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Serial assessment of the electrocardiographic strain pattern for prediction of new-onset heart failure during antihypertensive treatment: the LIFE study

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Aims Although the presence of the electrocardiographic (ECG) strain pattern has been associated with an increased risk of developing heart failure (HF), the relationship of regression vs. persistence vs. development of new ECG strain to subsequent HF is unclear.

Methods and results Electrocardiographic strain was evaluated at baseline and at year-1 in 7265 hypertensive patients without HF treated with atenolol- or losartan-based regimens. During 3.9 $\pm$ 0.7 years of follow-up after the year-1 ECG, 154 patients (2.1%) were hospitalized for HF. Five-year HF incidence was lowest in patients with no ECG strain (1.6%), intermediate in patients with regression of strain (5.4%), and highest in patients with persistent (7.1%) or new strain (7.0%; $P < 0.0001$ across groups). In the Cox multivariable analyses adjusting for the known predictive value of in-treatment ECG left ventricular hypertrophy by the Cornell product and Sokolow–Lyon voltage, in-treatment QRS duration, systolic and diastolic pressure, incident myocardial infarction and atrial fibrillation, randomized treatment and other risk factors for HF, regression of strain [hazards ratio (HR) 2.4, 95% confidence interval (CI) 1.2–5.0], persistence of strain (HR 1.9, 95% CI 1.2–3.2), and development of new ECG strain (HR 2.3, 95% CI 1.2–4.4) were all independently associated with an increased risk of new HF compared with the absence of ECG strain on both baseline and year-1 ECGs.

Conclusion The development of new ECG strain or persistence of ECG strain between baseline and year-1 is associated with an increased risk of HF. The regression of ECG strain between baseline and year-1 does not convey a decreased risk of HF.

Clinical trials registration: http://clinicaltrials.gov/ct/show/NCT00338260.

Keywords Electrocardiogram • Hypertension • Hypertrophy

Introduction

The classic strain pattern of lateral ST depression and T-wave inversion on the electrocardiogram (ECG) is a well-recognized marker of the presence and severity of anatomical left ventricular hypertrophy (LVH).[1–7] Electrocardiographic strain is associated with depressed LV function[5] and improves ECG detection of structural hypertrophy when incorporated into scores that include standard voltage criteria.[2,4] Electrocardiographic strain has been associated with adverse prognosis in a variety of populations,[8–14]

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including hypertensive patients,[8,9,12–14] and has often been the primary marker of untoward outcomes when ECG LVH criteria have been utilized for risk stratification.[8,12,13] Indeed, strain on the baseline ECG was an independent predictor of cardiovascular (CV) morbidity and mortality[9] and new-onset heart failure (HF)[14] among hypertensive patients with ECG LVH in the LIFE study.

The serial assessment of ECG voltage and voltage–duration product criteria for LVH has demonstrated that the regression of ECG LVH appears to confer a decreased risk of CV mortality and morbidity, including the development of new HF.[11–13,15–18] Among LIFE study patients,[18] a greater than median decrease in the Cornell product LVH was associated with a 36% lower adjusted risk of HF hospitalization, independent of treatment modality, blood pressure lowering, and other HF risk factors. The persistence or development of new ECG strain were strongly associated with an increased risk of CV morbidity and mortality in the LIFE study[19] and with an increased risk of a composite CV endpoint that included new-onset HF in patients with essential hypertension.[12] However, whether changes in the ECG strain pattern provide additional prognostic information for HF onset beyond that provided by changes in ECG LVH[18] and QRS duration[20] in the LIFE study population has not been examined. Therefore, the present study examined the relationship of the strain pattern on the baseline and year-1 ECGs in the LIFE study to the risk of HF hospitalization, independent of other HF risk factors, treatment effects, blood pressure reduction, and of the known effects of in-treatment QRS duration[20] and regression of ECG LVH on HF incidence.[18]

Methods

Subjects

The LIFE study[21,22] enrolled hypertensive patients with ECG LVH by the Cornell product[23] and/or Sokolow–Lyon voltage criteria[1] on a screening ECG in a prospective, double-blind study large enough ($n = 9193$) to demonstrate an appreciable reduction in mortality and morbid events with the use of losartan as opposed to atenolol.[21] Eligible patients were men and women aged 55–80 years with previously untreated or treated essential hypertension with mean blood pressure in the range 160–200/95–115 mmHg after 1 and 2 weeks on placebo. A total of 7265 patients with no history of HF by patient self-report prior to enrolment or during the first year of treatment in LIFE had baseline and year-1 ECGs on which the strain pattern could be determined (3906 women and 3359 men, mean age 67 ± 7 years).

Electrocardiography

Hard-copy ECGs were interpreted at a core laboratory by experienced readers blinded to clinical information as previously reported in detail.[5,9] QRS duration was measured to the nearest 4 ms in all 12 leads and R-wave amplitudes in leads aVL, V5, and V6 and S-wave amplitudes in leads V1 and V3 were measured to the nearest 0.5 mm (0.05 mV).[5,9,20] The product of QRS duration times the Cornell voltage combination [RaVL + SV3, with 6 mm (0.6 mV) added in women] >2440 mm ms[5,22] or the Sokolow–Lyon voltage (SV1 + RV5/6) >38 mm[1,22] was used to identify ECG LVH.

The determination of the presence or absence of ECG strain as a dichotomous variable was visually assessed on baseline and year-1 ECGs at Helsinki University Central Hospital as described previously.[5,9] Repolarization abnormalities in leads V5 and/or V6 were considered consistent with the presence of typical strain when there was a down-sloping convex ST-segment with an inverted asymmetrical T-wave with polarity opposite to the main QRS deflection.[5,9]

Endpoint determination

Hospitalization for HF was a pre-specified secondary endpoint in the LIFE study.[18,22] The diagnosis of HF was based on clinical and diagnostic findings modified from Framingham criteria[24] that are outlined in *Table 1*. Each case was reviewed and verified by the Endpoint Committee, which was blinded to study ECG strain and LVH results when classifying possible morbid events.[21,22]

Statistical methods

Data management and analysis were performed with SPSS version 12.0 software. Data are presented as mean ± SD for continuous variables and proportions for categorical variables. Patients were classified into four groups according to the presence or absence of strain at baseline and year-1 as follows: no strain on either ECG (absence of strain); strain at baseline but not at year-1 (regression of strain); strain on both ECGs (persistence of strain); or no strain at baseline and strain at year-1 (development of new strain). Differences in prevalences between groups were compared using χ^2 analyses and mean values of continuous variables were compared using one-way ANOVA, with *P*-values given for the statistical significance of the linear trend across groups.

Event rates were calculated and plotted according to the Kaplan–Meier product limit method and statistical significance tested for the linear trend across groups using the log-rank statistic. The relation of strain at baseline and year-1 to the risk of developing new HF was assessed using Cox's proportional hazards models. Partial residuals were plotted against survival times and visually examined to check the proportional hazards assumption. To test the independence of serial assessment of ECG strain for incident HF, the presence or absence of ECG strain at baseline and year-1 was entered into a multivariable Cox model that also included as covariates age, gender, treatment group, race, diabetes, history of ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation and smoking, baseline urinary albumin/creatinine ratio, total and HDL cholesterol, glucose, creatinine, uric acid, and body mass index as standard covariates, and baseline and in-treatment values of systolic and diastolic pressure, QRS duration, the Cornell product, the Sokolow–Lyon voltage, and incident myocardial infarction and atrial fibrillation as time-varying covariates.

Analyses were repeated stratifying the population by sex, age, race, treatment group, history of ischaemic heart disease, prevalent diabetes, and by the presence or absence of LVH by the Cornell product and Sokolow–Lyon voltage on the baseline ECG. The interaction between the presence or absence of strain at baseline and year-1 and these variables was formally tested by adding cross-product terms of strain and these variables into the models of the total population. For all tests, a two-tailed *P*-value of <0.05 was required for statistical significance.

Statement of responsibility

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

Table 1 Criteria for diagnosis of heart failure on hospitalization[a]

Major criteria	Minor criteria
Clinical findings	**Clinical findings**
Paroxysmal nocturnal dyspnoea	Night cough
Jugular venous distension	Dyspnoea on ordinary exertion
Pulmonary rales	Bilateral ankle oedema
Ventricular S_3 gallop	Hepatomegaly
Hepatojugular reflux	
Diuresis of 10 pounds or 5 kg in response to diuretic treatment with clinical improvement in congestive symptoms	
Diagnostic findings	**Diagnostic findings**
Chest X-ray	Chest X-ray
Acute pulmonary oedema on chest X-ray	Pleural effusion or pulmonary vascular engorgement or redistribution
Haemodynamic	Haemodynamic
Pulmonary capillary wedge pressure $\geq$20 mmHg	Pulmonary capillary wedge pressure of 16–19 mmHg
Left ventricular ejection fraction $\leq$35%	Left ventricular ejection fraction of 36–44%
Cardiac index $<$2.0 L/min	Cardiac index of 2.0–2.4 L/min
Evidence of severe valvular heart disease	Evidence of moderate valvular heart disease
Autopsy	
Pulmonary oedema, visceral congestion or cardiomegaly	

[a]A definite diagnosis of heart failure required a minimum of: one major clinical plus one major diagnostic finding; or one major clinical plus two minor diagnostic findings; or one minor clinical plus two major or minor diagnostic criteria. Minor criteria were accepted only if they could not be attributed to another disease process.[24]

Results

Electrocardiographic strain was absent on both baseline and year-1 ECGs in 6236 patients (85.8%), regressed from baseline to year-1 in 236 (3.2%), persisted on both ECGs in 517 (7.1%), and was absent at baseline but developed by year-1 in 276 patients (3.8%). Clinical and demographic characteristics of patients in relation to the presence or absence of ECG strain at baseline and year-1 are shown in *Table 2*. Patients without strain on either ECG were younger, more likely to be female, less likely to be black, current smokers or have diabetes, a history of ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease or atrial fibrillation, had higher total and HDL cholesterol levels, less albuminuria, and lower serum glucose, creatinine, and uric acid levels.

Blood pressure and ECG LVH measurements at baseline and changes in these measurements between baseline and last in-study determination in relation to the presence or absence of ECG strain on baseline and year-1 ECGs are shown in *Table 3*. The absence of strain on both ECGs was associated with lower baseline systolic pressures, the Cornell product and Sokolow–Lyon voltage, and with smaller reductions in systolic and diastolic pressure. The regression of strain between baseline and year-1 was associated with the greatest reductions in the Cornell product and Sokolow–Lyon voltage, whereas the development of new strain was associated with the smallest reductions in the Cornell product LVH during the course of the study.

During 3.9 $\pm$ 0.7 years of follow-up after the year-1 ECG, 154 patients (2.1%) had a new HF hospitalization. The relationship of serial evaluation of ECG strain at baseline and year-1 to HF hospitalization is shown in *Table 4* and *Figure 1*. Five-year incidence of hospitalization for HF was lowest in patients with no ECG strain (1.6%), intermediate in patients with regression of strain (5.4%), and highest in patients with persistent (7.1%) or new strain (7.0%; $P < 0.0001$ across groups). Strain on the baseline and/or year-1 ECG was associated with 39.6% (61 of 154) of new cases of HF, although strain was present in only 14.2% of the study population. In univariate Cox's analyses, the persistence of strain or development of a new ECG strain pattern was associated with the highest risk of developing HF, with 4.4- to 4.5-fold increased risks compared with the absence of strain on both ECGs, whereas patients with regression of strain between baseline and year-1 had a greater than three-fold increased risk of HF hospitalization.

Because patients who developed strain differed significantly from those who did not with respect to demographic and clinical variables which could affect outcome (*Tables 1* and *2*), the independent relation of new HF to the presence or absence of strain at baseline and year-1 was examined after adjusting for the possible effects of treatment, age, gender, race, prevalent diabetes, history of ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation and smoking, baseline urinary albumin/creatinine ratio, total and HDL cholesterol, glucose, creatinine, uric acid, and body mass index and for the possible effects of baseline and in-treatment systolic and diastolic blood pressure, QRS duration, the Cornell product and Sokolow–Lyon voltage, and incident myocardial infarction and atrial fibrillation treated as time-dependent covariates (*Table 4*). After adjusting for these factors, the development of new ECG strain, persistence of strain, and regression of ECG strain were each associated with an approximately two-fold increased risk of HF hospitalization. Importantly, in-treatment ECG LVH by the Cornell product and Sokolow–Lyon voltage, treated as time-varying covariates,

Table 2 Demographic and clinical characteristics in relation to the presence of electrocardiographic strain at baseline and year-1

Variables	Strain−/strain− (*n* = 6236), no strain	Strain+/strain− (*n* = 236), regression of strain	Strain+/strain+ (*n* = 517), persistent strain	Strain−/strain+ (*n* = 276), new strain	*P*-value[a]
Age (years)	66.3 ± 7.0	66.8 ± 7.1	67.9 ± 6.8	69.1 ± 6.8	<0.001
Sex (% female)	55.8	38.1	38.3	49.3	<0.001
Race (% Black)	4.2	9.3	15.3	8.0	<0.001
Diabetes (%)	11.5	14.4	18.0	17.0	<0.001
History of IHD (%)	11.3	26.3	30.9	22.8	<0.001
History of MI (%)	3.9	8.9	13.5	10.4	<0.001
History of stroke (%)	3.5	4.2	7.5	6.5	<0.001
History of PVD (%)	4.8	7.6	8.9	8.0	<0.001
History of AFib (%)	2.5	5.1	5.4	10.1	<0.001
Current smoker (%)	15.0	20.8	17.6	26.1	<0.001
Treatment with losartan (%)	50.6	53.8	48.2	41.7	0.014
Body mass index (kg/m^2)	28.1 ± 4.7	27.7 ± 4.4	27.7 ± 4.9	27.6 ± 5.0	0.134
Total cholesterol (mM)	6.06 ± 1.10	5.89 ± 1.18	5.91 ± 1.16	5.98 ± 1.14	0.003
HDL cholesterol (mM)	1.52 ± 0.44	1.41 ± 0.37	1.40 ± 0.40	1.41 ± 0.40	<0.001
UACR (mg/mM)	5.6 ± 28.2	8.0 ± 18.8	13.1 ± 42.2	12.9 ± 32.0	<0.001
Glucose (mM)	5.92 ± 2.00	6.26 ± 2.34	6.36 ± 2.89	6.30 ± 2.50	<0.001
Creatinine (μM)	84.6 ± 18.3	94.3 ± 24.9	95.4 ± 21.9	91.7 ± 20.2	<0.001
Uric acid (mg/mM)	325 ± 77	350 ± 77	347 ± 76	338 ± 76	<0.001

AFib, atrial fibrillation; IHD, ischaemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; UACR, urine albumin/creatinine ratio.
[a]Differences in prevalences between groups were compared using χ^2 analyses and mean values of continuous variables were compared using ANOVA for linear trend.

Table 3 Baseline and change from baseline to last in-study measurement of blood pressure and electrocardiographic left ventricular hypertrophy in relation to the presence of electrocardiographic strain at baseline and year-1

Variables	Strain−/strain− (*n* = 6236), no strain	Strain+/strain− (*n* = 236), regression of strain	Strain+/strain+ (*n* = 517), persistent strain	Strain−/strain+ (*n* = 276), new strain	*P*-value for linear trend
Baseline measurements					
Systolic BP (mmHg)	173.9 ± 14.4	176.4 ± 14.2	176.9 ± 14.8	177.4 ± 13.7	<0.001
Diastolic BP (mmHg)	98.2 ± 8.5	97.6 ± 9.8	97.4 ± 9.8	97.8 ± 9.6	0.222
Cornell's product (mm ms)	2618 ± 717	2932 ± 961	2923 ± 913	2853 ± 925	<0.001
Sokolow–Lyon voltage (mm)	28.9 ± 9.9	35.0 ± 10.5	37.8 ± 11.1	33.6 ± 10.9	<0.001
Change from baseline to last measurement					
Systolic BP (mmHg)	−29.8 ± 19.3	−32.0 ± 20.0	−32.1 ± 18.9	−32.7 ± 21.2	0.010
Diastolic BP (mmHg)	−17.3 ± 10.0	−18.0 ± 10.7	−18.7 ± 10.4	−18.0 ± 11.4	0.017
Cornell's product (mm ms)	−208 ± 692	−372 ± 857	−201 ± 929	−119 ± 936	0.001
Sokolow–Lyon voltage (mm)	−3.8 ± 6.8	−7.7 ± 8.9	−4.8 ± 9.9	−3.8 ± 9.2	<0.001

remained significant predictors of HF hospitalization in this multivariable Cox model (data not shown).

The predictive value of the presence or absence of ECG strain at baseline and year-1 for the development of new HF in relevant subsets of the population is examined in *Table 5*. The association between baseline and year-1 ECG strain and HF hospitalization was similar in men and women, blacks and other ethnicities, in both treatment arms of the study, in patients above and below 65 years of age, among patients with and without a history of ischaemic heart disease and with or without prevalent diabetes, and among patients with and without LVH on their baseline ECG by either the Cornell product or the Sokolow–Lyon voltage criteria, with non-significant interaction terms for these variables.

Table 4 Five-year heart failure incidence, univariate and multivariable Cox's regression analyses to assess the relation of new heart failure to electrocardiographic strain at baseline and year-1

Event	Strain−/strain− (*n* = 6236), no strain	Strain+/strain− (*n* = 236), regression of strain	Strain+/strain+ (*n* = 517), persistent strain	Strain−/strain+ (*n* = 276), new strain	*P*-value for linear trend
5-year event rates (%)					
Heart failure incidence (%)	1.6	5.4	7.1	7.0	<0.0001
Hazard ratios (95% confidence intervals)					
Univariate Cox's model	1	3.2 (1.7–6.1)	4.5 (3.1–6.7)	4.4 (2.6–7.4)	<0.001
Multivariate Cox's model[a]	1	2.4 (1.2–5.0)	1.9 (1.2–3.2)	2.3 (1.2–4.4)	<0.001

[a]Adjusted for possible effects of treatment with losartan vs. atenolol, age, gender, race, prevalent diabetes, history of ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation or smoking, baseline albumin/creatinine ratio, total and HDL cholesterol, glucose, creatinine, uric acid, and body mass index entered as standard covariates, and baseline and in-treatment systolic and diastolic blood pressure, QRS duration, the Sokolow–Lyon voltage, the Cornell voltage–duration product, and incident myocardial infarction and atrial fibrillation entered as time-varying covariates.

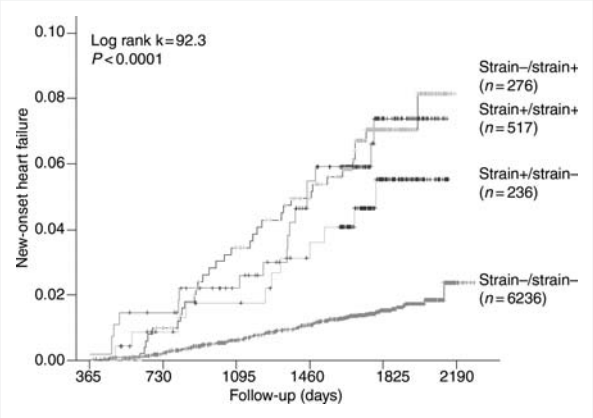

Figure 1 Kaplan–Meier curves comparing new-onset heart failure rates between patients according to the presence or absence of electrocardiographic strain on their baseline and year-1 electrocardiograms. (*n* = number of patients; strain−/strain− represents the absence of strain on baseline and year-1 electrocardiogram; strain+/strain− represents the presence of strain on baseline electrocardiogram and the absence of strain on year-1 electrocardiogram, regression of strain; strain+/strain+ represents the presence of strain on baseline and year-1 electrocardiogram, persistence of strain; strain−/strain+ represents the absence of strain on baseline electrocardiogram and the presence of strain on year-1 electrocardiogram, development of new strain).

Discussion

This study demonstrates that the development of new ECG strain or persistence of ECG strain between baseline and year-1 during the LIFE study was associated with an increased risk of hospitalization for new HF and that the regression of ECG strain between baseline and year-1 does not convey a decreased risk of developing HF. The increased risk of HF associated with ECG strain at baseline and/or year-1 was independent of the previously demonstrated predictive values of in-treatment ECG LVH[18] and QRS duration[20] for new HF, of the baseline and in-treatment severity of hypertension, and persisted after adjusting for randomized treatment and the higher prevalence of other CV disorders and HF risk factors associated with ECG strain. These findings highlight the adverse prognostic value of ECG strain, even if not persistent between ECG evaluations, for new HF in hypertensive patients in the setting of substantial decreases in both systolic and diastolic pressure and suggest that more aggressive therapy may be warranted in hypertensive patients who have ECG strain to reduce the risk of developing new HF.

Electrocardiographic strain and the prediction of heart failure

Although the relationship of CV risk to the ECG strain pattern on a single ECG has been demonstrated in population-based studies and patients with hypertension,[8–13] the relationship of ECG strain to new-onset HF has been less well characterized.[8,13,14] Verdecchia *et al.*[8] found strain on a baseline ECG to be associated with a greater than two-fold increased risk of a composite CV endpoint that included a small number of hospitalizations for new HF in 1717 hypertensive subjects, but did not separately examine the predictive value of ECG strain for new HF. Similarly, among over 28 000 patients enrolled in either ONTARGET or TRANSCEND,[13] baseline strain alone was associated with a 1.7-fold increased risk and strain in combination with ECG LVH by modified Cornell's voltage criteria with a 2.2-fold increased risk of a composite CV endpoint which included the development of new HF. However, the predictive value of ECG strain for new HF alone was not reported.[13] In contrast, previous evaluation in the LIFE study[14] revealed that strain on a baseline ECG was an independent predictor of new-onset HF and was associated with a 70% increased risk of developing HF. However, these studies did not examine the relationship of ECG strain over time to CV outcomes or the development of new HF.

The relationship of the presence or absence of ECG strain over time to CV outcomes has not been extensively evaluated[11,12,19] and no previous study has examined the predictive value of serial evaluation of ECG strain for new HF. In contrast, the present study demonstrates that the development of new strain, persistence of strain, and regression of ECG strain between

Table 5 Cox's analyses to assess the predictive value of electrocardiographic strain at baseline and year-1 for new-onset heart failure in relevant subgroups of the study population

Subgroup	HF (*n*)	Strain−/strain− (*n* = 6236), no strain	Strain+/strain− (*n* = 236), regression of strain	Strain+/strain+ (*n* = 517), persistent strain	Strain−/strain+ (*n* = 276), new strain	*P*-value for interaction
Sex						
Male (*n* = 3359)	77	1	1.7 (0.6–4.8)	4.4 (2.6–7.4)	3.8 (1.8–8.0)	0.286
Female (*n* = 3906)	77	1	6.0 (2.7–13.2)	4.5 (2.4–8.4)	5.0 (2.4–10.1)	
Race						
White or other (*n* = 6877)	136	1	2.3 (1.1–5.1)	4.7 (3.1–7.2)	4.3 (2.5–7.5)	0.167
Black (*n* = 388)	18	1	6.8 (2.0–23.3)	2.4 (0.7–7.4)	3.5 (0.7–16.7)	
Treatment						
Atenolol (*n* = 3617)	78	1	1.9 (0.6–6.1)	4.6 (2.6–8.0)	5.9 (3.2–11.0)	0.261
Losartan (*n* = 3648)	76	1	4.4 (2.1–9.4)	4.5 (2.6–8.0)	2.4 (0.9–6.7)	
Age (years)						
Less than 65 (*n* = 2902)	37	1	2.2 (0.5–9.5)	6.2 (2.9–13.4)	5.0 (1.5–16.7)	0.626
65 or greater (*n* = 4363)	117	1	3.7 (1.8–7.4)	3.9 (2.4–6.2)	3.8 (2.1–6.7)	
History of IHD						
No (*n* = 6277)	100	1	4.0 (1.9–8.4)	3.5 (2.0–6.2)	5.5 (3.1–10.1)	0.104
Yes (*n* = 988)	54	1	1.2 (0.4–4.1)	3.2 (1.8–5.7)	1.6 (0.6–4.7)	
Diabetes						
No (*n* = 6373)	110	1	3.6 (1.7–7.5)	5.9 (3.7–9.2)	4.8 (2.6–9.0)	0.082
Yes (*n* = 892)	44	1	2.2 (0.7–7.1)	1.6 (0.7–3.9)	2.7 (1.1–7.1)	
CP LVH						
No (*n* = 2583)	41	1	2.4 (0.6–10.2)	4.2 (1.7–10.1)	6.5 (2.7–15.9)	0.682
Yes (*n* = 4682)	113	1	3.4 (1.7–6.8)	4.4 (2.8–6.9)	3.6 (1.9–6.8)	
SL LVH						
No (*n* = 5712)	103	1	3.9 (1.8–8.5)	5.5 (3.3–9.3)	5.0 (2.7–9.3)	0.233
Yes (*n* = 1553)	51	1	1.9 (0.7–5.3)	2.5 (1.3–4.8)	2.8 (1.1–7.3)	

CP, Cornell product; HF, heart failure; IHD, ischaemic heart disease; SL, Sokolow–Lyon voltage.

baseline and year-1 were associated with an increased risk of new HF, independent of the possible impact of standard CV risk factors, randomized treatment assignment, baseline and in-treatment diastolic and systolic blood pressure, and of the previously demonstrated prognostic value of in-treatment ECG LVH and QRS duration for new HF in this population.[18,20] In addition, the association of baseline and year-1 strain and new HF was similar in all relevant subsets of the population. Furthermore, similar to the predictive value of baseline and year-1 strain for CV morbidity and mortality in the LIFE study population,[19] the regression of ECG LVH by the Cornell product and Sokolow–Lyon voltage retained the predictive value for new HF outcomes in the current study when the serial assessment of ECG strain is taken into account, emphasizing the need for the serial assessment of both standard ECG LVH criteria and lateral repolarization abnormalities to accurately assess changing risk over time in the hypertensive population.

Although the precise mechanisms linking the development of ECG strain to the development of HF are not known, the strong association of strain with abnormalities of CV structure and function may in part explain the adverse prognosis associated with strain. In the present study, patients with new or persistent strain were older, had higher prevalences of diabetes, history of various forms of heart and vascular disease, and evidence of greater end-organ damage as manifested by albuminuria. In addition, patients who developed new ECG strain had the least regression of ECG LVH by the Cornell product criteria, suggesting less improvement in LVH despite similar reductions in blood pressure in this group. However, new ECG strain remained predictive of outcomes in the current study after adjusting for the possible impact of these factors. In the echocardiographic substudy of LIFE[5] and a cross-sectional study of 440 patients with resistant hypertension,[7] baseline ECG strain was strongly related to the presence of coronary heart disease, increased LV mass, and echocardiographic LVH that was more likely to be concentric, factors that predispose to increased CV risk. Further analysis of baseline LV mass and function in relation to both baseline and year-1 ECG strain in the echocardiographic substudy of LIFE[5] demonstrated that baseline LV mass index was highest and LV midwall shortening was lowest and most likely to be abnormal in patients with persistent or new ECG strain and that baseline LV mass was also elevated in patients with regression of strain between baseline and year-1. The absence of a significant association between baseline ECG strain and echocardiographic measures of

diastolic dysfunction[25] further suggests that the predictive value of ECG strain for new HF may be mediated via abnormalities of LV systolic function. However, the small number of incident HF cases among the 770 patients in the LIFE echocardiography substudy who were included in the present study ($n = 12$) precludes meaningful analysis of the relationship of LV systolic or diastolic function to new-onset HF in this population. This problem and the strong association of hypertension with impaired LV diastolic function in a recent population-based study[26] suggests that further evaluation of the relationship of ECG strain to the development of LV systolic and diastolic dysfunction and HF will be necessary. In addition to the possible relation of ECG strain to coronary heart disease and LV mass,[5,7] ST depression and T-wave inversion may reflect true subendocardial ischaemia in the absence of coronary disease, because of hypertrophy-induced compensatory increases in coronary artery diameter that are inadequate for the magnitude of increased LV mass and wall thickness.[27–29] This concept is supported by the association of ECG strain with increased wall stress–mass–heart rate product among hypertensive patients with ECG LVH but no evidence of coronary disease in the LIFE study,[5] providing evidence of a demand-side predisposition to myocardial ischaemia in these patients.

Study limitations and perspectives

The independent relation of the presence of ECG strain at baseline and/or year-1 to increased risk of HF in LIFE despite aggressive blood pressure reduction suggests that the presence or development of new strain on the ECG may be used to identify hypertensive patients with ECG LVH who require more aggressive antihypertensive therapy aimed at further reducing HF risk in these patients. However, there are several potential limitations of our study that warrant review. First, the use of hospitalization for HF to define incident HF most certainly underestimates the true incidence of HF, potentially reducing precision of the estimates of the relationship of ECG strain changes to HF incidence. Secondly, the relatively small number of cases of HF associated with strain potentially limits the ability to differentiate the impact between old and new strain on HF incidence. Thirdly, although it would be of interest to examine changes in LV structure and function according to changes in ECG strain and the development of new HF, the small number of incident HF cases in the echocardiographic substudy of LIFE precludes meaningful analyses along these lines. Fourthly, the inferences that may be drawn from the present study are potentially limited by the lack of ECG strain data on ECGs obtained after year-1 and by the absence of quantitative data assessing the degree of ST depression in this population. Previous observations that the magnitude of ST depression in the lateral leads is strongly related to the presence and severity of LVH[6] and that measured ST depression and echocardiographic LV mass provide complimentary prognostic information[30] suggest that the serial assessment of the magnitude of lateral repolarization abnormality may provide additional prognostic benefit in hypertensive patients. Further study will be necessary to address this important question. Finally, given that a clinical diagnosis of HF in the community is commonly based, at least in part, on findings on the ECG,[31] the current findings suggest that the serial evaluation of the presence of strain on the ECG may increase the utility of the ECG in detecting new-onset HF.

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