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

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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.

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Key Words: atrial fibrillation ■ blood pressure ■ electrocardiography ■ hypertension ■ hypertrophy

Atrial fibrillation (AF) is a common arrhythmia[1,2] that is increasing in prevalence.[2] The incidence of AF increases with age[1] and is increased in patients with heart failure, left ventricular hypertrophy (LVH), coronary heart disease, and hypertension.[3–14] The higher risk of death,[3–5] sudden cardiac death,[6] heart failure,[5] and stroke[3,7,8] in patients with AF and the substantial risks associated with antithrombotic therapies aimed at decreasing the risk of embolic sequelae[15] make prevention of the development of new AF a major clinical and epidemiological goal.

Hypertension is the most important risk factor for new AF, estimated to account for between 14% and 22% of the population-attributable risk[9,11]; AF risk is also related to the severity of hypertension.[8,13,14] Some,[16–18] but not all, studies[13] suggest that reductions in blood pressure (BP) can reduce the risk of developing new AF. Recent work found that even upper normal levels of systolic BP (SBP) were associated with an increased long-term risk of AF,[19] suggesting that more aggressive BP control may further decrease AF risk. More intensive antihypertensive treatment aimed at greater reduction of BP or a lower achieved pressure to further reduce cardiovascular risk has produced mixed outcomes[16,20–24] and remains controversial.[25,26] However, there are only limited data on whether achievement of a lower SBP during treatment of hypertension is associated with a decreased risk of AF.[14,16] Therefore, the purpose of this study was to examine whether lower achieved SBP (≤130 mm Hg) is associated with a lower incidence of AF compared with typical SBP control (131–141 mm Hg) and less-adequate control (SBP ≥142 mm Hg) in hypertensive patients with ECG LVH, independent of treatment modality, baseline risk factors, in-treatment diastolic BP, and the previously demonstrated predictive value of in-treatment heart rate and regression of ECG LVH by Cornell product criteria for new AF in this population.[27,28]

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Methods

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study[3,6,27–30] enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage–duration product[31] or Sokolow–Lyon voltage criteria[32] 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,[29] as previously described.[3,6,27–30] 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,[29] electrocardiographic methods,[6,27–32] and end point determination[27] 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 χ^2 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.[33] 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

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

Variables	No AF, n=8130	New AF, n=701	*P* Value
Age, y	66.6±7.0	69.8±6.5	<0.001
Sex, male, %	45.1	50.8	0.004
Race, black, %	6.1	3.6	0.009
Treatment with losartan, %	50.6	46.2	0.028
Diabetes mellitus, %	12.3	14.6	0.103
History of ischemic heart disease, %	14.7	22.5	<0.001
History of myocardial infarction, %	5.8	8.4	0.006
History of stroke, %	4	6	0.014
History of peripheral vascular disease, %	5.3	6.4	0.26
History of heart failure, %	1.3	3.1	<0.001
Current smokers, %	16.5	15.1	0.384
Body mass index, kg/m^2	28.0±4.8	28.0±4.9	0.932
Serum glucose, mmol/L	6.00±2.18	6.09±2.18	0.303
Serum creatinine, μmol/L	86.5±19.9	87.6±22.0	0.176
Total cholesterol, mmol/L	6.06±1.12	5.96±1.13	0.028
HDL cholesterol, mmol/L	1.50±0.44	1.48±0.43	0.384
Uric acid, μmol/L	329±78	331±75	0.537
Urine albumin/creatinine ratio, mg/mmol	6.6±27.4	12.3±47.2	0.003

AF indicates atrial fibrillation; and HDL, high-density lipoprotein.

Table 2. 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

Variables	No AF, n=8130	New AF, n=701	*P* Value
Baseline measurements			
Systolic blood pressure, mm Hg	174±14	177±14	<0.001
Diastolic blood pressure, mm Hg	98±9	97±9	<0.001
Heart rate, bpm	74±11	73±11	0.025
QRS duration, ms	101±18	103±19	0.002
Cornell voltage–duration product, mm·ms	2804±1015	2941±1014	0.001
Sokolow–Lyon voltage, mm	29.8±10.2	31.7±11.6	<0.001
Change from baseline to last measurement*			
Systolic blood pressure, mm Hg	−29±19	−34±21	<0.001
Diastolic blood pressure, mm Hg	−17±10	−17±11	0.572
Heart rate, bpm	−5±13	−3±15	<0.001
QRS duration, ms	2±12	3±15	0.002
Cornell voltage–duration product, mm·ms	−204±825	−103±1091	0.018
Sokolow–Lyon voltage, mm	−3.8±7.1	−4.2±8.8	0.292

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 AF[8,9,11] 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 results[16,20–24] and remains controversial[25,26] 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,[14] 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

Systolic Blood Pressure Determination	Univariate Cox Models			Multivariable Cox Models*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
In-Treatment SBP Group						
SBP ≤130 mm Hg	0.54	0.45–0.69	<0.001	0.60	0.45–0.82	0.001
SBP 131–141 mm Hg	0.54	0.45–0.65	<0.001	0.76	0.62–0.93	0.007
SBP ≥142 mm Hg	1	…	…	1	…	…
In-Treatment SBP as a continuous variable						
SBP (per 10- mm Hg decrease)	0.76	0.74–0.79	<0.001	0.87	0.83–0.91	<0.001

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.

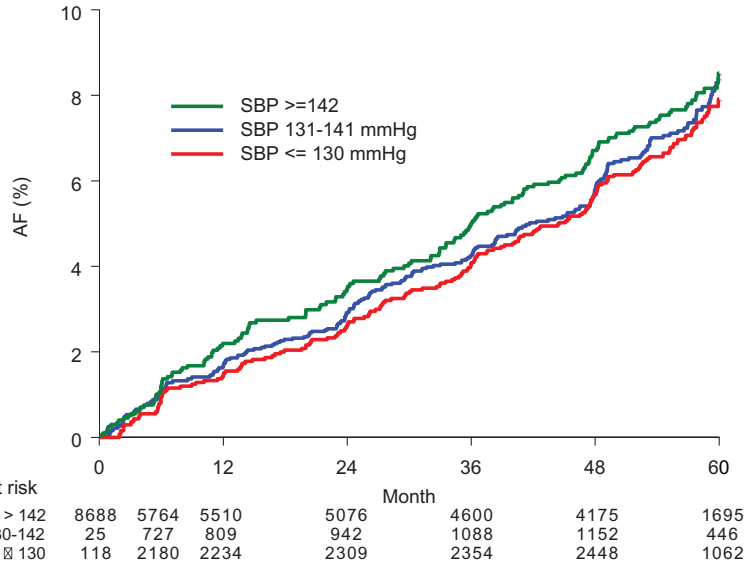

Figure 1. Univariate modified Kaplan–Meier survival curves illustrating the rate of new-onset atrial fibrillation (AF) according to time-varying persistence or development of a systolic blood pressure (SBP) of ≤130 mm Hg and of 131 to 141 mm Hg compared with a systolic blood pressure of ≥142 mm Hg during follow-up. Patient group assignment is adjusted at the time of each blood pressure determination based on the systolic blood pressure at each time.[33]

did not take into account time to incident AF. In contrast, in Cardio-Sis,[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 ≤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,[3] and in-treatment ECG LVH and heart rate in this population.[27,28] 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[23] demonstrated that an achieved SBP of ≤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 ≤125 mm Hg. These findings, the lower risk of AF at SBP <130 in the Cardio-Sis study[16] but the increased risk of AF found at SBP <120 in the case–control study,[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[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.[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,[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

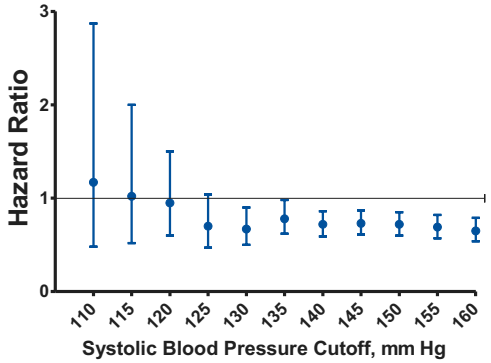

Figure 2. Hazard ratios for new-onset atrial fibrillation according to on-treatment systolic blood pressure by 5 mm Hg cutoff values, adjusted for the effects of treatment with losartan versus atenolol, age, sex, race, diabetes mellitus, history of ischemic heart disease, myocardial infarction or heart failure, previous antihypertensive therapy, baseline serum glucose and creatinine, urine albumin/creatinine ratio, Sokolow–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, high-density lipoprotein cholesterol (HDL), and non-HDL cholesterol entered as time-varying covariates.

correlate with risk of AF recurrence after ablation therapy.[39] 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.[40] 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,[27] the possibility that cases of paroxysmal AF were missed cannot be excluded.

Perspectives

Given the increasing prevalence of AF[2] and the particularly strong association of AF with hypertension,[9,11] 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.[3,5,7,8,35]

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, Serodeus, 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 Cereno Scientific, and served as a consultant or on scientific advisory boards for MSD, Novartis, and Vicore Pharma. Dr Devereux has served on an advisory board for GE Medical Systems and received honoraria from Edwards Life Sciences and Merck & Co.

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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.

Summary

Further study is necessary to determine whether giving patients with high blood pressure more medications to lower their systolic blood pressure to a lower treatment goal can reduce atrial fibrillation without increasing the risk of other cardiovascular problems or side effects.