Original Article

Effect of Lower On-Treatment Systolic Blood Pressure on the Risk of Atrial Fibrillation in Hypertensive Patients

Peter M. Okin; Darcy A. Hille; Anne Cecilie K. Larstorp; Kristian Wachtell; Sverre E. Kjeldsen; Björn Dahlöf; Richard B. Devereux

Abstract—There is a well-established association between hypertension and atrial fibrillation (AF); indeed, even upper normal systolic blood pressures (SBP) are long-term predictors of incident AF. These findings suggest that more aggressive BP control may reduce the risk of new AF. However, whether lower achieved SBP is associated with a lower incidence of AF remains unclear. The risk of new-onset AF was examined in relation to last in-treatment SBP before AF diagnosis or last in-study measurement in the absence of new AF in 8831 hypertensive patients with ECG left ventricular hypertrophy with no history of AF, in sinus rhythm on their baseline ECG, randomly assigned to losartan- or atenolol-based treatment. Patients with in-treatment SBP ≤130 mm Hg (lowest quintile at last measurement) and SBP between 131 and 141 mm Hg were compared with patients with in-treatment SBP ≥142 mm Hg (median SBP at last measurement). During follow-up of 4.6±1.1 years, new-onset AF was diagnosed in 701 patients (7.9%). In multivariate Cox analyses, compared with in-treatment SBP ≥142 mm Hg, in-treatment SBP ≤130 mm Hg entered as a time-varying covariate was associated with a 40% lower risk (95% confidence interval, 18%–55%) and in-treatment SBP of 131 to 141 mm Hg with a 24% lower risk (95% confidence interval, 7%–38%) of new AF. Thus, achieved SBP ≤130 mm Hg is associated with a lower risk of new-onset AF in hypertensive patients with ECG left ventricular hypertrophy. Further study is needed to determine whether targeting hypertensive patients without AF to lower SBP goals can reduce the burden of new AF in this high-risk population.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00338260.

Key Words: atrial fibrillation ■ blood pressure ■ electrocardiography ■ hypertension ■ hypertrophy
Methods
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage–duration product or Sokolow–Lyon voltage criteria on a screening ECG in a prospective, double-blind randomized study that compared cardiovascular morbidity and mortality with losartan– as opposed to atenolol-based treatment, as previously described. A total of 362 patients had a history of AF (n=342) or AF on their LIFE baseline ECG (n=135), leaving 8831 patients without AF by history or baseline ECG in the present post hoc, retrospective analysis (4809 women and 4022 men; mean age, 67±7 years). Treatment regimens, electrocardiographic methods, and end point determination have been discussed in detail previously and are outlined in detail in the online-only Data Supplement.

Data management and analyses were performed by the investigators using SPSS version 22.0 (IBM, Inc, Armonk, NY). Data are presented as mean±SD for continuous variables and proportions for categorical variables. Differences in mean values between patients grouped according to the development of new AF were compared using unpaired t-tests; comparison of proportions between groups was performed using χ² tests.

The relative predictive value for new-onset AF of in-treatment SBP ≤130 mm Hg and in-treatment SBP between 131 and 141 mm Hg was compared with that of in-treatment SBP ≥142 mm Hg using Cox proportional hazards models in which each SBP group was included as a time-varying covariate. Baseline risk factors and a treatment group indicator were entered as standard covariates, and incident myocardial infarction, incident heart failure, and in-treatment diastolic BP, Cornell product LVH, heart rate, and high-density lipoprotein cholesterol and non–high-density lipoprotein cholesterol were entered as time-varying covariates. To illustrate the results of time-varying covariate analyses, new-onset AF rate over time was plotted as a function of changing in-treatment SBP group using a univariate modified Kaplan–Meier method, implemented in SAS Release 8.2 on the WIN_PRO platform. Additional multivariable Cox analyses were performed in which hazard ratios for new-onset AF were calculated for 5-mm Hg decrements of in-treatment SBP, in which for each cutoff value AF risk was compared between patients with SBP at that level or lower and patients with SBP greater than that level. Adjusted hazard ratios were plotted versus in-treatment SBP. Finally, univariate and multivariable Cox models were performed in which AF risk was related to in-treatment SBP treated as a continuous variable, with hazard ratios calculated as a function of a lower SBP of 10 mm Hg. For all tests, a 2-tailed P value of <0.05 was required for statistical significance.

Results
Patient Characteristics in Relation to Development of AF
During mean follow-up of 4.6±1.1 years, new-onset AF occurred in 701 patients (7.9%). Clinical and demographic characteristics of patients in relationship with the development of new AF are shown in Table 1. Hypertensive patients who developed new AF were older, more likely to be men, nonblack, have a history of ischemic heart disease, previous myocardial infarction, stroke and heart failure, had lower total cholesterol levels, greater albuminuria, and were less likely to be randomized to losartan-based treatment, but they were similar with respect to other baseline characteristics.

Blood pressure and ECG measurements at baseline and changes in these measurements between baseline and last in-study determination or the development of new-onset AF are shown in Table 2. Patients with new-onset AF had slightly higher mean baseline SBP, lower baseline diastolic blood pressure, and greater reduction in SBP but similar change in diastolic blood pressure. New-onset AF was associated with slightly lower mean baseline heart rate, slightly longer QRS duration, and more severe baseline ECG LVH by Cornell product and Sokolow–Lyon voltage criteria. Patients who developed AF had smaller reduction in mean heart rate, slightly greater increase in QRS duration, and less regression of LVH by Cornell product criteria but had similar change in Sokolow–Lyon voltage compared with patients who did not develop AF.

New-Onset AF in Relation to In-Treatment SBP
The relationships of new-onset AF with in-treatment SBP are shown in Table 3 and Figure 1. In univariate analyses, compared with in-treatment SBP ≥142 mm Hg, both in-treatment SBP between 131 and 141 mm Hg and in-treatment SBP ≤130 mm Hg entered as a time-varying covariates identified patients with statistically significant 46% lower risk of new-onset AF. In multivariable Cox analyses adjusting for baseline risk factors and randomized treatment as standard covariates and baseline and in-treatment diastolic BP, Cornell product LVH, heart rate, high-density lipoprotein cholesterol, and non–high-density lipoprotein cholesterol as time-varying covariates, an in-treatment achieved SBP of 131 to 141 remained associated with a statistically significant 24% decreased risk of new AF and patients who achieved a SBP of ≤130 mm Hg had a 40% reduction in the risk of developing new AF compared with patients with in-treatment SBP ≥142 mm Hg (Table 3). Multivariable Cox analyses for prediction of new-onset AF were repeated using 5-mm Hg cutoff increments for in-treatment SBP (Figure 2), demonstrating that the association of low SBP with the development of new AF was similar.

Table 1. Demographic and Clinical Characteristics in Relation to Development of New Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variables</th>
<th>No AF, n=8130</th>
<th>New AF, n=701</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.6±7.0</td>
<td>69.8±6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>45.1</td>
<td>50.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Race, black, %</td>
<td>6.1</td>
<td>3.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Treatment with losartan, %</td>
<td>50.6</td>
<td>46.2</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>12.3</td>
<td>14.6</td>
<td>0.103</td>
</tr>
<tr>
<td>History of ischemic heart disease, %</td>
<td>14.7</td>
<td>22.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>5.8</td>
<td>8.4</td>
<td>0.006</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>4</td>
<td>6</td>
<td>0.014</td>
</tr>
<tr>
<td>History of peripheral vascular disease, %</td>
<td>5.3</td>
<td>6.4</td>
<td>0.26</td>
</tr>
<tr>
<td>History of heart failure, %</td>
<td>1.3</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>16.5</td>
<td>15.1</td>
<td>0.384</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.0±4.8</td>
<td>28.0±4.9</td>
<td>0.932</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>6.00±2.18</td>
<td>6.09±2.18</td>
<td>0.303</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>86.5±19.9</td>
<td>87.6±22.0</td>
<td>0.176</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.0±1.12</td>
<td>5.96±1.13</td>
<td>0.028</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.50±0.44</td>
<td>1.48±0.43</td>
<td>0.384</td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>329±78</td>
<td>331±75</td>
<td>0.537</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio, mg/mmol</td>
<td>6.6±27.4</td>
<td>12.3±47.2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and HDL, high-density lipoprotein.
Baseline and Change From Baseline to Development of New AF or Last In-Study Measurement of Blood Pressure, Heart Rate, QRS Duration, and Electrocardiographic Left Ventricular Hypertrophy in Relation to Development of New AF

<table>
<thead>
<tr>
<th>Variables No AF, n=8130 New AF, n=701</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline measurements</strong></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>174±14</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>98±9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74±11</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>101±18</td>
</tr>
<tr>
<td>Cornell voltage–duration product, mm ms</td>
<td>2804±1015</td>
</tr>
<tr>
<td>Sokolow–Lyon voltage, mm</td>
<td>29.8±10.2</td>
</tr>
<tr>
<td><strong>Change from baseline to last measurement</strong>*</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>−29±19</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>−17±10</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>−5±13</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>2±12</td>
</tr>
<tr>
<td>Cornell voltage–duration product, mm ms</td>
<td>−204±825</td>
</tr>
<tr>
<td>Sokolow–Lyon voltage, mm</td>
<td>−3.8±7.1</td>
</tr>
</tbody>
</table>

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

Achieved SBP with decreased new AF was not dependent on use of the 3 SBP groups used in this study. In these analyses, lower SBP down to a cutoff of ≤130 mm Hg remained associated with statistically significant decreased risk of new-onset AF and it was only at SBP levels of ≤125 mm Hg that lower SBP was no longer associated with a significantly reduced risk of AF (Figure 2). Of note, in univariate and parallel multivariable Cox analyses in which SBP was entered as a continuous variable, with no assumptions on the threshold of SBP that might be associated with new AF, every 10- mm Hg decrease in SBP as a continuous variable was associated with 24% and 13% lower risks of new-onset AF, respectively. In addition, there were no significant interactions between the level of SBP achieved and age treated either as a continuous variable or partitioned at age 60 in these multivariable analyses.

Discussion

Previous studies have established a strong relationship between hypertension and development of AF8,9,11 and that AF risk is proportional to the severity of hypertension.8,13,14 Although, some,16–18 but not all,13 studies suggest that reductions in BP are associated with a reduced risk of AF, several studies have found that the increased risk of developing AF persists even into the upper normal range of BP;17,19 raising the attractive hypothesis that more aggressive BP control in hypertensive patients could further reduce AF risk compared with standard BP control.34

More aggressive treatment of hypertension aimed at greater reduction of BP or a lower achieved BP to produce greater reduction of cardiovascular risk has had mixed results16,20–24 and remains controversial25,26 pending results of the ongoing Systolic Blood Pressure Intervention Trial (SPRINT).35 To date, there are only limited and conflicting data on the relationship of AF to the degree of SBP control in hypertensive patients.14,16 In a case-controlled study of patients undergoing treatment for hypertension,22 compared with a reference level of 120 to 129 mm Hg, both SBP ≥150 and SBP <120 were associated with an increased risk of incident AF in multivariable logistic regression models. However, patients and controls were only matched on the basis of age, sex, and index year of presentation, multivariate models did not take into account either previous myocardial infarction or heart failure, which could be variably related to pre-existing hypertension and independently contribute to the risk of new AF, and

Table 3. Univariate and Multivariable Cox Regression Analyses to Assess the Risk of New-Onset Atrial Fibrillation in Relation to In-Treatment Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Systolic Blood Pressure Determination</th>
<th>Univariate Cox Models</th>
<th>Multivariable Cox Models*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI P Value</td>
<td>HR 95% CI P Value</td>
</tr>
<tr>
<td>In-Treatment SBP Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≤130 mm Hg</td>
<td>0.54 0.45–0.69 &lt;0.001</td>
<td>0.60 0.45–0.82 0.001</td>
</tr>
<tr>
<td>SBP 131–141 mm Hg</td>
<td>0.54 0.45–0.65 &lt;0.001</td>
<td>0.76 0.62–0.93 0.007</td>
</tr>
<tr>
<td>SBP ≥142 mm Hg</td>
<td>1       ...</td>
<td>1</td>
</tr>
<tr>
<td>In-Treatment SBP as a continuous variable</td>
<td>0.76 0.74–0.79 &lt;0.001</td>
<td>0.87 0.83–0.91 &lt;0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and SBP, systolic blood pressure.

*Adjusted for randomized treatment allocation, age, sex, race, diabetes mellitus, history of ischemic heart disease, myocardial infarction or heart failure, previous antihypertensive therapy, baseline serum glucose and creatinine, urine albumin/creatinine ratio, Sokolow–Lyon voltage and QRS duration entered as standard covariates and incident myocardial infarction, incident heart failure and baseline and in-treatment diastolic blood pressure, Cornell product left ventricular hypertrophy, heart rate, HDL, and non-HDL cholesterol entered as time-varying covariates.
did not take into account time to incident AF. In contrast, in Cardio-Sis,\textsuperscript{16} treatment to a more aggressive SBP target (<130 mm Hg) was associated with a significantly lower incidence of the secondary end point of new-onset AF than treatment to a less aggressive target SBP of <140 mm Hg (10/557, 1.8% versus 21/553, 3.8%; hazard ratio, 0.46; 95% confidence interval, 0.22–0.98; \( P=0.044 \)) but with few cases of new AF.

This study extends these findings to a large and well-characterized population of hypertensive patients at substantially higher risk of developing new AF, demonstrating that achievement of a SBP of \( \leq 130 \) mm Hg was associated with a decreased risk of incident AF, independent of standard AF risk factors and of the previously demonstrated relationship of AF risk to randomized treatment,\textsuperscript{3} and in-treatment ECG LVH and heart rate in this population.\textsuperscript{23,28} Importantly, the decreased risk of new AF with lower achieved SBP persists after adjusting for both incident myocardial infarction and incident heart failure, which are independently associated with new AF and could also be associated with lower achieved SBP. Treating SBP as a time-varying covariate in these analyses in which the last SBP before the development of new AF is used in the Cox models further mitigates the potential for reverse causality in which new AF associated with either new myocardial infarction or heart failure could potentially further contribute to a lower a SBP by using the SBP measurement before development of AF and also adjusting for incident myocardial infarction or heart failure. Furthermore, previous analyses in the overall LIFE study population\textsuperscript{23} demonstrated that an achieved SBP of \( \leq 130 \) mm Hg was not associated with any increased risk of ischemic events, such as myocardial infarction or stroke. Analysis of risk of AF in relation to SBP over the full spectrum of measurements (Figure 2) demonstrates that the significantly decreased risk of new AF at lower achieved SBP levels is attenuated once achieved SBP is \( \leq 125 \) mm Hg. These findings, the lower risk of AF at SBP <130 in the Cardio-Sis study\textsuperscript{16} in the case–control study,\textsuperscript{14} suggest a target SBP of 120 to 129 mm Hg for future studies of this question.

There are many possible explanations for the relationship between lower SBP and decreased AF incidence. First, direct or indirect effects of SBP on left atrial (LA) remodeling could mediate the relationship of lower achieved SBP with reduced AF incidence. Less LA dilatation could be mediated indirectly via lower achieved BP reducing LV stiffness\textsuperscript{36} or via a potentially greater regression of LVH with lower BP achieved and the previously demonstrated relationship of LA enlargement to ECG LVH over time.\textsuperscript{37} However, the lower incidence of AF with lower achieved SBP in this study persisted even after controlling for the potential effect of changing ECG LVH over time, suggesting that this effect may be mediated by a hypertrophy-independent mechanism. Indeed, reversal of experimental LA volume overload in sheep can reverse abnormal electrophysiological LA remodeling,\textsuperscript{38} even when hypertrophy persists. Similarly, either direct or indirect effects of lower achieved SBP on LA fibrosis could mediate the relationship with AF as the extent of LA fibrosis has been demonstrated to

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**Figure 1.** Univariate modified Kaplan–Meier survival curves illustrating the rate of new-onset atrial fibrillation (AF) according to time-varying persistence or development of a systolic blood pressure (SBP) of \( \leq 130 \) mm Hg and of 131 to 141 mm Hg compared with a systolic blood pressure of \( \geq 142 \) mm Hg during follow-up. Patient group assignment is adjusted at the time of each blood pressure determination based on the systolic blood pressure at each time.\textsuperscript{23}

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**Figure 2.** Hazard ratios for new-onset atrial fibrillation according to on-treatment systolic blood pressure by 5 mm Hg cutoff values, adjusted for the effects of treatment with losartan versus atenolol, age, sex, race, diabetes mellitus, history of ischemic heart disease, myocardial infarction or heart failure, previous antihypertensive therapy, baseline serum glucose and creatinine, urine albumin/creatinine ratio, Sokolow–Lychn voltage and QRS duration entered as standard covariates and incident myocardial infarction, incident heart failure and baseline and in-treatment diastolic blood pressure, Cornell product left ventricular hypertrophy, heart rate, high-density lipoprotein cholesterol (HDL), and non-HDL cholesterol entered as time-varying covariates.
correlate with risk of AF recurrence after ablation therapy. Further work is necessary to determine whether lower achieved SBP is independently associated with less LA enlargement and less regression of ECG LVH over time and whether changes in these anatomic and ECG measures are associated with corresponding prevention or reduced progression of LA electrophysiological and fibrotic substrate for AF.

Several limitations of this study warrant review. First, this is a post hoc analysis of a previously conducted randomized clinical trial that did not randomize patients to different SBP control groups. This could lead to possible sources of confounding because of differences between the SBP groups both at baseline and during the trial. Although we control for known, measured differences between groups and for the possible effects of randomized treatment, incident heart failure and myocardial infarction and in-treatment diastolic BP, heart rate and ECG LVH on outcome, multivariable analyses may not fully adjust for these differences and cannot adjust for other potential factors that were not measured. As a consequence, whether low achieved SBP may be a marker of less extensive underlying structural or functional abnormalities that reduce the predisposition to AF cannot be definitively addressed using this approach. Second, the absence of data on LA size in the vast majority of patients and the small number of cases of incident AF in the echocardiographic substudy of LIFE who were free of AF at study baseline (n=70) preclude a meaningful evaluation of whether the relationship of SBP to incident AF could be in part explained by differences in LA size in patients who develop new AF as observed in the general LIFE echocardiographic substudy and other populations while in sinus rhythm. Third, 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. Finally, because incident AF was only ascertained on study ECGs and at study visits, the possibility that cases of paroxysmal AF were missed cannot be excluded.

Perspectives

Given the increasing prevalence of AF and the particularly strong association of AF with hypertension, these findings have important implications for the treatment of high BP. Further study is necessary to determine whether targeting hypertensive patients without AF to lower BP goals can reduce the burden of AF in hypertensive patients and hence reduce the downstream consequences of AF, including increased stroke and heart failure risks.

Disclosures

Dr Okin has received grant support from and served as a consultant to Novartis. Dr Wachtell has received honoraria from Merck & Co, Inc. D.A. Hille is employed by Merck & Co, Inc, and owns stock or stock options in Merck & Co, Inc. Dr Larstorp has received honoraria from Merck & Co, Inc, and from Hemo Sapiens. Dr Kjeldsen has received grant support from Pronova and Astra-Zeneca, honoraria from Astra-Zeneca, Bayer, MSD, Medtronic, and Takeda and served as a consultant to Bayer, Medtronic, Serodex, and Takeda. Dr Dahlöf has served on speakers’ bureaus for Pfizer, Vicore Pharma, MSD, Novartis, and Boehringer-Ingelheim, has an ownership interest in Mintage Scientific and Cereon Scientific, and served as a consultant or on scientific advisory boards for MSD, Novartis, and Vicere Pharma. Dr Devereux has served on an advisory board for GE Medical Systems and received honoraria from Edwards Life Sciences and Merck & Co.

References


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**Novelty and Significance**

**What Is New?**

- In a group of patients with high blood pressure in whom a large enough number develop atrial fibrillation to allow meaningful analysis, achieving lower goals of systolic blood pressure was associated with a lower risk of developing atrial fibrillation than treating to more standard systolic blood pressure goals.

**What Is Relevant?**

- This study suggests that patients with high blood pressure at high risk of developing atrial fibrillation may benefit from more aggressive treatment to lower their blood pressure to decrease the risk of developing atrial fibrillation.
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ONLINE SUPPLEMENT

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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 BP 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 ACE-inhibitors) was added to the double-blind treatment regimen (1).

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 (2-4). Cornell product >2,440 mm-msec or Sokolow-Lyon voltage >38 mm were used to identify LVH (1-7).

Endpoint Determination

New-onset AF was identified in a total of 701 patients, either from protocol-mandated in-study ECGs undergoing Minnesota coding at the ECG core lab (n=405) and/or by adverse event reports of AF by the investigators (n=572) (3). In patients who had new AF by both criteria, the earliest onset of AF was taken as the time to new AF for this analysis. Atrial flutter was not independently coded.
REFERENCES


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摘要——高血压与心房颤动 (atrial fibrillation, AF) (简称 “房颤”) 之间的关联已得到了确认; 甚至是正常收缩压 (systolic blood pressure, SBP) 上限也是房颤事件的长期预测因素。这些发现提示, 更为积极的BP控制可能会降低新发房颤的风险。然而，治疗后更低的SBP是否与房颤发病率降低相关尚未知。研究纳入8831例ECG提示左室肥厚的高血压患者，无房颤病史，基线ECG为窦性心律，随机分配至氯沙坦或阿替洛尔治疗，检测新发房颤风险与治疗期间诊断为房颤前的末次SBP或无新发房颤时研究末次SBP之间的关系。治疗期间SBP≤130 mm Hg(末次测量时的最低五分位数)、SBP 131~141 mm Hg的患者与SBP≥142 mm Hg(末次测量时的SBP中位数) 患者进行比较。在随访4.6±1.1年期间，701例 (7.9%) 患者诊断为新发房颤。在多变量Cox分析中，与治疗期间SBP≥142 mm Hg相比，治疗期间SBP≤130 mm Hg作为时变变量，新发房颤风险降低40% (95%可信区间: 18%~55%)，治疗期间SBP 131~141 mm Hg的新发房颤风险降低24% (95%可信区间: 7%~38%)。因此，在ECG提示左室肥厚的高血压患者中，目标SBP≤130 mm Hg与新发房颤风险更低相关。然而对于无房颤的高血压患者，是否更低的SBP靶目标能够降低这一高危人群新发房颤的负担，仍需进一步研究证实。

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00338260. (Hypertension. 2015;66:368-373. DOI: 10.1161/HYPERTENSIONAHA.115.05728.)

关键词：心房颤动 ■ 血压 ■ 心电图 ■ 高血压 ■ 肥厚
大或目标血压更低，以进一步降低心血管风险，但研究结果不尽相同[16,20-24]，对此仍有争议[25,26]。然而，有关高血压治疗期间达标SBP更低是否与房颤风险降低相关的数据相当有限[14,16]。因此，本研究的目的是在ECG提示LVH的高血压患者中探讨与标准SBP控制(131~141 mm Hg)和SBP控制不佳(SBP ≥ 142 mm Hg)相比，达标SBP更低(≤130 mm Hg)是否与更低的房颤发病率有关，这种相关性不依赖于治疗模式、基线风险因素、治疗期间舒张压以及先前研究在该人群中根据Cornell乘积标准显示的治疗期间心率和ECG LVH逆转对新发房颤的预测值[27,28]。

方法

研究者采用SPSS 22.0版(IBM, Inc, 阿蒙克市，纽约)进行数据管理和分析。连续变量以均值±SD表示，分类变量以比例表示。采用未配对t检验比较根据新发房颤分组患者之值的差异；采用χ²检验比较组间比例。采用Cox比例风险模型，比较治疗期间SBP ≤ 130 mm Hg、SBP 131~141 mm Hg与SBP ≥ 142 mm Hg对新发房颤的相对预测值，将每一SBP组列入时变协变量。基线风险因子和接受的随机治疗作为标准协变量，心肌梗死事件、心力衰竭事件、治疗期间舒张压、Cornell乘积LVH、心率、高密度脂蛋白胆固醇和非高密度脂蛋白胆固醇作为时变协变量。为阐明时变变量分析的结果，采用单变量改良Kaplan–Meier法，在WIN_PRO系统应用SAS 8.2版软件，以治疗期间不同SBP组间绘制新发房颤发生率随时间变化的曲线[33]。另外进行多变量Cox分析，根据治疗期间SBP以5- mmHg的递减量计算新发房颤的风险比，在SBP处于或低于该水平与高于该水平的患者之间比较每一截断值的房颤风险。分析与治疗期间SBP相关的校正后风险比。最后，采用单变量和多变量Cox模型，将与房颤风险相关的治疗期间SBP作为连续变量，计算SBP每降低10 mm Hg的风险比。所有检验的双侧P值<0.05为具有统计学意义。

结果
与房颤发生相关的患者特征
在平均随访4.6±1.1年期间，701例(7.9%)患者出现新发房颤。表1和图1所示为新发房颤与治疗期间SBP之间的关系。表1和图1所示为新发房颤与治疗期间SBP之间的
表2. 与新发房颤有关的血压、心率、QRS持续时间和心电图左室肥厚的基线测量以及从基线至新发房颤或研究未次测量之间的变化

<table>
<thead>
<tr>
<th>变量</th>
<th>无房颤 n=8130</th>
<th>新发房颤 n=701</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>收缩压, mmHg</td>
<td>174±14</td>
<td>177±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>舒张压, mmHg</td>
<td>98±9</td>
<td>97±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>心率, bpm</td>
<td>74±11</td>
<td>73±11</td>
<td>0.025</td>
</tr>
<tr>
<td>QRS持续时间, ms</td>
<td>101±18</td>
<td>103±19</td>
<td>0.002</td>
</tr>
<tr>
<td>Cornell电压-持续时间乘积, mm·ms</td>
<td>2804±1015</td>
<td>2941±1014</td>
<td>0.001</td>
</tr>
<tr>
<td>Sokolow–Lyon电压, mm</td>
<td>29.8±10.2</td>
<td>31.7±11.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

从基线至末次测量的变化*

收缩压, mmHg -29±19 -34±21 <0.001
舒张压, mmHg -17±10 -17±11 0.572
心率, bpm -5±13 -3±15 <0.001
QRS持续时间, ms 2±12 3±15 0.002
Cornell电压-持续时间乘积, mm·ms -204±825 -103±1091 0.018
Sokolow–Lyon电压, mm -3.8±7.1 -4.2±8.8 0.292

*从基线至研究末次测量或新发房颤之前末次测量之间的变化。

关系。在单变量分析中，将治疗期间SBP作为时变变量识别患者，与治疗期间SBP＞142 mm Hg相比，SBP 131~141 mm Hg和SBP＜130 mm Hg的新发房颤风险降低46%，具统计学家意义。在多变量Cox分析中，将基线风险因子和接受的随机治疗作为标准协变量，基线和治疗期间舒张压、Cornell乘积LVH、心率、高密度脂肪蛋白胆固醇和非高密度脂蛋白胆固醇作为时变变量，进行校正。

此外, 在这些多变量分析中, 年龄无论是作为连续变量还是以60岁为界, 与新发房颤风险降低不再有显著相关性 (表2)。

**讨论**

以往的研究已证明高血压与房颤之间具有强相关性，房颤的发生风险与高血压的严重程度呈正比。虽然有一些研究提示降低BP与房颤风险的降低相关，但并非所有研究均如此。有数项研究发现房颤发生的风险增加甚至在BP正常范围的上限亦存在，因此提出了这个备受关注的假设：与标准BP控制相比，对高血压患者进行更为积极的BP控制可能会进一步降低房颤的发生风险。为进行更为严格的抗高血压治疗，需等待进一步的收缩压干预试验 (Systolic Blood Pressure Intervention Trial, SPIRT) 的结果。但是，迄今为止有关高血压患者SBP控制的程度与房颤关系的数据有限，且互相冲突。在一项纳入接受高血压治疗患者的病例对照研究中，与SBP 120~129 mmHg的参考水平相比，SBP ≥150 mmHg和SBP＜120 mmHg在多变量 Logistic回归模型中均与房颤事件风险的增加相关。

表3. 评价新发房颤事件风险与治疗期间收缩压关系的单变量和多变量Cox回归分析

<table>
<thead>
<tr>
<th>收缩压</th>
<th>HR</th>
<th>95% CI</th>
<th>P值</th>
<th>HR</th>
<th>95% CI</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>治疗期间SBP组</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP＜130 mmHg</td>
<td>0.54</td>
<td>0.45~0.69</td>
<td>&lt;0.001</td>
<td>0.60</td>
<td>0.45~0.82</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP 131~141 mmHg</td>
<td>0.54</td>
<td>0.45~0.65</td>
<td>&lt;0.001</td>
<td>0.76</td>
<td>0.62~0.93</td>
<td>0.007</td>
</tr>
<tr>
<td>SBP≥142 mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>治疗期间SBP作为连续变量</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP(每降低10- mmHg)</td>
<td>0.76</td>
<td>0.74~0.79</td>
<td>&lt;0.001</td>
<td>0.87</td>
<td>0.83~0.91</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI (confidence interval)；可信区间，HR (hazard ratio)；风险比，SBP (systolic blood pressure)；收缩压。

* 以随机治疗分配，年龄、性别、种族、糖尿病、缺血性心脏病病史、心肌梗死或心力衰竭病史、既往抗高血压治疗、基线血清葡萄糖和肌酐、尿白蛋白/肌酐比值、Sokolow–Lyon电压和QRS持续时间作为标准协变量，以心肌梗死事件、心力衰竭事件、基线和治疗期间舒张压、Cornell乘积LVH、心率、高密度脂蛋白胆固醇和非高密度脂蛋白胆固醇作为时变变量，进行校正。
而这些可能会因先已存在的高血压而变化并与新发房颤的风险独立相关，也未将发生房颤事件的时间考虑进去。与之相反，在Cardio-Sis试验中[16]，更为积极的SBP靶目标（<130 mmHg）治疗相较于不够积极的SBP靶目标（<140 mmHg）,次级终点新发房颤的发病率显著降低（10/557，1.8% vs 21/553，3.8%；风险比，0.46；95%可信区间，0.22~0.98；P=0.044），但新发房颤病例数不多。本研究将这些试验发现扩展至一个大型且特征良好的具有新发房颤极高风险的高血压患者人群，结果显示在该人群中达到SBP ≤ 130 mmHg与房颤事件的风险降低相关，独立于标准房颤风险因子以及之前研究提示的与房颤风险相关的随机治疗[3]、治疗期间ECG LVH和心率[27,28]。重要的是，达成更低的SBP使新发房颤风险的降低在对心肌梗死事件和心力衰竭事件进行校正后依然持续，心肌梗死事件和心力衰竭事件与新发房颤独立相关，也与达成更低的SBP相关。在这些分析中将SBP作为时变协变量，Cox模型中采用新发房颤之前未次SBP，并对心肌梗死或心力衰竭事件进行校正，进一步减轻了新发房颤与新发心肌梗死或心力衰竭之间的反向因果关系的影响，可以进一步归因于更低的SBP。此外，先前对LIFE研究总人群的分析[23]显示，达成SBP≤130 mmHg与诸如心肌梗死或卒中等出血性事件的风险增加不相关。对全部SBP测量值与房颤风险相关性的分析（图2）显示，一旦SBP≤125 mmHg，更低SBP水平显著降低新发房颤风险的效应减弱。Cardio-Sis研究中SBP<130 mmHg时房颤风险较低[18]，而病例对照研究发现SBP<120 mmHg时房颤风险增加[14]，这些研究结果提示未来应对SBP 120~129 mmHg的靶目标进行研究。

更低的SBP与房颤发病率降低之间的关系有很多可能的解释。首先，SBP对左心房（left atrial, LA）重构的直接或间接效应可能介导了更低的目标SBP与房颤发病率降低之间的关系。达到更低的BP通过减轻LV僵硬度[36]，或通过逆转LVH，间接引起LA扩张较小，既往有研究提示LA扩张随时间与ECG LVH相关[17]。然而，在本研究中，甚至在对ECG LVH随时间改变的潜在效应进行控制之后，达成降低的SBP使房颤发病率较低的作用依然持续，提示该效应可能由独立于肥厚的机制进行介导。实际上，羊逆转实验中LA容量超负荷可以逆转LA重构电生理学异常[38]，即使在肥厚持续时依然如此。同样，达到更低的SBP对LA纤维化的直接或间接效应可能介导了其与房颤风险降低间的联系。
颤之间的关系，因为研究显示消融治疗之后LA纤维化的程度与房颤复发的风险相关。有必要开展进一步的研究，以确定达成更低的SBP是否与LA扩张较小，以及ECG LVH随时间的逆转较少独立相关，解剖学和ECG的这些改变是否与造成房颤的LA电生理学和纤维基质的相应预防或延缓进展相关。

本研究存在几个局限性。首先，这是对之前开展的一项随机临床试验的事后分析，该试验未将患者随机化分至不同的SBP控制组。这可能会因基线和试验期间的SBP组间差异，造成混杂因素的产生。虽然研究对组间的已知所测差异进行了控制，但多变量分析可能未对这些差异进行完全的校正，也无法对未测量的其他可能因素进行校正。因此，对于减少房颤发生的倾向，达成更低的SBP是否为影响房颤发生风险的许多潜在结构性或功能性异常轻的一个标志，采用这种方法不能最终解释这个问题。其次，绝大多数患者缺乏LA大小的数据，LIFE的心电图亚组研究中基线无房颤的患者发生房颤事件病例数少(n=70)，碍于对SBP是否与房颤事件相关作出有意义的评价，而在总体LIFE心电图亚组研究以及窦性心律的其他人群中观察到新发房颤患者的LA大小存在差异。第三，LIFE研究采用ECG LVH标准来选择患者，增加了人群的基线风险，提示这些研究发现推广至较低风险的高血压患者时应谨慎小心。最后，由于仅根据研究访视时的ECG来确定房颤事件，不能排除有丢失阵发性房颤病例的可能性。

**观点**

由于房颤的患病率日益增加，尤其是与高血压强相关，这些研究发现对于高血压治疗具有重要的影响。应开展进一步研究，以确定对于无房颤高血压患者是否更低的血压靶目标能够降低高血压患者的房颤负担，进而减少房颤后续结果包括卒中以及心力衰竭的风险。

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**参考文献**

新颢性和重要性

有何新意?
• 在有足够数量新发心房颤动可以进行有意义分析的高血压患者中，与标准的收缩压治疗目标相比，收缩压目标值越低与新发心房颤动的风险降低相关。

有何相关意义?
• 该研究提示，具有新发心房颤动高风险的高血压患者可以从更为积极的降压治疗中获益，以降低心房颤动发生的风险。

总结
有必要开展进一步研究，以确定给予高血压患者更多的药物使其收缩压降低至更低的治疗目标，是否能减少心房颤动而不增加其他心血管风险或不良反应。