q1	7,165	7.51 (2.23)	0–10
Q2	6,838	12.51 (1.11)	11–14
Q3	5,819	16.39 (1.11)	15–18
Q4	6,562	23.48 (4.76)	19–64
Year 2	18,762	14.39 (6.43)	
Q1	5,370	7.37 (2.27)	0–10
Q2	4,935	12.49 (1.11)	11–14
Q3	4,107	16.39 (1.12)	15–18
Q4	4,350	23.30 (4.65)	19–63
Difference from baseline	18,751	−0.15 (4.84)	
Cornell voltage Yes	1,080	4.67 (7.64)	
Cornell voltage No	17,671	−0.44 (4.44)	
Year 4	15,913	14.51 (6.63)	
Q1	4,646	7.38 (2.33)	0–10
Q2	4,019	12.51 (1.10)	11–14
Q3	3,366	16.40 (1.12)	15–18
Q4	3,882	23.47 (4.81)	19–61
Difference from baseline	15,903	−0.02 (5.28)	
Cornell voltage Yes	1,023	6.05 (7.76)	
Cornell voltage No	14,880	−0.44 (4.79)	
Year 6	5,324	14.67 (6.92)	
Q1	1,560	7.31 (2.34)	0–10
Q2	1,308	12.53 (1.11)	11–14
Q3	1,132	16.44 (1.12)	15–18
Q4	1,324	25.93 (5.20)	19–51
Difference from baseline	5,319	−0.04 (5.78)	
Cornell voltage Yes	375	7.03 (8.40)	
Cornell voltage No	4,944	−0.57 (5.16)	

Similar relationships to CHD were seen when baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables; higher baseline Cornell voltage, baseline ECG LVH presence, Cornell voltage in the 4th quartile and the 75th percentile were associated with higher risk of CHD (Table 5).

Nonfatal Myocardial Infarction. In multivariable (Table 4) Cox analyses, higher baseline Cornell voltage and baseline ECG LVH presence were associated with higher risk of NFMI. Similar relationships to NFMI were seen when baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables, with statistically significant associations with NFMI for higher baseline Cornell voltage, baseline ECG LVH presence, Cornell voltage in the 4th quartile or the 75th percentile in multivariable analyses (Table 5).

Stroke. In multivariable (Table 4) Cox analysis, higher baseline Cornell voltage examined as a continuous variable and ECG LVH presence were strongly associated with higher risk of stroke. Furthermore, having a Cornell voltage in the 3rd or 4th quartile or the 75th percentile were associated with higher risk of stroke compared to the 1st quartile and the lower than 75th percentile, respectively. Similar relationships to stroke were seen when baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables, with statistically significant associations with stroke for all analyses (Table 5).

Angina. In multivariable Cox analyses higher baseline Cornell voltage, baseline ECG LVH presence, as well as Cornell voltage in the 4th quartile or the 75th percentile, were associated with angina.

When baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables (Table 5), higher baseline Cornell voltage examined as a continuous variable and ECG LVH presence were associated with higher risk of angina. Furthermore, having a Cornell voltage in the 3rd or the 4th quartile or the 75th percentile were associated with higher risk of angina compared to the 1st quartile and the lower than 75th percentile, respectively (Table 5).

Heart failure. In multivariable analysis (Table 4), higher baseline Cornell voltage examined as a continuous variable and ECG LVH presence were strongly associated with higher risk of HF. Furthermore, having a Cornell voltage in the 4th quartile or the 75th percentile were associated with higher risk of HF compared to the 1st quartile and the lower than 75th percentile, respectively. Similar relationships to HF were seen when baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables, with statistically significant associations with HF for all analyses (Table 5).

Peripheral arterial disease. In multivariable analyses, higher baseline Cornell voltage, along with a Cornell voltage in the 4th quartile or the 75th percentile, were associated with higher risk of PAD (Table 4). However, there was no association of baseline Cornell voltage or ECG LVH presence to PAD when baseline ECG LVH presence and Cornell voltage were replaced with on-treatment measures of Cornell voltage treated as time-dependent variables, with no statistically significant associations with PAD for any analyses (Table 5).

DISCUSSION

This study provides the first evidence; from a large population of hypertensive patients not selected to have LVH at

Table 4. Multivariable Cox hazard ratios (95% confidence intervals) for baseline Cornell voltage left ventricular hypertrophy

	Death[a]	*P*	Coronary heart disease[b]	*P*	Nonfatal myocardial infarction[c]	*P*	Stroke[d]	*P*	Angina[e]	*P*	Heart failure[f]	*P*	Peripheral arterial disease[g]	*P*
Cornell voltage (per mm)														
Total	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.042	1.03 (1.02–1.04)	<0.001	1.01 (1.00–1.02)	0.005	1.03 (1.02–1.04)	<0.001	1.01 (1.00–1.02)	0.038
LVH by Cornell voltage														
Total	1.30 (1.15–1.47)	<0.001	1.29 (1.09–1.51)	0.002	1.28 (1.00–1.64)	0.049	1.71 (1.41–2.07)	<0.001	1.18 (1.01–1.39)	0.041	1.92 (1.63–2.27)	<0.001	0.97 (0.71–1.33)	0.859
Cornell voltage quartile	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2														
Total	1.07 (0.97–1.18)	0.176	1.04 (0.92–1.18)	0.505	0.93 (0.78–1.11)	0.426	1.09 (0.91–1.31)	0.345	1.01 (0.91–1.13)	0.858	0.97 (0.84–1.14)	0.740	1.05 (0.86–1.29)	0.618
Q3														
Total	1.10 (0.99–1.21)	0.074	1.13 (1.00–1.29)	0.049	1.10 (0.93–1.32)	0.271	1.25 (1.04–1.50)	0.018	1.04 (0.93–1.17)	0.487	0.97 (0.83–1.14)	0.736	1.16 (0.94–1.42)	0.177
Q4														
Total	1.28 (1.16–1.41)	<0.001	1.28 (1.13–1.44)	<0.001	1.10 (0.93–1.32)	0.268	1.60 (1.35–1.90)	<0.001	1.14 (1.03–1.28)	0.016	1.58 (1.38–1.82)	<0.001	1.26 (1.03–1.55)	0.025
Cornell voltage 75th percentile														
Total	1.21 (1.13–1.31)	<0.001	1.21 (1.10–1.33)	<0.001	1.10 (0.95–1.27)	0.213	1.45 (1.27–1.65)	<0.001	1.13 (1.03–1.23)	0.010	1.61 (1.44–1.80)	<0.001	1.19 (1.00–1.40)	0.046

Abbreviations: BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Adjusted for baseline variables of:

[a]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, DBP, BMI, potassium, glucose, GFR, HDL, and triglycerides; females-age, treatment group, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, BMI, glucose, GFR, HDL, and triglycerides; males-age, treatment group, race, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, potassium, glucose, GFR, and triglycerides.

[b]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, BMI, potassium, glucose, GFR, LDL, and HDL; females-age, treatment group, ethnicity, history of diabetes, history of CHD, current or former smoker, SBP, BMI, potassium, glucose, GFR, total cholesterol, and HDL; males-age, treatment group, race, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, glucose, GFR, and total cholesterol.

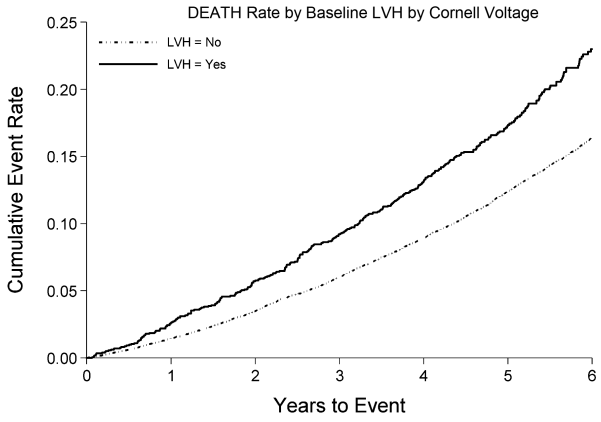
[c]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, BMI, glucose, GFR, HDL, and total cholesterol; females-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, BMI, potassium, glucose, total cholesterol, LDL, and triglycerides; males-age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, GFR, LDL, and HDL.

[d]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, BMI, glucose, GFR, LDL, and HDL; females-age, treatment group, ethnicity, history of diabetes, current or former smoker, SBP, glucose, GFR, and HDL; males - age, treatment group, race, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, BMI, glucose, GFR, LDL, and HDL.

[e]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, heart rate, DBP, BMI, LDL, HDL, and triglycerides; females-age, treatment group, ethnicity, history of CHD, aspirin use, DBP, BMI, LDL, and triglycerides; males-age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, heart rate, BMI, total cholesterol, HDL, and triglycerides.

[f]Total = age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, glucose, GFR, and HDL; females-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, glucose, and GFR; males-age, treatment group, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, DBP, BMI, glucose, GFR, LDL, and HDL.

[g]Total = age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, potassium, glucose, GFR, total cholesterol, HDL, and triglycerides; females-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, BMI, potassium, and HDL; males-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, BMI, potassium, glucose, GFR, HDL, total cholesterol.



Mortality Rates by LVH at Baseline

	Mortality					
	With LVH			Without LVH		
Year	Number of Deaths	Interval Mortality per 1000 person-years	6 year mortality per 100 persons (SE)	Number of Deaths	Interval Mortality per 1000 person-years	6 year mortality per 100 persons (SE)
1	45	26.3		357	14.6	
2	54	32.6		499	20.8	
3	60	37.5		612	26.2	
4	67	44.1		706	31.6	
5	56	50.1		642	38.7	
6	43	69.9	22.88 (1.20)	420	46.1	16.30 (0.28)

Figure 1. Death rates by baseline electrocardiographic left ventricular hypertrophy. Abbreviation: LVH, left ventricular hypertrophy.

baseline, that both baseline and time-varying ECG LVH as well as higher baseline and time-varying Cornell voltage as a continuing variable are associated with higher rates of morbidity and mortality in a middle aged population of hypertensive patients with stage 1 or 2 hypertension plus an additional risk factor for CHD.

In an echocardiographic LIFE substudy,[11] the presence of ECG LVH by Cornell product and/or Sokolow-Lyon voltage criteria identified patients with hypertension having a greater than 70% likelihood of having echocardiographic LVH as well as those not fulfilling the strict cutoff criteria for echocardiographic LVH but with high normal values of indexed LV mass. Moreover, regression of ECG LVH by Cornell product criteria was associated with greater reductions in LV mass and a higher likelihood of regression of echocardiographic LVH in the LIFE study,[12] suggesting that changes in ECG LVH and echocardiographic LVH are linked.

Previous studies show that ECG LVH regression is associated with lower rates of CV events and mortality.[2,5,13,14] The Framingham Heart Study showed in an observational study with ECG LVH by various criteria[2] that a significant decline in Cornell voltage was associated with lower risk of CV disease, whereas a significant increase in Cornel voltage identified individuals at increased risk of CV disease. As a proof of concept, the LIFE study demonstrated that regression of ECG LVH improved prognosis, independent of improvements in BP during antihypertensive therapy.[5,15–17]

The LIFE study[5] included hypertensive patients with ECG LVH as a surrogate of increased risk of CV events, whereas the present study included hypertensive patients with an additional risk factor for CHD including; previous (6 > months) myocardial infarction or stroke, LVH demonstrated by ECG or echocardiography, history of type 2 diabetes, current cigarette smoking, low high-density lipoprotein cholesterol or other documented other atherosclerotic CV disease. The use of Cornell voltage and Sokolow-Lyon voltage to select patients in the LIFE study[5] limits the generalizability of these findings which may not be representative of other hypertensive populations. In contrast, only 8% of patients had ECG LVH at baseline in the present study. Despite the different population, the present study detected significant increased rates of CV events and all-cause mortality in patients with baseline ECG LVH and higher Cornell voltage independent of antihypertensive treatment and co-morbidity. Moreover, during antihypertensive treatment persistence or development of ECG LVH was significantly associated with increased rates of CV events and all-cause mortality independent of BP.

In a study of 126 never-treated subjects with essential hypertension, echocardiographic LV hypertrophy predicted complex ventricular arrhythmias independently of age and high nocturnal BP.[18] In the LIFE study, lower in-treatment Cornell voltage-duration product was associated with a lower risk of SCD, death resulting from HF, CV death after 24 hours, and death resulting from other CV causes but not death resulting from non-CV death.[17] Other studies have shown that ECG LVH can lead to scars in the myocardium and thereby create a substrate of electrophysiology disorders and fatal arrhythmias irreversible to antihypertensive treatment.[19] This may in part explain not only why patients with LVH have increased rates of CV mortality and SCD, but also explain why some patients with LVH are less responsive to antihypertensive treatment.

Moderate LVH and some geometrical hypertrophic patterns might be an adaption to the moderate higher afterload and

Table 5. Multivariable Cox hazard ratios (95% confidence intervals) for time-varying Cornell voltage left ventricular hypertrophy

	Death[a]	*P*	Coronary heart disease[b]	*P*	Nonfatal myocardial infarction[c]	*P*	Stroke[d]	*P*	Angina[e]	*P*	Heart failure[f]	*P*	Peripheral arterial disease[g]	*P*
Cornell voltage (per mm)														
Total	1.02 (1.02–1.02)	<0.001	1.03 (1.02–1.03)	<0.001	1.02 (1.01–1.03)	<0.001	1.03 (1.03–1.04)	<0.001	1.01 (1.01–1.02)	<0.001	1.04 (1.03–1.05)	<0.001	1.01 (1.00–1.02)	0.265
LVH by Cornell voltage														
Total	1.41 (1.26–1.59)	<0.001	1.63 (1.41–1.88)	<0.001	1.64 (1.31–2.04)	<0.001	1.75 (1.45–2.12)	<0.001	1.26 (1.08–1.47)	0.004	1.98 (1.69–2.32)	<0.001	0.99 (0.73–1.35)	0.966
Cornell voltage quartile (Q)	1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Q2														
Total	1.07 (0.97–1.18)	0.156	1.07 (0.95–1.22)	0.262	0.93 (0.77–1.11)	0.424	1.10 (0.91–1.32)	0.330	1.07 (0.96–1.19)	0.244	1.11 (0.95–1.30)	0.183	0.95 (0.77–1.17)	0.629
Q3														
Total	1.05 (0.95–1.16)	0.358	1.23 (1.08–1.39)	0.002	1.29 (1.08–1.54)	0.005	1.34 (1.12–1.62)	0.002	1.14 (1.01–1.28)	0.027	1.20 (1.03–1.41)	0.023	1.18 (0.96–1.45)	0.120
Q4														
Total	1.34 (1.22–1.47)	<0.001	1.50 (1.33–1.69)	<0.001	1.32 (1.11–1.57)	0.002	1.76 (1.49–2.09)	<0.001	1.22 (1.10–1.37)	<0.001	1.83 (1.58–2.11)	<0.001	1.14 (0.93–1.40)	0.194
Cornell voltage 75th percentile														
Total	1.29 (1.20–1.39)	<0.001	1.37 (1.25–1.50)	<0.001	1.25 (1.08–1.44)	0.002	1.55 (1.36–1.76)	<0.001	1.15 (1.05–1.26)	0.003	1.66 (1.49–1.86)	<0.001	1.11 (0.93–1.31)	0.240

Abbreviations: BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Adjusted for baseline variables of:

[a]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, DBP, BMI, potassium, glucose, GFR, HDL, and triglycerides; females-age, treatment group, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, BMI, glucose, GFR, HDL, and triglycerides; males-age, treatment group, race, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, potassium, glucose, GFR, and triglycerides.

[b]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, BMI, potassium, glucose, GFR, LDL, and HDL; females-age, treatment group, ethnicity, history of diabetes, history of CHD, current or former smoker, SBP, BMI, potassium, glucose, GFR, LDL, and HDL; males-age, treatment group, race, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, glucose, GFR, and total cholesterol.

[c]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, BMI, potassium, glucose, GFR, total cholesterol, and HDL; females-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, potassium, glucose, total cholesterol, LDL, and triglycerides; males-age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, GFR, LDL, and HDL.

[d]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, BMI, glucose, GFR, LDL, and HDL; females-age, treatment group, race, ethnicity, history of diabetes, current or former smoker, SBP, glucose, GFR, and HDL; males-age, treatment group, race, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, BMI, GFR, LDL, and HDL.

[e]Total = age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, heart rate, DBP, BMI, LDL, HDL, and triglycerides; females-age, treatment group, ethnicity, history of CHD, aspirin use, DBP, BMI, LDL, and triglycerides; males-age, treatment group, race, ethnicity, history of diabetes, history of CHD, aspirin use, heart rate, BMI, total cholesterol, HDL, and triglycerides.

[f]Total = age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, glucose, GFR, and HDL; females-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, glucose, and GFR; males-age, treatment group, ethnicity, history of diabetes, history of CHD, current or former smoker, heart rate, SBP, DBP, BMI, glucose, GFR, LDL, and HDL.

[g]Total = age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, heart rate, SBP, DBP, BMI, potassium, glucose, GFR, HDL, total cholesterol; females-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, BMI, potassium, and HDL; males-age, treatment group, ethnicity, history of diabetes, history of CHD, aspirin use, current or former smoker, SBP, DBP, BMI, potassium, glucose, GFR, and total cholesterol.

angiotensin concentration in hypertensive patients. However, severe LVH can result in some irreversible inappropriate geometrical hypertrophic pattern of LV which has shown to be associated with increased risk of CV events and all-cause mortality independent of antihypertensive treatment.[20] Compared to the present study, the Heart Outcomes Prevention Evaluation (HOPE) trial had similar prevalence (8.2%) of baseline LVH,[13] and showed in accordance with our findings, that persistence or development of LVH was associated with higher risk of death; and regression of LVH was associated with better outcome. A subanalysis of patients without baseline LVH in the HOPE trial showed that these patients had a lower risk of developing LVH if they received antihypertensive treatment with angiotensin-converting enzyme inhibitor compared to other subgroups in their study. These findings suggest that hypertensive patients with severe LVH at baseline may have too great a burden of myocardial scar or fibrosis and/or developed inappropriate geometrical hypertrophic pattern with little or no effect of antihypertensive treatment on myocardial regression and thereby no improvement of survival.

Limitations of the study

The present study was undertaken in patients selected for the combination of mild to moderate hypertension and an additional risk factor for CHD but without HF and thereby may not be directly applicable to patients with isolated hypertension or patients with more severe hypertension or HF. Also, the absence of information on QRS duration precluded calculation of Cornell voltage-duration product criteria that have been utilized in analyses from the LIFE study.[21]

As analyses was only adjusted to baseline and not time-varying BP, we cannot exclude that lower drop in BP caused by treatment resistance or low compliance could have contributed to the increased risk of mortality and morbidity associated with baseline LVH.

In conclusion, the present study extends findings from previous studies showing that higher Cornell voltage, as well as ECG LVH, is an independent risk factor of higher rates of CV events and all-cause mortality, not only in patients know with LVH but also in patients with only mild to moderate hypertension and low prevalence of LVH at baseline.

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Drs Okin and Devereux received grant support from Merck & Co. Dr Devereux consults for Merck & Co, Inc and General Electric Medical Systems. Dr Davis has worked as a consultant for Takeda, Merck, and Glaxo Smith Kline. The other authors declared no conflict of interest.

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