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All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy

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Background Although higher heart rate (HR) at baseline has been associated with an increased risk of cardiovascular (CV) and all-cause mortality, the relationship of in-treatment HR over time to mortality in hypertensive patients with ECG left ventricular hypertrophy (LVH) has not been examined.

Methods and results Heart rate was evaluated over time in 9190 hypertensive patients treated with losartan- or atenolol-based regimens and followed with annual ECGs. During a mean follow-up of 4.8 ± 0.9 years, 814 patients (8.9%) died, 438 (4.8%) from CV causes. In univariate Cox analyses, every 10 bpm higher HR on in-treatment ECGs was associated with a 25% increased risk of CV death [95% confidence interval (CI): 14–32%] and a 27% greater risk of all-cause mortality (95% CI: 21–34%). In an alternative analysis, persistence or development of a HR ≥84 bpm (upper quintile of baseline HR) was associated with an 89% greater risk of CV death (95% CI: 49–141%) and a 97% increased risk of all-cause mortality (95% CI: 65–135%). After adjusting for treatment with losartan vs. atenolol, baseline risk factors for death, baseline HR, baseline and in-treatment systolic and diastolic pressure, incident myocardial infarction, and the known predictive value of baseline and in-treatment QRS duration and ECG LVH, higher in-treatment HR in time-varying multivariable Cox models remained strongly predictive of mortality: every 10 bpm higher HR was associated with a 16% increased adjusted risk of CV mortality (95% CI: 6–27%) and a 25% greater risk of all-cause mortality (95% CI: 17–33%), with persistence or development of a HR ≥84 associated with a 55% greater risk of CV death (95% CI: 16–105%) and a 79% greater adjusted risk of all-cause mortality (95% CI: 46–121%).

Conclusion Higher in-treatment HR on serial ECGs predicts greater likelihood of subsequent CV or all-cause mortality, independent of treatment modality, blood pressure lowering, regression of ECG LVH and changing QRS duration in hypertensive patients with ECG LVH. These findings support the value of serial assessment of HR for improved risk stratification in hypertensive patients.
Clinical trials registration: http://clinicaltrials.gov/ct/show/NCT00338260?order=1cp.

Keywords Electrocardiography • Heart rate • Hypertension • Mortality

Assessment of resting heart rate (HR) is a routine part of clinical evaluation that is easy and inexpensive to perform and high HR has been proposed as a potential simple marker of risk in a variety of populations[1,2] that may be a target for treatment.[2] An elevated resting HR at a baseline evaluation has been associated with an increased risk of cardiovascular (CV) and all-cause

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mortality in population-based studies,[3–5] patients with coronary artery disease[6] and in some[6–8] but not all studies[9] of patients with hypertension. Because HR may increase or decrease over time in response to changes in clinical condition and treatment, the predictive value of a single HR measurement at initial evaluation for events often occurring many years in the future may be less robust than serial assessment of HR over time for prediction of risk. However, few studies have examined the predictive value of changing level of resting HR over time for risk stratification,[5,6,10,11] and the relationship of in-treatment HR over time to all-cause and CV mortality in hypertensive patients has not been evaluated. Therefore, the present study examined whether higher HR over time is associated with an increased risk of CV and all-cause mortality in hypertensive patients undergoing treatment, independent of the effects of in-treatment blood pressure and other risk factors for mortality and of the previously demonstrated relationship of in-treatment ECG left ventricular hypertrophy (LVH) to mortality.[12]

Methods

The LIFE Study[10,12–14] enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage-duration product[15] and/or Sokolow-Lyon voltage criteria[16] on a screening ECG in a prospective, double-blind randomized study that compared CV morbidity and mortality with use of losartan- as opposed to atenolol-based treatment,[13] as previously described in detail.[10,12–14] A total of three patients with missing baseline HR data were excluded from analyses, leaving 9190 patients in the present study.[10] Blinded treatment begun with losartan 50 mg or atenolol 50 mg daily and matching placebo of the other agent, with up-titration of study medication and addition of additional non-study medications to achieve a target pressure of 140/90 mmHg or lower as previously reported in detail.[13]

Study ECGs were obtained at baseline, at 6-months, and at yearly follow-up intervals until study termination or patient death and were interpreted as previously reported in detail.[10,12,13] Cornell product >2440 mm · msec[15] or Sokolow-Lyon voltage >38 mm[16] were used to identify LVH.[11] HR was measured to the nearest bpm on each protocol-mandated study ECG.[10]

All-cause and CV mortality were prespecified endpoints in the LIFE trial.[13,14] All deaths were ascertained and then verified by an expert Endpoint Committee, as previously described.[12–14]

Data management and analyses were performed by the investigators using SPSS version 12.0. Data are presented as mean $\pm$ SD for continuous variables and proportions for categorical variables. Differences in mean values between patients grouped according to baseline HR partitioned at 84 bpm (the upper quintile of baseline HR in this population and a value previously shown to stratify risk[10,17]) were compared using unpaired *t*-tests; comparison of proportions between groups was performed using chi-square tests.

The relationship of HR on baseline and in-study ECGs to risk of CV and all-cause mortality was assessed using Cox proportional hazards models. Baseline risk factors, a treatment group indicator, and baseline HR, systolic and diastolic pressure, Cornell product, and Sokolow-Lyon voltage were included as standard covariates, and subsequent in-treatment blood pressure, HR, Cornell product and Sokolow-Lyon voltage measurements, and incident myocardial infarction were entered as time-varying covariates. In addition, the relationship of persistence or development of a HR $\geq$84 vs. a HR $<$84 bpm treated as a dichotomous time-varying variable to CV and all-cause mortality was also analysed. Hazard ratios for mortality associated with in-treatment HR treated as a continuous variable were computed per 10 bpm higher HR values. Analyses were repeated stratifying the population by relevant subgroups by adding cross-product terms of time-varying HR and these subgroup variables into models in the total population.

To illustrate the results of time-varying covariate analyses, CV and all-cause mortality rates over time were plotted as functions of changing presence or absence of HR $\geq$84 bpm using a univariate modified Kaplan–Meier method,[18] implemented in SAS Release 8.2 on the WIN_PRO platform. Two-tailed $P < 0.05$ was required for statistical significance.

Results

Patient characteristics in relation to baseline heart rate

Clinical and demographic characteristics of patients in relation to baseline HR partitioned at 84 bpm are shown in *Table 1*. Hypertensive patients with a baseline HR $\geq$84 were older, more likely to be female, non-black, have diabetes, a history of heart failure and

Table 1 Demographic and clinical characteristics in relation to baseline heart rate

Variables	HR <84 bpm (*n* = 7316)	HR ≥84 bpm (*n* = 1874)	*P*-value
Age (years)	66.8 ± 7.0	67.5 ± 6.9	<0.001
Sex (% female)	51.6	63.3	<0.001
Race (% black)	6.1	4.7	0.031
Randomized to losartan (%)	50.3	49.1	0.348
Diabetes (%)	12.2	16.2	<0.001
History of ischaemic heart disease (%)	15.9	16.4	0.575
History of myocardial infarction (%)	6.1	6.6	0.487
History of stroke (%)	4.4	4.1	0.504
History of peripheral vascular disease (%)	5.7	5.5	0.776
History of atrial fibrillation (%)	3.3	4.5	0.014
History of heart failure (%)	1.6	2.6	0.004
Current smokers (%)	15.5	19.5	<0.001
Body mass index (kg/m^2)	27.9 ± 4.7	28.3 ± 5.2	0.006
Serum glucose (mmol/L)	5.91 ± 2.08	6.48 ± 2.53	<0.001
Serum creatinine (mmol/L)	87.1 ± 20.3	86.2 ± 19.7	0.087
Total cholesterol (mmol/L)	6.00 ± 1.11	6.12 ± 1.16	0.001
HDL cholesterol (mmol/L)	1.49 ± 0.43	1.50 ± 0.45	0.496
Urine albumin/creatinine ratio (mg/mM)	6.8 ± 28.1	10.6 ± 50.9	<0.001

HR, heart rate.

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Table 2 Baseline and change from baseline to last in-study measurement of blood pressure and electrocardiographic left ventricular hypertrophy in relation to baseline heart rate

Variables	HR <84 bpm (n = 7316)	HR ≥84 bpm (n = 1874)	P-value
Baseline measurements			
Systolic blood pressure (mmHg)	174 ± 14	175 ± 15	0.020
Diastolic blood pressure (mmHg)	97 ± 9	100 ± 9	<0.001
Cornell voltage-duration product (mm · msec)	2814 ± 1026	2863 ± 1055	0.064
Sokolow-Lyon voltage (mm)	30.3 ± 10.4	28.9 ± 10.2	<0.001
Change from baseline to Last measurement[a]			
Systolic blood pressure (mmHg)	−30 ± 20	−30 ± 20	0.776
Diastolic blood pressure (mmHg)	−17 ± 10	−18 ± 11	<0.001
Cornell voltage-duration product (mm · msec)	−191 ± 861	−217 ± 829	0.252
Sokolow-Lyon voltage (mm)	−3.9 ± 7.3	−3.5 ± 7.4	0.045

HR, heart rate.
[a]Change from baseline to last in-study measurement or last measurement prior to death.

Table 3 Univariate and multivariable Cox regression analyses to assess the predictive value of changing in-treatment heart rate for the development of cardiovascular and all-cause mortality

Predictor variable	P-value	Hazard ratio	95% CI
Univariate			
Cardiovascular mortality			
Heart rate (per 10 bpm increase)	<0.001	1.23	1.14–1.32
Heart rate (persistence or development of a HR ≥84 bpm)[a]	<0.001	1.89	1.49–2.41
All-cause mortality			
Heart rate (per 10 bpm increase)	<0.001	1.27	1.21–1.34
Heart rate (persistence or development of a HR ≥84 bpm)[a]	<0.001	1.97	1.65–2.35
Multivariable[b]			
Cardiovascular mortality			
Heart rate (per 10 bpm increase)	0.001	1.16	1.06–1.27
Heart rate (persistence or development of a HR ≥84 bpm)[a]	0.003	1.55	1.16–2.05
All-cause mortality			
Heart rate (per 10 bpm increase)	<0.001	1.25	1.17–1.33
Heart rate (persistence or development of a HR ≥84 bpm)[a]	<0.001	1.79	1.46–2.21

[a]Cardiovascular death occurred in 80 patients and death from any cause in 153 patients with in-treatment persistence or development of a HR ≥84 bpm, rates of 15.4 and 30.3 per 1000 patient-years, respectively; CV death occurred in 358 patients and death from any cause in 661 patients with in-treatment development or continued presence of a HR <84 bpm, rates of 9.0 and 17.0 per 1000 patient-years.
[b]Adjusted for possible effects of treatment with losartan vs. atenolol, age, gender, race, prevalent diabetes, history of ischaemic heart disease, myocardial infarction, atrial fibrillation, congestive heart failure, stroke, peripheral vascular disease or smoking, baseline heart rate, albumin/creatinine ratio, total and HDL cholesterol, serum creatinine, body mass index, incident myocardial infarction, baseline and in-treatment systolic and diastolic blood pressure, QRS duration, Sokolow-Lyon voltage and Cornell voltage-duration product.

current smokers, had higher body mass indexes, glucose and total cholesterol levels, and greater albuminuria, but were similar with respect to treatment randomization and other baseline characteristics.

Blood pressure and ECG LVH measurements at baseline and changes in these measurements between baseline and last in-study determination or the last measurement prior to dying in relation to HR at baseline are shown in *Table 2*. Patients with a baseline HR ≥84 had slightly higher baseline systolic and diastolic pressures and greater reduction in diastolic pressure but similar changes in systolic pressure. Higher baseline HR was associated with less severe LVH by Sokolow-Lyon voltage, but similar baseline severity of Cornell product LVH and similar changes in both ECG LVH criteria.

In-treatment heart rate and mortality

During mean follow-up of 4.8 ± 0.9 years, 814 patients died (8.9%), 438 (4.8%) from CV causes. Compared with patients who survived, patients who died had smaller decreases in HR to last in-treatment ECG or last ECG prior to death (−2.4 ± 14.6 vs. −5.3 ± 12.7 bpm, $P < 0.001$), whether on losartan- (−0.5 ± 14.0 vs. −2.4 ± 11.0 bpm, $P = 0.014$) or atenolol-based treatment (−4.1 ± 14.9 vs. −8.2 ± 12.7, $P < 0.001$). Cardiovascular death occurred in 80 patients and death from any cause in 153 patients with in-treatment persistence or development of a HR ≥84 bpm, rates of 15.4 and 30.3 per 1000 patient-years, respectively; CV death occurred in 358 patients and death from any cause in 661 patients with in-treatment development or continued presence of a HR <84 bpm, rates of 9.0 and 17.0 per 1000 patient-years.

In univariate Cox analyses in which time-varying HR was treated as a continuous variable (*Table 3*), higher in-treatment values of HR were strongly associated with an increased risk of dying: every 10 bpm higher HR was associated with a 23% increased risk of CV death and with a 27% greater risk of all-cause mortality. In parallel analyses in which in-treatment HR was treated as a dichotomous variable based on a threshold value of ≥84 bpm, in-treatment persistence or development of a HR ≥84 bpm was associated with an 89% greater risk of CV death and a 97% increased

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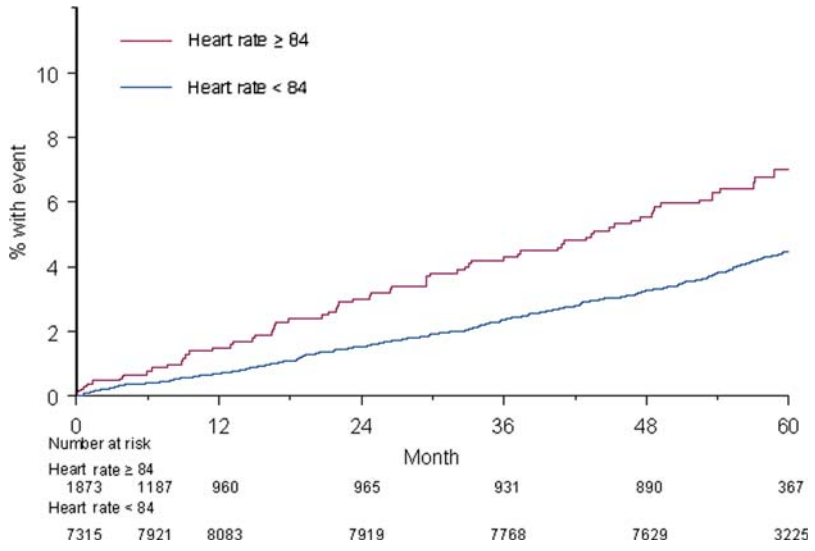

Figure 1 Survival curves illustrating the rate of cardiovascular mortality according to time-varying persistence or development of a heart rate ≥84 bpm during follow-up. Patient group assignment is adjusted at the time of each ECG based on the heart rate at each time.[24]

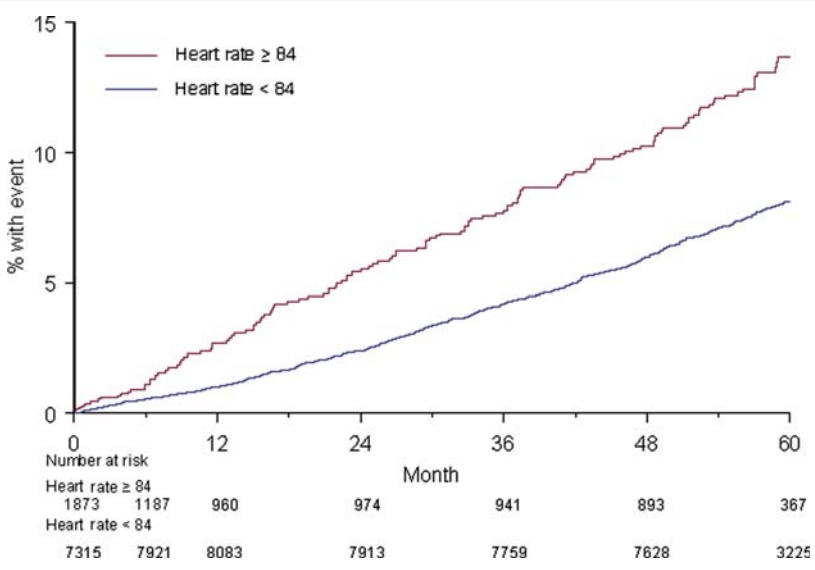

Figure 2 Survival curves illustrating the rate of all-cause mortality according to time-varying persistence or development of a heart rate ≥84 bpm during follow-up. Patient group assignment is adjusted at the time of each ECG based on the heart rate at each time.[24]

risk of all-cause mortality compared with in-treatment development or continued presence of a HR <84. Modified Kaplan–Meier curves[18] comparing the rate of CV death (*Figure 1*) and all-cause mortality (*Figure 2*) according to HR of 84 bpm over the time course of the study, demonstrate that persistence or development of a HR ≥84 was associated with a greater risk of CV death and all-cause mortality as compared with a HR <84, with persistence or development of a HR ≥84 bpm associated with an estimated 2.2% higher absolute incidence of CV death, and a 4.3% higher incidence of all-cause mortality after 4 years of follow-up.

The relations of CV and all-cause mortality to in-treatment HR were further examined after adjusting for the possible effects of randomized treatment, age, gender, race, prevalent diabetes, history of ischaemic heart disease, myocardial infarction, heart failure, stroke, peripheral vascular disease and smoking, prevalent atrial fibrillation by history or baseline ECG, baseline HR, urinary albumin/creatinine ratio, total and HDL cholesterol, serum creatinine, body mass index, and for incident myocardial infarction, baseline and in-treatment systolic and diastolic blood pressure, QRS duration, Cornell product and Sokolow-Lyon voltage (*Table 3*). After adjusting for these factors, every 10 bpm higher in-treatment HR was associated with a 16% greater risk of CV death and with a 25% higher risk of all-cause mortality. In parallel analyses, in-treatment

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persistence or development of a HR ≥84 bpm was associated with a 55% increased adjusted risk of CV death and 79% greater risk of all-cause mortality.

The predictive value of time-varying HR for CV and all-cause mortality in relevant subsets of the population is examined in *Tables 4* and *5*. The association of CV and all-cause mortality with

Table 4 Multivariate Cox analyses to assess the predictive value of time-varying in-treatment heart rate for cardiovascular mortality in relevant subgroups of the study population

Subgroup	CV deaths (*n*)	Hazard ratio[a]	95% CI	*P*-value for interaction*
Sex				0.180
Male (*n* = 4229)	246	1.08	0.96–1.23	
Female (*n* = 4961)	192	1.28	1.10–1.47	
Race				0.575
White or other (*n* = 8657)	401	1.16	1.06–1.28	
Black (*n* = 533)	37	1.21	0.84–1.72	
Treatment				0.642
Atenolol (*n* = 4587)	234	1.16	1.03–1.31	
Losartan (*n* = 4603)	204	1.15	1.00–1.33	
Age (years)				0.019
Less than 65 (*n* = 3488)	70	1.37	1.14–1.63	
65 or greater (*n* = 5702)	368	1.15	1.03–1.27	
History of congestive heart failure				0.583
No (*n* = 9024)	413	1.15	1.05–1.27	
Yes (*n* = 166)	25	1.57	0.97–2.52	
History of ischemic heart disease				0.404
No (*n* = 7721)	309	1.20	1.08–1.32	
Yes (*n* = 1469)	129	1.05	0.88–1.27	
History of myocardial infarction				0.238
No (*n* = 8621)	377	1.20	1.09–1.32	
Yes (*n* = 569)	61	1.03	0.75–1.41	
Diabetes				0.350
No (*n* = 7995)	339	1.17	1.06–1.31	
Yes (*n* = 1195)	99	1.12	0.92–1.36	
Atrial fibrillation by history or on baseline ECG				0.932
No (*n* = 8828)	379	1.16	1.05–1.27	
Yes (*n* = 362)	59	1.29	0.95–1.76	
Cornell product LVH on baseline ECG				0.141
No (*n* = 3012)	112	1.06	0.88–1.29	
Yes (*n* = 6178)	326	1.21	1.09–1.33	
Sokolow-Lyon voltage LVH on baseline ECG				0.388
No (*n* = 7241)	324	1.17	1.06–1.31	
Yes (*n* = 1949)	114	1.10	0.92–1.32	
Heart rate on baseline ECG				<0.001
<84 bpm (*n* = 7316)	324	1.12	1.00–1.24	
≥84 bpm (*n* = 1874)	114	1.44	1.22–1.68	

CV, cardiovascular.

[a]Hazard ratio per 10 bpm higher heart rate, adjusted for possible effects of treatment with losartan vs. atenolol, age, gender, race, prevalent diabetes, history of ischaemic heart disease, myocardial infarction, atrial fibrillation, congestive heart failure, stroke, peripheral vascular disease or smoking, baseline heart rate, albumin/creatinine ratio, total and HDL cholesterol, serum creatinine, body mass index, incident myocardial infarction, baseline and in-treatment systolic and diastolic blood pressure, QRS duration, Sokolow-Lyon voltage and Cornell voltage-duration product.

**P*-values for interaction term in Cox models between time-varying heart rate as a continuous variable and the subgroup variable coded as absent or present.

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Table 5 Multivariate Cox analyses to assess the predictive value of time-varying in-treatment heart rate for all-cause mortality in relevant subgroups of the study population

Subgroup	Deaths (*n*)	Hazard ratio[a]	95% CI	*P*-value for interaction*
Sex				0.020
Male ($n = 4229$)	448	1.15	1.06–1.26	
Female ($n = 4961$)	366	1.41	1.28–1.58	
Race				0.880
White or other ($n = 8657$)	743	1.26	1.18–1.34	
Black ($n = 533$)	71	1.28	0.99–1.66	
Treatment				0.720
Atenolol ($n = 4587$)	431	1.26	1.16–1.36	
Losartan ($n = 4603$)	383	1.23	1.12–1.36	
Age (years)				0.004
Less than 65 ($n = 3488$)	144	1.45	1.28–1.64	
65 or greater ($n = 5702$)	670	1.22	1.14–1.31	
History of congestive heart failure				0.799
No ($n = 9024$)	771	1.24	1.17–1.32	
Yes ($n = 166$)	43	1.61	1.14–2.26	
History of ischemic heart disease				0.995
No ($n = 7721$)	606	1.26	1.17–1.34	
Yes ($n = 1469$)	208	1.24	1.09–1.41	
History of myocardial infarction				0.779
No ($n = 8621$)	717	1.27	1.20–1.34	
Yes ($n = 569$)	97	1.20	0.94–1.51	
Diabetes				0.215
No ($n = 7995$)	647	1.26	1.18–1.34	
Yes ($n = 1195$)	167	1.24	1.07–1.40	
Atrial fibrillation by history or on baseline ECG				0.886
No ($n = 8828$)	732	1.26	1.17–1.33	
Yes ($n = 362$)	82	1.28	1.00–1.64	
Cornell product LVH on baseline ECG				0.584
No ($n = 3012$)	249	1.24	1.10–1.40	
Yes ($n = 6178$)	565	1.26	1.17–1.36	
Sokolow-Lyon voltage LVH on baseline ECG				0.389
No ($n = 7241$)	599	1.27	1.18–1.36	
Yes ($n = 1949$)	215	1.16	1.02–1.32	
Heart rate on baseline ECG				0.083
<84 bpm ($n = 7316$)	612	1.21	1.12–1.29	
≥ 84 bpm ($n = 1874$)	202	1.40	1.24–1.57	

[a]Hazard ratio per 10 bpm higher heart rate, adjusted for possible effects of treatment with losartan vs. atenolol, age, gender, race, prevalent diabetes, history of ischaemic heart disease, myocardial infarction, atrial fibrillation, congestive heart failure, stroke, peripheral vascular disease or smoking, baseline albumin/creatinine ratio, total and HDL cholesterol, serum creatinine, body mass index, incident myocardial infarction, baseline and in-treatment systolic and diastolic blood pressure, QRS duration, Sokolow-Lyon voltage and Cornell voltage-duration product.
**P*-values for interaction term in Cox models between time-varying heart rate as a continuous variable and the subgroup variable coded as absent or present.

in-treatment HR was similar in patients grouped according to race, treatment allocation, history of congestive heart failure, ischaemic heart disease or myocardial infarction, prevalent diabetes, prevalent or history of atrial fibrillation and baseline presence or absence of ECG LVH by Cornell product and Sokolow-Lyon criteria. In contrast, patients younger than 65 years old had significantly

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greater increment in the risks of CV and all-cause mortality for every 10 bpm higher in-treatment HR than patients 65 and older; women had a significantly steeper increase in risk of all-cause mortality with higher in-treatment HR than men. There was a significant interaction between in-treatment HR and baseline HR partitioned at 84 bpm for the prediction of CV death: every 10 bpm higher in-treatment HR was associated with a 44% increased risk of CV death in patients with a baseline HR $\geq$84 as opposed to only a 12% greater risk in patients with a baseline HR $<$84 bpm. There was a similar trend for a higher risk of all-cause mortality for every 10 bpm higher in-treatment HR in patients with baseline HR $\geq$84 than with lower baseline HR, but the test for interaction did not reach statistical significance ($P = 0.083$).

Discussion

These findings demonstrate that higher in-treatment HR during antihypertensive therapy is strongly associated with increased risks of CV and all-cause mortality, independent of blood pressure lowering, randomized treatment assignment, other risk factors, and of the previously demonstrated relationship of mortality to in-treatment ECG LVH.[12,19] These findings suggest that serial assessment of HR may provide additional information regarding the risk of dying in hypertensive patients with ECG LVH and that further evaluation of patients with persistence or development of an increased HR during antihypertensive therapy should be considered to evaluate possible underlying abnormalities that may put these patients at increased mortality risk.

Heart rate and mortality

An elevated resting HR at a baseline evaluation has been associated with an increased risk of CV and all-cause mortality in population-based studies,[3–5] patients with coronary disease[6] and in some[6–8] but not all studies[9] of patients with hypertension. Among over 4000 men and women with hypertension in the Framingham Heart Study who were not taking antihypertensive medications,[7] after adjusting for other potential risk factors, each HR increment of 40 bpm was associated with a significantly increased risk of all-cause mortality and with an increased risk of CV mortality in men. In elderly subjects enrolled in the Systolic Hypertension in Europe Trial,[8] a resting HR $\geq$80 bpm (upper quintile) was associated with an 89% increased risk of mortality in the placebo arm but was not a significant predictor of mortality in the active treatment arm. Similarly, a resting HR $\geq$80 bpm was associated with a 47% increased adjusted risk of all-cause mortality in 3275 persons with prehypertension from the Atherosclerosis Risk in Community (ARIC) study during mean follow-up of 10.1 years[20] and higher resting HR was associated with an increased risk of the composite event of death, myocardial infarction, or stroke in hypertensive patients with coronary disease enrolled in the INternational VErapamil SR/trandolapril STudy.[6] In contrast, resting HR was not a significant predictor of fatal coronary heart disease, stroke, or total CV events in the 12 759 hypertensive patients in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), with no difference between the atenolol- and amlodipine-based treatment groups.[9] Because HR may increase or decrease over time in response to changes in clinical condition and treatment, the predictive value of a single HR determination at baseline for outcomes that often occur many years in the future may be less accurate than serial assessment of HR over time. However, few studies have examined the predictive value of changing level of resting HR over time for risk stratification.[5,6,10,11]

In middle aged, healthy working men followed for 20 years or more, the combination of a high resting HR and the highest tertile of change in HR between rest and year 5 of follow-up was associated with a modestly increased long-term all-cause mortality risk.[5] In patients with coronary artery disease and hypertension, higher mean follow-up HR was associated with an increased risk of composite event of death, myocardial infarction, or stroke.[6] Using HR determined at each patient's initial and final clinic visit, Paul *et al.*[11] examined subsequent all-cause and CV mortality in relation to changes in pulse rate in over 4000 hypertensive patients followed at the Glasgow Blood Pressure Clinic. In multivariate analyses that adjusted for age, sex, body mass index, smoking, systolic pressure, serum cholesterol, and the use of HR-limiting medications during their clinic visits, patients who increased their HR $\geq$5 bpm between baseline and their final clinic visit had a 51% increased risk of dying (HR: 1.51, 95% CI: 1.03–2.20, $P = 0.035$). In alternative analyses, compared with patients whose HR was $\leq$80 bpm at both initial and final clinic visits, patients whose HR was $>$80 bpm at both visits had a 78% increased all-cause mortality risk (HR: 1.78, 95% CI: 1.31–2.41, $P < 0.001$). However, the time period from initial to final clinic visit was not standardized and ranged from 7 to 7087 days and follow-up was continued out to as long as 20 years after the final clinic visit with no determination of HR or blood pressure during this period. In contrast, the current study demonstrates that in-treatment HR measured yearly during the period of study follow-up strongly predicts both CV and all-cause mortality, whether HR is examined as a continuous variable over the full range of HR values or as a dichotomous variable in which persistence or development of a HR $\geq$84 bpm is associated with substantially increased risk. The increased mortality associated with higher in-treatment HR was independent of randomized treatment allocation, many other potential risk factors for death, including incident myocardial infarction, and the previously demonstrated relationship of mortality to LVH regression in this population.[12,19]

Although the association of CV and all-cause mortality with in-treatment HR was similar in most patient subgroups examined (*Tables 4* and *5*), some important differences warrant comment. Every 10 bpm higher in-treatment HR was associated with significantly greater risks of CV and all-cause mortality in patients less than 65 years old than in older patients and with a significantly steeper increase in risk of all-cause mortality in women than in men, suggesting that higher HR may have a more serious adverse impact in these subgroups. Interesting, although in-treatment HR was a significant predictor of CV and all-cause mortality in patients with resting HR $<$84 bpm or $\geq$84 bpm in multivariable analyses (*Tables 4* and *5*), every 10 bpm higher in-treatment HR was associated with a significantly higher increased risk of CV death and with a trend towards greater risk of all-cause mortality in patients with a baseline HR $\geq$84 vs. $<$84 bpm, further emphasizing that the greatest mortality risk appears to reside at higher absolute in-treatment HR levels. The similar predictive value of in-treatment HR in

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atenolol- and losartan-treated patients is of note given the greater in-treatment reductions in HR among atenolol-treated patients in the current study and the trend towards higher mortality among atenolol-treated patients in LIFE,[14] but this finding is supported by the absence of an interaction of amlodipine vs. atenolol-based treatment with resting HR for prediction of outcome in ASCOT[9] and by the absence of a significant effect of HR-limiting treatment on outcome when HR was examined in the Glasgow Blood Pressure Clinic cohort.[11]

It is important to recognize that the similar increase in risk associated with higher in-treatment HR in the two treatment groups in LIFE does not imply that atenolol-treated patients should have a lower mortality because they on-average had lower in-treatment HR measurements than the losartan-treated group. Although use of time-varying covariates to assess the relationship of mortality to in-treatment HR precludes meaningful comparisons of mortality rates according to HR dichotomized at 84, simple life-table analyses examining treatment differences in mortality after year 1 in relation to HR at year 1 provide additional insight into this issue. Among patients with a year-1 HR $\geq$84 bpm, subsequent mortality over 3.8 years was similarly increased in both atenolol- and losartan-treated patients (11.4 vs. 10.8%). However, among patients with a year-1 HR $<$84, subsequent mortality was significantly higher in the atenolol-treated patients (8.4 vs. 6.8%, $P = 0.036$), although this difference is no longer significant after adjusting for other risk factors ($P = 0.082$), mirroring the overall trend towards higher mortality among atenolol-treated patients in the original LIFE outcome analyses.[14]

Potential mechanisms linking increased HR to mortality include roles of higher HR as a marker of increased sympathetic tone, cause of increased myocardial ischemia; as a promoter of atherosclerosis, via an association with plaque disruption in the coronary arteries and other circulations; and as a possible marker of subclinical decreased LV systolic function. Increased HR is a known marker of increased sympathetic tone, which has been associated with increased susceptibility to ventricular arrhythmias. Increased HR is associated with increased myocardial ischaemia in patients with coronary atherosclerosis both by increasing myocardial oxygen demand and also potentially by decreasing myocardial blood flow by producing coronary vasoconstriction.[21] Increased HR was associated with an increased development of atherosclerosis and a two-fold higher coronary artery stenosis score in young patients post-myocardial infarction[22] and an increased risk of coronary plaque disruption in coronary disease patients undergoing serial angiography.[23] In addition, elevated HR has been shown to promote experimental atherosclerosis,[24] perhaps via exposure of coronary endothelium to increased oscillatory shear stress.[25] Further supporting these hypotheses, lower HR retards the development of atherosclerosis in monkeys[26] and HR lowering with a selective $I_{(f)}$ channel inhibitor, ivabradine, decreases markers of vascular oxidative stress, improves endothelial function and reduces atherosclerotic plaque formation in apolipoprotein E-deficient mice.[27]

Methodologic issues and study limitations

Several limitations of the present study warrant review. The use of ECG LVH criteria to select patients for LIFE increased the baseline risk of the population, suggesting that caution should be used in generalizing these findings to hypertensive patients at lower risk. However, it has been estimated that nearly 8 million patients in the first 15 member nations of the EU would meet LIFE entry criteria, with similar numbers in the remainder of Europe and the US, indicating that the present results are applicable to a substantial patient population.[28] Second, higher HR was associated with a greater burden of risk factors for adverse outcome. Although higher HR remained a strong predictor of CV and all-cause mortality after adjusting for these potential confounders, multivariable analyses may not fully take into account the possible impact of these and other unmeasured confounders on outcomes. Careful clinical matching of patients according to baseline HR at the time of recruitment would be necessary to more clearly demonstrate the independent predictive value of increased heart rate. Third, sampling of HR annually on in-study ECGs almost certainly underestimates the true relationship of changing HR over time to mortality, which might have been improved by examining day-to-day variability in HR or mean HR or measures of HR variability on serial 24 h ECGs. Finally, this was a *post hoc* analysis of findings from the LIFE study and, as such, further study will be necessary to explore and confirm the relationship of changing HR over time to CV and all-cause mortality.

Implications

The present findings suggest that persistence or development of a high normal to elevated HR over time is a marker of increased mortality risk in hypertensive patients with ECG LVH and support the serial evaluation of HR in hypertensive patients to monitor mortality risk. The current findings, taken together with the potential of HR lowering with ivabradine to significantly reduce the risk of fatal and non-fatal myocardial infarction in the subset of patients with coronary disease and decreased LV function in the BEAUTIFUL study with resting HR $\geq$70 bpm[29] and to improve endothelial function and reduce atherosclerotic plaque formation in an experimental model of atherosclerosis,[27] provide further support for the hypothesis that therapy aimed at reducing HR in hypertensive patients may reduce risk. However, further study will be necessary to determine whether direct HR lowering therapy can reduce all-cause and CV mortality in hypertensive patients with ECG LVH.

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