Incidence of Atrial Fibrillation in Relation to Changing Heart Rate Over Time in Hypertensive Patients
The LIFE Study

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Background—Onset of atrial fibrillation (AF) has been linked to changes in autonomic tone, with increasing heart rate (HR) immediately before AF onset in some patients suggesting a possible role of acute increases in sympathetic activity in AF onset. Although losartan therapy and decreasing ECG left ventricular hypertrophy are associated with decreased AF incidence, the relationship of HR changes over time to development of AF has not been examined.

Methods and Results—HR was evaluated in 8828 hypertensive patients without AF by history or on baseline ECG in the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. Patients were treated with losartan- or atenolol-based regimens and followed with serial ECGs annually which were used to determine HR and ECG left ventricular hypertrophy by Cornell product and Sokolow-Lyon voltage criteria. During mean follow-up of 4.7±1.1 years, new-onset AF occurred in 701 patients (7.9%). Patients with new AF had smaller decreases in HR to last in-treatment ECG or last ECG before AF (−2.7±13.5 versus −5.2±12.5 bpm), whether on losartan- (−0.4±13.5 versus −2.2±11.7 bpm) or atenolol-based treatment (−5.3±12.8 versus −8.3±12.6 bpm, all P<0.001). In univariate Cox analyses, higher HR on in-treatment ECGs was associated with an increased risk of new-onset AF, with a 15% greater risk of AF for every 10 bpm higher HR (95% CI 8% to 22%). In alternative analyses, persistence or development of a HR ≥84 (upper quintile of baseline HR) was associated with a 46% greater risk of developing AF (95% CI 19% to 80%). After adjusting for treatment with losartan versus atenolol, baseline risk factors for AF, baseline and in-treatment systolic and diastolic pressure and the known predictive value of baseline and in-treatment ECG left ventricular hypertrophy for new AF, higher in-treatment HR remained strongly associated with new AF with a 19% higher risk for every 10 bpm higher HR (95% CI 10% to 28%) or a 61% increased rate of AF in patients with persistence or development of a HR ≥84 (95% CI 27% to 104%, all P<0.001).

Conclusion—Higher in-treatment HR on serial ECGs is associated with an increased likelihood of new-onset AF, independent of treatment modality, blood pressure lowering, and regression of ECG left ventricular hypertrophy in patients with essential hypertension. (Circ Arrhythmia Electrophysiol. 2008;1:337-343.)

Key Words: electrocardiography  ■  fibrillation  ■  heart rate  ■  hypertension  ■  hypertrophy

Atrial fibrillation (AF) is a common arrhythmia1-2 that is increasing in prevalence.2 The incidence of AF increases with age1 and is increased in patients with hypertension, left ventricular hypertrophy (LVH), coronary heart disease, and particularly in patients with heart failure.3-10 The increased risk of death,3-5 heart failure,5 and stroke3,6,7 in patients with AF and the significant risks associated with antiarrhythmic and antithrombotic therapies aimed at preventing AF recurrences and decreasing the risk of embolic sequelae,11-13 highlight the importance of preventing AF and the need to identify epidemiological risk factors that may predispose to AF.14 The possible role of the sympathetic nervous system in the triggering and maintenance of AF15-20 and the strong relationship of underlying heart failure to the development of AF,3-10 taken together with findings that

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increased heart rate (HR) may reflect subclinical impairment of LV function,\textsuperscript{21} suggest that increasing HR during sinus rhythm may be an important marker of risk for the development of AF. However, the relationship of changing HR over time to the development of new AF has not been evaluated.\textsuperscript{22} Accordingly, the present study examined whether higher HR over time is associated with an increased rate of AF in hypertensive patients undergoing treatment, independent of the effects of in-treatment blood pressure and other risk factors for AF, and of the previously demonstrated impact of losartan-based therapy and in-treatment ECG LVH on AF incidence.\textsuperscript{3,23}

**Methods**

**Subjects**

The Losartan Intervention for End Point Reduction in Hypertension (LIFE) study\textsuperscript{24–28} enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage-duration product\textsuperscript{29,30} or Sokolow-Lyon voltage criteria\textsuperscript{31} on a screening ECG in a prospective, double-blind, randomized study that compared cardiovascular morbidity and mortality with the use of losartan- as opposed to atenolol-based treatment,\textsuperscript{26} as previously described in detail.\textsuperscript{24–28} A total of 362 patients with either a history of AF (n=342) or AF on their LIFE baseline ECG (n=135) and 3 patients with missing baseline HR data were excluded from analyses, leaving 8826 patients without AF by history or baseline ECG in the present study.

**Treatment Regimens**

Blinded treatment was begun with losartan 50 mg or atenolol 50 mg daily and matching placebo of the other agent, with a target pressure of 140/90 mm Hg or lower. During clinic visits at frequent intervals for the first 6 months and at 6-month intervals thereafter, study therapy could be up-titrated by addition of hydrochlorothiazide 12.5 mg, followed by increase in blinded losartan or atenolol to 100 mg daily. In patients whose blood pressure was still not controlled, additional open-label upward titration of hydrochlorothiazide and if necessary institution of therapy with a calcium channel blocker or additional other medications (excluding AT1- or $\beta$-blockers or angiotensin-converting enzyme inhibitors) was added to the double-blind treatment regimen.\textsuperscript{26}

**Electrocardiography**

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.\textsuperscript{24–27} Cornell product \textgreek{r}>2440 mm\textgreek{m}m$^9$ or Sokolow-Lyon voltage \textgreek{r}>38 mm$^9$ were used to identify LVH.\textsuperscript{24,25} HR was measured to the nearest bpm on each protocol-mandated study ECG. New-onset AF was identified from protocol-mandated in-study ECGs undergoing Minnesota coding at the ECG core laboratory and/or by adverse event reports of AF by the investigators.\textsuperscript{3,23}

**Statistical Analyses**

Data management and analyses were performed by the investigators using SPSS version 12.0. Data are presented as mean±SD for continuous variables and proportions for categorical variables. Differences in mean values between patients 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 mortality risk\textsuperscript{32}) were compared using unpaired $t$ tests; comparison of proportions between groups was performed using $\chi^2$ tests.

The relation of HR during sinus rhythm on baseline and in-study ECGs to risk of developing AF 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR&lt;84 bpm</th>
<th>HR≥84 bpm</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.7±7.0</td>
<td>67.3±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>52.0</td>
<td>64.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, % black</td>
<td>6.1</td>
<td>4.8</td>
<td>0.042</td>
</tr>
<tr>
<td>Treatment with Losartan, %</td>
<td>50.5</td>
<td>49.4</td>
<td>0.453</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.8</td>
<td>15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of ischemic heart disease, %</td>
<td>15.3</td>
<td>15.8</td>
<td>0.577</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>5.9</td>
<td>6.2</td>
<td>0.645</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>4.3</td>
<td>3.6</td>
<td>0.265</td>
</tr>
<tr>
<td>History of peripheral vascular disease, %</td>
<td>5.5</td>
<td>5.0</td>
<td>0.400</td>
</tr>
<tr>
<td>History of heart failure, %</td>
<td>1.3</td>
<td>2.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>15.6</td>
<td>19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>28.0±4.7</td>
<td>28.3±5.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.90±2.08</td>
<td>6.45±2.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>86.5±20.2</td>
<td>85.6±19.6</td>
<td>0.070</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.03±1.11</td>
<td>6.14±1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.50±0.43</td>
<td>1.51±0.45</td>
<td>0.479</td>
</tr>
<tr>
<td>Uric acid, $\mu$mol/L</td>
<td>329±77</td>
<td>328±80</td>
<td>0.646</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio, mg/mM</td>
<td>6.6±27.8</td>
<td>9.1±35.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

HR indicates heart rate.

Sokolow-Lyon voltage measurements from routine in-study ECGs were entered as time-varying covariates. In addition, the relation of persistence or development of a HR≥84 versus a HR<84 bpm treated as a dichotomous time-varying variable to the development of AF was also analyzed. Treating HR as a time-varying covariate, HR from the last ECG in sinus rhythm before the development of AF or from the last in-treatment ECG will enter into the model. Hazard ratios for incidence of AF 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, new AF rate over time was plotted as a function of changing presence or absence of a HR≥84 bpm using a univariate modified Kaplan–Meier method,\textsuperscript{33} implemented in SAS Release 8.2 on the WIN_PRO platform. Two-tailed $P<0.05$ 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.

**Results**

Patient Characteristics in Relation to Baseline HR

Clinical and demographic characteristics of patients in relationship to baseline HR partitioned at 84 bpm are shown in Table 1. Hypertensive patients with a baseline HR≥84 were older, more likely to be female, non-black, have diabetes, a history of heart failure, and to be current smokers, had higher body mass indexes, glucose, and total cholesterol levels, and

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1. LIFE (Losartan Intervention for End Point Reduction in Hypertension) study
2. HR (Heart Rate)
3. LVH (Left Ventricular Hypertrophy)
4. Cox proportional hazards models
5. Cornell voltage-duration product
6. Sokolow-Lyon voltage criteria
7. $\chi^2$ test
8. Minnesota coding
9. SPSS (Statistical Package for the Social Sciences)
10. Serum glucose, mmol/L
11. Serum creatinine, mmol/L
12. Total cholesterol, mmol/L
13. HDL cholesterol, mmol/L
14. Uric acid, $\mu$mol/L
15. Urine albumin/creatinine ratio, mg/mM
16. $P$ value
17. HR≥84 bpm
18. HR<84 bpm
19. Cox proportional hazards models
20. Cornell product
21. Sokolow-Lyon voltage criteria
22. $t$ test
23. $\chi^2$ test
24. LIFE (Losartan Intervention for End Point Reduction in Hypertension) study
25. Cornell voltage-duration product
26. Sokolow-Lyon voltage criteria
27. $t$ test
28. $\chi^2$ test
29. Minnesota coding
30. SPSS (Statistical Package for the Social Sciences)
31. Serum glucose, mmol/L
32. Serum creatinine, mmol/L
33. Total cholesterol, mmol/L
34. HDL cholesterol, mmol/L
35. Uric acid, $\mu$mol/L
36. Urine albumin/creatinine ratio, mg/mM
37. $P$ value
38. HR≥84 bpm
39. HR<84 bpm
40. Cox proportional hazards models
41. Cornell product
42. Sokolow-Lyon voltage criteria
43. $t$ test
44. $\chi^2$ test
45. Minnesota coding
46. SPSS (Statistical Package for the Social Sciences)
47. Serum glucose, mmol/L
48. Serum creatinine, mmol/L
49. Total cholesterol, mmol/L
50. HDL cholesterol, mmol/L
51. Uric acid, $\mu$mol/L
52. Urine albumin/creatinine ratio, mg/mM
53. $P$ value
54. HR≥84 bpm
55. HR<84 bpm
56. Cox proportional hazards models
57. Cornell product
58. Sokolow-Lyon voltage criteria
59. $t$ test
60. $\chi^2$ test
61. Minnesota coding
62. SPSS (Statistical Package for the Social Sciences)
greater albuminuria, but were similar with respect to treatment randomization and other baseline characteristics. Among patients with baseline HR<84, compared with those whose HR remained <84 throughout the study, patients who went on to develop a HR≥84 before the development of AF or before last follow-up if remaining in sinus rhythm (n=558) had similar differences in baseline characteristics as noted in Table 1 with the exception that patients who developed a HR≥84 were more likely to be black (9.4% versus 5.8%, \( P=0.002 \)) and to have taken losartan (65.9% versus 49.2%, \( P<0.001 \)), but had similar total cholesterol levels (6.09±1.09 versus 6.03±1.11 mmol/L, \( P=0.200 \)).

Blood pressure and ECG LVH measurements at baseline and changes in these measurements between baseline and last in-study determination or the development of new-onset AF 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 reductions in diastolic pressure but similar changes in systolic pressure. Higher baseline HR was associated with less severe LVH by Sokolow-Lyon voltage and Cornell voltage-duration product.

### 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR&lt;84 bpm (n=7046)</th>
<th>HR≥84 bpm (n=1782)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>174±14</td>
<td>175±15</td>
<td>0.030</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>97±9</td>
<td>100±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cornell voltage-duration product, mm-ms</td>
<td>2806±1010</td>
<td>2852±1039</td>
<td>0.084</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mm</td>
<td>30.2±10.4</td>
<td>28.9±10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline to last measurement*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>−30±19</td>
<td>−30±20</td>
<td>0.573</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−17±10</td>
<td>−18±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cornell voltage-duration product, mm-ms</td>
<td>−190±856</td>
<td>−219±816</td>
<td>0.189</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mm</td>
<td>−3.9±7.3</td>
<td>−3.6±7.2</td>
<td>0.133</td>
</tr>
</tbody>
</table>

*Change from baseline to last in-study measurement or last measurement before onset of new atrial fibrillation.

HR indicates heart rate.

### In-Treatment HR and New AF

During mean follow-up of 4.7±1.1 years, new-onset AF occurred in 701 patients (7.9%). Compared with patients who did not develop AF, patients who developed AF had smaller decreases in HR to last in-treatment ECG or last ECG before AF (−2.7±13.5 versus −5.2±12.5), whether on losartan (−0.4±13.5 versus −2.2±11.7 bpm) or atenolol-based treatment (−5.3±12.8 versus −8.3±12.6, all \( P<0.001 \)). Mean time from the last ECG in sinus rhythm to development of new AF was 156±117 days, with a mean HR of 70±13 bpm.

New-onset AF occurred in 100 patients with in-treatment persistence or development of a HR≥84 bpm, a rate of 21.1 per 1000 patient-years, and in 601 patients with in-treatment development or continued presence of a HR<84 bpm, a rate of 16.4 per 1000 patient-years.

The relationship of new-onset AF to in-treatment HR is examined in Table 3 and in the Figure. In univariate Cox analyses in which time-varying HR was treated as a continuous variable, higher in-treatment values of HR were strongly associated with an increased risk of developing AF: a 10-bpm higher HR was associated with a 15% increased risk of new AF. 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 a 1.19-fold increase in risk of developing AF (95% CI: 1.10–1.24), with a rate of 21.1 per 1000 patient-years.

### Table 3. Univariate and Multivariable Cox Regression Analyses to Assess the Predictive Value of Changing In-Treatment Heart Rate for the Development of New-Onset Atrial Fibrillation

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (per 10 bpm increase)</td>
<td>&lt;0.001</td>
<td>1.15</td>
</tr>
<tr>
<td>Heart rate (persistence or development of a HR≥84 bpm)*</td>
<td>&lt;0.001</td>
<td>1.46</td>
</tr>
<tr>
<td>Multivariable†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (per 10 bpm increase)</td>
<td>&lt;0.001</td>
<td>1.19</td>
</tr>
<tr>
<td>Heart rate (persistence or development of a HR≥84 bpm)*</td>
<td>&lt;0.001</td>
<td>1.61</td>
</tr>
</tbody>
</table>

*New-onset atrial fibrillation occurred in 601 patients with in-treatment decrease to or continued absence of a heart rate ≥84 bpm for a rate of 15.8 per 1000 patient-years and in 100 patients with in-treatment persistence or development of a heart rate ≥84 bpm for a rate of 20.2 per 1000 patient years.

†Adjusted for possible effects of treatment with losartan vs atenolol, age, gender, race, prevalent diabetes, history of ischemic heart disease, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease or smoking, baseline albumin/creatinine ratio, total and HDL cholesterol, serum creatinine, body mass index, for baseline and in-treatment systolic and diastolic blood pressure, and for baseline and in-treatment Sokolow-Lyon voltage and Cornell voltage-duration product.
bpm was associated with a 46% greater risk of developing AF compared with in-treatment development or continued presence of a HR <84. Modified Kaplan–Meier curves comparing the rate of new AF according to a HR of 84 bpm over the time course of the study (Figure) demonstrate that persistence or development of a HR ≥84 was associated with a greater risk of developing AF when compared with a HR <84, with persistence or development of a HR ≥84 associated with an estimated 6.0% higher absolute incidence of AF after 4 years of follow-up. The predictive value of time-varying HR for new AF was not dependent on whether AF was ascertained on annual study ECG or by adverse clinical event with associated AF: higher in-treatment HR by 10 bpm was similarly predictive of increased incidence of AF defined by annual ECGs (n=405, HR 1.25, 95% CI 1.15 to 1.34) or by adverse event reports (n=572, HR 1.16, 95% CI 1.08 to 1.24).

The relation of new-onset AF to in-treatment HR was further examined after adjusting for the possible effects of treatment, age, gender, race, prevalent diabetes, history of ischemic heart disease, myocardial infarction, heart failure, stroke, peripheral vascular disease and smoking, baseline urinary albumin/creatinine ratio, total and high-density lipoprotein cholesterol, serum creatinine, body mass index, and for baseline and in-treatment systolic and diastolic blood pressure, Cornell product, and Sokolow-Lyon voltage (Table 3). After adjusting for these factors, a 10 bpm higher in-treatment HR was associated with a 19% greater risk of new AF; in a parallel analysis, in-treatment persistence or development of a HR ≥84 was associated with a 61% higher incidence of AF; in a parallel analysis, in-treatment persistence or development of an increased HR was similarly predictive of increased incidence of AF defined by annual ECGs (n=405, HR 1.25, 95% CI 1.15 to 1.34) or by adverse event reports (n=572, HR 1.16, 95% CI 1.08 to 1.24).

The predictive value of time-varying HR for new-onset AF in relevant subsets of the population is examined in Table 4. The association between new-onset AF and in-treatment HR was similar in men and women, both treatment arms of the study, patients above and below 65 years of age, patients with and without diabetes or a history of ischemic heart disease, myocardial infarction, or heart failure, and patients with and without Cornell product LVH on their baseline ECGs. Higher in-treatment HR was associated with trends toward a greater increase in AF among black as opposed to non-black patients and in patients without as opposed to with LVH by Sokolow-Lyon voltage on their baseline ECGs.

**Discussion**

These findings demonstrate that higher HR, in sinus rhythm during antihypertensive therapy, is associated with a greater likelihood of new-onset AF, independent of blood pressure lowering, the beneficial effect of losartan-based therapy on the development of AF, and of the previously demonstrated relationship of AF incidence to in-treatment ECG LVH. These findings suggest that serial assessment of HR may provide additional information regarding the risk of developing AF in hypertensive patients 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 predispose patients to the development of AF.

**HR and AF**

The relationship of HR during sinus rhythm to the risk of developing AF has not been well characterized. Among 2576 subjects in the Framingham Heart Study followed for a mean of 10.5 years, baseline HR was similar in the 132 patients who developed AF and the 2444 who remained in sinus rhythm (75±13 versus 73±10), but HR over time was not reported in these patients. Among patients with heart failure who were in sinus rhythm, Pozzoli et al found that 18 patients who developed chronic AF had an increase in HR from 72±16 to 75±13 bpm between baseline and last evaluation in sinus rhythm when compared with a decrease in HR from 75±13 to 73±13 over the same period in 290 patients who remained in sinus rhythm, but did not test the statistical significance of these changes. In contrast, the current study demonstrates that hypertensive patients who developed AF had smaller decreases in HR during losartan- or atenolol-based treatment than patients who remained in sinus rhythm and that higher in-treatment HR was strongly associated with an increased risk of developing AF, independent of the beneficial effect of losartan therapy on AF incidence, and other potential AF risk factors, and of the preva-
ously demonstrated relationship of AF incidence to LVH regression in this population. The similar reductions in systolic and diastolic pressure among patients with and without a HR/H11350 and continued strong association of higher in-treatment HR with increased risk of AF after adjusting for in-treatment systolic and diastolic pressure (Table 4), demonstrate that the association between HR and AF risk was not a marker of lesser blood pressure control among patients with higher in-treatment HR. Importantly, the association between in-treatment HR and new-onset AF was robust across all subsets of the population (Table 4), including similar effects in patients taking losartan or atenolol despite the different HR responses to therapy in these groups, and among patients with and without a history of heart failure despite the strong association of heart failure with subsequent AF.

Possible mechanisms by which increased HR may relate to an increased risk of AF include as a marker of increased sympathetic activity15–20,34 and of subclinical reductions in LV function.21 The role of the sympathetic nervous system in triggering and maintenance of AF has been more extensively examined,15–20,34 although most studies have focused only on short-term variations in HR variability preceding the development of AF.15 Tachycardia per se can shorten atrial effective refractory period, potentially facilitating AF initiation and propagation.14,15,35 Subclinical LV dysfunction or early heart failure as a cause for increasing HR over time may also impact directly on the risk of AF incidence.23

Table 4. Bivariate Cox Analyses to Assess the Predictive Value of Time-Varying In-Treatment Heart Rate for New-Onset Atrial Fibrillation in Relevant Subgroups of the Study Population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>New-Onset Atrial Fibrillation (n)</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>P for Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=4021)</td>
<td>356</td>
<td>1.13</td>
<td>1.04–1.23</td>
<td>0.197</td>
</tr>
<tr>
<td>Female (n=4807)</td>
<td>345</td>
<td>1.22</td>
<td>1.12–1.33</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White or other (n=6310)</td>
<td>676</td>
<td>1.14</td>
<td>1.07–1.22</td>
<td>0.057</td>
</tr>
<tr>
<td>Black (n=518)</td>
<td>25</td>
<td>1.52</td>
<td>1.15–2.02</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.969</td>
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<tr>
<td>Atenolol (n=4391)</td>
<td>377</td>
<td>1.19</td>
<td>1.08–1.29</td>
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<td>Losartan (n=4437)</td>
<td>324</td>
<td>1.20</td>
<td>1.09–1.31</td>
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<tr>
<td>Age, y</td>
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<td>0.468</td>
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<td>Less than 65 (n=3411)</td>
<td>155</td>
<td>1.20</td>
<td>1.05–1.37</td>
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<td>65 or greater (n=5417)</td>
<td>546</td>
<td>1.13</td>
<td>1.05–1.21</td>
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<tr>
<td>History of congestive heart failure</td>
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<td></td>
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<td>0.998</td>
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<tr>
<td>No (n=8699)</td>
<td>679</td>
<td>1.15</td>
<td>1.08–1.23</td>
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<tr>
<td>Yes (n=129)</td>
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<td>1.14</td>
<td>0.78–1.66</td>
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<tr>
<td>History of ischemic heart disease</td>
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<td>0.637</td>
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<tr>
<td>Yes (n=1357)</td>
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<td>0.98–1.27</td>
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<td>History of myocardial infarction</td>
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<td>0.493</td>
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<td>No (n=8301)</td>
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<td>Yes (n=527)</td>
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<td>1.14</td>
<td>0.90–1.42</td>
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<tr>
<td>Diabetes</td>
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<td>Cornell product LVH on baseline ECG</td>
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<td>0.795</td>
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<td>No (n=2906)</td>
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<td>1.02–1.28</td>
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<td>Yes (n=5922)</td>
<td>499</td>
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<td>Sokolow-Lyon voltage LVH on baseline ECG</td>
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<tr>
<td>Yes (n=1854)</td>
<td>192</td>
<td>1.05</td>
<td>0.92–1.18</td>
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*Hazard ratio per 10 bpm higher heart rate.
†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.
LVH indicates left ventricular hypertrophy.
developing AF via increases in left atrial pressure and stretch that can promote AF. Experimental heart failure induced by rapid ventricular pacing promoted the induction of sustained AF in dogs by causing atrial interstitial fibrosis and cellular electrophysiological remodeling distinct from that produced by atrial tachycardia. Study of the relationship of changing HR over time to changes in LV structure and function and left atrial size will be necessary to clarify this relationship.

Methodologic Issues and Study Limitations

Several limitations of the present study warrant review. Use of ECG LVH criteria to select patients for LIFE increased the baseline risk of the study population, suggesting that caution should be used in generalizing these findings to hypertensive patients at lower risk. Although the present findings may not be representative of hypertensive populations with less severe disease, it has been estimated that 7.8 million patients would have met LIFE eligibility criteria in the first 15 member nations of the European Union, with similar numbers in the rest of Europe and in the United States. Second, although annual ECGs and adverse event reports by treating LIFE investigators were used to detect AF, the true incidence of AF, particularly asymptomatic AF, may have been underestimated, potentially reducing precision of the estimates of the relation of AF to in-treatment HR. Third, higher HR was associated with a greater burden of preexisting heart and vascular disease and of risk factors for adverse outcome. Although increased HR remained a strong predictor of new AF 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. Fourth, sampling of HR annually on 12-lead ECG almost certainly underestimates the true relationship of changing HR over time to incident AF, which might have been improved by examining 24-hour mean HR or measures of HR variability on serial 24-hour ECGs performed over time. 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 incident AF to changing HR over time.

Implications

These findings have potential implications for the management of patients with hypertension and LVH. Given the increasing incidence and prevalence of AF in the population and the increased risk of death, stroke, and heart failure associated with AF in LIFE and other studies, these data support the serial evaluation of HR in hypertensive patients to monitor the risk of developing AF. These observations suggest 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 predispose patients to the development of AF. Further study will be required to determine the relationship between increasing HR and structural abnormalities of left atrial size and LV size and function that may predispose to the development of AF.

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Dr Okin has received research grants from Merck & Co, Inc. Dr Wachtell has received research grants and honoraria from Merck & Co Inc. Dr Kjeldsen has received honoraria from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Merck, Novartis, Pfizer, and Sankyo. Dr Julius has been a member of speakers’ bureaus and received honoraria from Merck, Novartis, Servier, and Takeda. Dr Lindholm has received a research grant from the Swedish MRC, honoraria from Astra Zeneca, Merck/MSD, Myogen, and Novartis and has served as a consultant to Myogen. Dr Dahlöf has received research grants from Boehringer-Ingelheim, Novartis and Pfizer, served as a consultant to Boehringer-Ingelheim, Merck/MSD, and Novartis, and has been a member of speakers’ bureaus sponsored by Boehringer-Ingelheim, Merck/MSD, Novartis, Pfizer, and Servier. Dr Devereux has served as a consultant to Merck and Novartis, received grants from Merck, and has been a member of speakers’ bureaus sponsored by Merck.

Disclosures

D.A. Hille and Dr Edelman are employees of Merck & Co Inc, the sponsor of the LIFE study, and may own stock or hold stock options in Merck & Co Inc. Dr Nieminen has no disclosures relevant to this study.

References

Before AF onset in some patients, suggesting a possible role of acute increases in sympathetic activity in AF onset. Our observations suggest that further evaluation of patients with persistence or development of an increased HR during antihypertensive treatment should be considered to evaluate possible underlying abnormalities that may predispose patients to the development of AF, such as increasing left atrial size, worsening left ventricular systolic function, or both.

**CLINICAL PERSPECTIVE**

Onset of atrial fibrillation (AF) has been linked to changes in autonomic tone, with increasing heart rate (HR) immediately before AF onset in some patients, suggesting a role of acute increases in sympathetic activity in AF onset. Our study demonstrates that higher in-treatment HR is an independent and important predictor of the development of new AF in hypertensive patients, with a 19% higher risk of developing AF for every 10 beats per minute higher HR or a 61% increased risk in patients whose HR stays or becomes ≥84 beats per minute while undergoing treatment. The increased risk of new AF associated with higher HR is independent of the decreased risk of new AF associated with losartan-based therapy and the decreased risk associated with regression of electrocardiographic left ventricular hypertrophy. These findings have potential implications for the management of patients with hypertension and left ventricular hypertrophy. Given the increasing incidence and prevalence of AF in the population and the increased risk of death, stroke, and heart failure associated with AF in the Losartan Intervention For Endpoint reduction in Hypertension (LIFE) study, baseline characteristics of 9,194 patients with left ventricular hypertrophy. Hypertension. 1998;82(9):989–997.

**Additional References**

Incidence of Atrial Fibrillation in Relation to Changing Heart Rate Over Time in Hypertensive Patients: The LIFE Study
Peter M. Okin, Kristian Wachtell, Sverre E. Kjeldsen, Stevo Julius, Lars H. Lindholm, Björn Dahlöf, Darcy A. Hille, Markku S. Nieminen, Jonathan M. Edelman and Richard B. Devereux

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