Blood Pressure Control and Cardiovascular Outcomes in Patients With Atrial Fibrillation (From the ORBIT-AF Registry)

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Systolic blood pressure (SBP) and its association with clinical outcomes in atrial fibrillation (AF) patients in community practice are poorly characterized. In patients with AF, we sought to (1) examine the prevalence of baseline uncontrolled hypertension and the overall change in SBP control, (2) identify predictors of uncontrolled SBP over 2 years of follow-up, and (3) determine the relation between SBP and clinical outcomes. We analyzed 10,132 patients with AF at 176 clinics in the ORBIT-AF registry between 2010 and 2014, classified as: (1) no history of hypertension; (2) controlled hypertension (baseline SBP <140 mm Hg); (3) and uncontrolled hypertension (baseline SBP >140 mm Hg). Predictors of SBP >140 mm Hg at baseline or in follow-up were identified with pooled logistic regression. Random effects Cox regression models were used to compare cardiovascular outcomes and major bleeding as a function of continuous, time-dependent SBP. Overall 8,383 (83%) of patients with AF had hypertension. Of these, 24.2% (n = 2032) had uncontrolled baseline SBP, with little change over 2 years. Predictors of elevated follow-up SBP included uncontrolled baseline SBP, females, previous percutaneous coronary intervention, and diabetes. For every 5 mm Hg increase in follow-up SBP, the adjusted risk of stroke or systemic embolism or transient ischemic attack (adjusted hazard ratio [aHR] 1.05, 95% confidence interval [CI] 1.01 to 1.08, p = 0.01), myocardial infarction (aHR 1.05, 95% CI 1.00 to 1.11, p = 0.04), and major bleeding (aHR 1.03, 95% CI 1.00 to 1.06, p = 0.04) increased modestly. In conclusion, in patients with AF, higher SBP was associated with increasing adverse events; therefore, more rigorous blood pressure control should be emphasized. **(Am J Cardiol 2019;123:1628−1636)**

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a significantly increased risk of death, stroke and systemic embolism, heart failure, and acute coronary syndromes.[1] Importantly, hypertension is a well-recognized risk factor for the development of AF[2] and is thought to account for 14% of all AF.[3] More recently, even prehypertension has been recognized as a risk factor for the development of AF[2]. Previous studies in AF have demonstrated that poorly controlled systolic blood pressure (SBP) is a significant predictor of stroke or systemic embolism,[4−7] and all-cause mortality.[8] However, few studies have evaluated SBP control and patient outcomes in those with AF.[7,9] In this analysis, we describe patterns of SBP control and antihypertensive use, identify predictors of failure to achieve SBP control, and describe hypertension-related cardiovascular outcomes.

Methods

The ORBIT-AF study is a registry of US outpatients with AF, managed by primary care physicians, cardiologists, and/or electrophysiologists. Sites enrolled consecutive patients, 18 years or older, with electrocardiographically documented AF. Patients were followed up every 6 months for at least 2 years and could not be included if AF was due to a reversible cause (e.g., in the setting of cardiac surgery or hyperthyroidism) or if life expectancy was <6 months.

Data elements included patient demographics, medical history, components of AF history (including previous treatment and symptoms), medical therapies, vital signs,

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See page 1634 for disclosure information.

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laboratory and imaging measures, and incident procedures and adverse events. Detailed medication data were collected, including oral anticoagulation use, monitoring, and international normalized ratio data. All patients provided written, informed consent, and the ORBIT-AF registry was approved by the Duke University Institutional Review Board. Each site also obtained institutional review board approval pursuant to local regulation. The present analysis includes 2-year data from ORBIT-AF, and all patients with at least 1 follow-up visit were included.

Patients with baseline data including SBP in ORBIT-AF from June 29th 2010 through August 9th 2011 were included in the analysis. BP was assessed at individual enrolling sites per clinical routine at 6-month intervals for a minimum of 2 years after enrollment. Study patients were further categorized into the following subgroups: (1) No hypertension included participants with no history of hypertension at baseline, irrespective of baseline BP, (2) controlled hypertension included participants with a history of hypertension and baseline SBP <140 mm Hg, and (3) uncontrolled hypertension included participants with a history of hypertension and baseline SBP ≥140 mm Hg. Follow-up SBP was assessed every 6 months until study exit. Sequential SBPs were averaged over adjacent visits (6 month, 12 month) (12 month, 18 month) (18 month, 24 month) and SBP was considered uncontrolled if the average of any adjacent follow-up visits was ≥140 mm Hg.

Death, stroke or non-central nervous system (CNS) systemic embolism and transient ischemic attack (TIA) were defined as per each enrolling investigator. Major bleeding was defined as overt bleeding meeting at least one of the following 4 criteria: (1) fall in hemoglobin ≥ 2g/dl, (2) transfusion of 2 or more units of packed red blood cells or whole blood, (3) bleeding in a critical site (intracranial, intraocular, intraspinal, pericardial, intra-articular, retroperitoneal, or intramuscular with compartment syndrome), and (4) death due to bleeding. Bleeding and cardiovascular hospitalizations were defined as hospitalization due to bleeding and cardiovascular etiologies as the primary causes for admission, respectively. All outcomes were assessed at 6-month intervals for a minimum of 2 years after enrollment.

Baseline data are displayed in categories of baseline SBP. Categorical variables are summarized as percentages (counts), and differences were tested with the Pearson chi-square test; continuous variables are summarized as median (25th and 75th percentiles); and differences were tested with the Wilcoxon rank-sum test. Risk relations are presented as adjusted odds ratios with 95% confidence intervals derived from the adjusted logistic regression models with generalized estimating equations.

To assess risk factors associated with uncontrolled SBP at any follow-up, we created logistic regression models with generalized estimating equations. For this model, SBP was treated as a time-dependent covariate with sequential SBPs being averaged over adjacent visits[10] (6 month, 12 month) (12 month, 18 month) (18 month, 24 month). SBP was considered uncontrolled if the average of any adjacent follow-up visits was ≥140 mm Hg. The logistic regression outcome variable was a binary variable indicating controlled BP at any follow-up versus uncontrolled BP at any follow-up. Covariates in the regression model were selected from candidate baseline characteristics listed in appendix A using backward selection, with an alpha for exclusion of 0.05 in the first imputed dataset. Missing data on the covariates used in the modeling was handled with multiple imputations. All variables had <4% of missingness except for category and/or severity of left atrial diameter (14%), category and/or severity of left ventricular ejaction fraction (10%), pulse (10%), and hyperlipidemia (7%). Risk estimates were attained by combining results from the 5 imputed data sets. All continuous covariates were tested for linearity, and nonlinear relations were accounted for using linear splines.

To assess 2-year cardiovascular outcomes by time-dependent continuous SBP after adjustment, we created random effects cox regression (frailty regression) models to account for site heterogeneity. In this time dependent analysis, the follow-up time for each patient was divided into different time windows. For each time window, a separate Cox frailty regression was carried out using the specific value of systolic BP at the beginning of that specific time window, then a weighted average of all the time window-specific hazard ratios was calculated.[11] Outcomes examined included cardiovascular events (death, stroke, TIA, systemic embolism, myocardial infarction (MI), revascularization, or cardiovascular hospitalization), cardiovascular composite of death and/or stroke and/or TIA and/or MI, and bleeding events (major bleeding or bleeding hospitalization). The final regression model for each outcome was adjusted for selected risk factors from a previously developed and validated model. Additionally, statin use and antiplatelet use, defined as use of aspirin or clopidogrel or prasugrel or ticagrelor or Aggrenox, were forced into each model as covariates. All continuous variables were tested for linearity, and nonlinear relations were accounted for using linear splines. Where the relation between BP and outcome was nonlinear, knots ("cutpoints") for spline analyses were determined by visual inspection of plots of BP versus outcome. This was done separately for each outcome. The final covariates for each endpoint are listed in Appendix B. As a sensitivity analysis, we also repeated the modeling after forcing anticoagulant use into each model as a covariate.

All analyses of the aggregate, deidentified data were performed by the Duke Clinical Research Institute using SAS software (version 9.3; SAS Institute, Cary, North Carolina).

Results

A total of 10,132 outpatients with AF from 176 practices enrolled in the ORBIT-AF registry between June 29, 2010 and August 9, 2011. Excluding 34 patients missing SBP at baseline yielded a study population of 10,098. Of these, 1,715 (17.0%) had no history of hypertension at baseline. Among 8,383 patients with AF and a history of hypertension, 2,032 (24.2%) had uncontrolled hypertension at baseline. Of these, 1,640 (19.6%) had an SBP between 140 mm Hg and 160 mm Hg and 392 (4.7%) had an SBP ≥160 mm Hg. Compared with those with controlled SBP

(SBP <140 mm Hg) at baseline, those with uncontrolled SBP at baseline were older, more frequently female, had a lower incidence of sleep apnea, severe renal disease, coronary artery disease, and congestive heart failure, but a higher incidence of diabetes, peripheral arterial disease, and previous stroke or TIA (Table 1). Additionally, patients with uncontrolled SBP at baseline were more likely to be Black or Hispanic, and were less likely to have at least college level education.

Of note, in those with no history of hypertension, 213 (12.6%) had an elevated SBP (≥140 mm Hg) at baseline. In those with a history of hypertension, 2,392 (28.5%) had an SBP <120 mm Hg at baseline. Compared with those with 120 mm Hg ≤ SBP <140 mm Hg at baseline, these patients were similar in age, more likely to be male, more likely to have: heart failure, history of coronary artery disease, previous MI, and lower ejection fraction (eTable 1). In those with a history of hypertension and without heart failure at baseline, 26.0% of patients had an SBP <120 mm Hg at baseline.

Over 2 years of follow-up, there was only modest improvement in SBP control rates in the entire registry population. (Figure 1). Among 2,032 patients with a history of hypertension and uncontrolled SBP at baseline, 1,228 became controlled. Yet, 987 patients with hypertension and controlled SBP at baseline and another 184 patients without a history of hypertension at baseline had uncontrolled SBP at 2-year study exit. Thus, overall BP control of the entire population did not change substantially over time from 79.8% at baseline to 80.4% at 2-year study exit.

Over the 2 years of follow-up, 698 of 7,766 (9.0%) patients categorized into "No Hypertension at baseline" or "Hypertension & Controlled SBP at baseline" had at least one elevated clinic BP (SBP ≥140 mm Hg). The strongest independent predictors associated with one or more elevated BPs in follow-up included uncontrolled SBP at baseline, female gender, history of percutaneous coronary intervention (odds ratio 1.20, 95% confidence interval 1.06 to 1.36), and diabetes (eTable 2). Additionally, in patients with increasing baseline stroke risk as measured by $CHADS_2$-VASc score, there is an increasing risk of uncontrolled SBP at any follow-up ($p = 0.02$ for trend; Figure 2).

In those patients with hypertension who had elevated clinic SBP in follow-up, diuretic use at any point was 66.0%, calcium channel blocker use at any point was 51.6%, angiotensin-converting-enzyme-inhibitor or angiotensin receptor blocker use at any point was 70.6%, beta-β use at any point was 70.6%, and aldosterone antagonist (AA) use at any point was 5.7%. A similar minority of hypertensive AF patients were on ≥ 3 antihypertensives in those with uncontrolled versus controlled SBP over follow-up (40.8% vs 38.9%, $p = 0.32$). The distribution of diuretic, calcium channel blocker, and angiotensin-converting-enzyme-inhibitor/angiotensin receptor blocker combinations for those on 1-2 antihypertensive and those on ≥3 antihypertensive was not substantially clinically different (eFigure 1A and 1B).

For every 5 mm Hg increase in time-dependent SBP, the adjusted risk of 2-year stroke or non-CNS embolism or TIA, and MI increased linearly (Figure 3). The relation between time dependent SBP and major bleeding was nonlinear. Above 116 mm Hg, every 5 mm Hg increase in SBP was associated with an increased adjusted risk of major bleeding. For SBP ≤116 mm Hg, every 5 mm Hg increase in SBP was associated with decreased adjusted risk of major bleeding (Figure 3).

The relation between time dependent SBP and all-cause death was also nonlinear. At or below 120 mm Hg, every 5 mm Hg increase in SBP was associated with a decreased adjusted risk of death. Above 120 mm Hg, every 5 mm Hg increase in SBP was not significantly associated with adjusted risk of all-cause death.

As a sensitivity analysis, we added anticoagulant use to the covariates in the cardiovascular outcomes model and this showed consistent results (eTable 3).

Discussion

This analysis of SBP control in patients in the ORBIT-AF Registry identifies 5 major findings. First, hypertension is quite common in ambulatory AF patients with >80% having a history of high BP. Second, of those with a history of hypertension, approximately a quarter did not have their SBP controlled at baseline per JNC 7 recommendations and 71.6% did not have their BP below the successful intervention arm of the Systolic Blood Pressure Intervention Trial.[12,13] Third, on a population level, BP control improved only modestly over 2-year period of follow-up (with up to 19.6% remaining uncontrolled 2 years later). Fourth, patients not achieving SBP control were often on suboptimal combinations of guideline recommended antihypertensive therapy. Fifth, increasing time dependent SBP was associated with an increased adjusted hazard of stroke and/or non-CNS systemic embolism and/or TIA, MI, major bleeding, bleeding hospitalization, and cardiovascular hospitalization.

The Systolic Blood Pressure Intervention Trial reported a reduction in cardiovascular outcomes in high risk patients with existing cardiovascular or renal disease randomized to a target SBP of <120 mm Hg.[13] In the present study, although a significant percentage of patients with controlled hypertension had an SBP <120 mm Hg at baseline, these patients were more likely to have heart failure with depressed ejection fraction and were more likely to be treated with aldosterone antagonists, perhaps as a result of heart failure rather than hypertension. Our data suggests that in outpatients with AF and hypertension and without heart failure, only about one quarter currently achieve an SBP <120 mm Hg. Given a relative under-use of guideline indicated antihypertensive medications in our study population,[14–17] more effort is mandatory to achieve better BP control.

Given that higher SBP has been associated with increased rates of stroke[4–7] as well as bleeding[18,19] in patients with AF, efforts to improve BP control should likely focus on those with the highest baseline risk of stroke and bleeding. In this context, our finding that baseline uncontrolled SBP, female sex, history of percutaneous coronary intervention, and diabetes were significantly

Table 1
Baseline demographics by hypertension status

Variable	Overall (n = 10,098)	Baseline values			p Value
		No hypertension (n = 1,715) (17.0%)	Hypertension & controlled systolic Blood pressure (n = 6,351) (62.9%)	Hypertension & uncontrolled systolic blood pressure (n = 2,032) (16.2%)	
Age (year)	73.5 (11.0)	69.8 (13.4)	74.0 (10.3)	74.7 (10.2)	<0.0001
Male	57.7%	64.1%	58.6%	49.5%	<0.0001
Race					<0.0001
White	89.3%	91.7%	89.2%	87.2%	
Black	5.0%	3.0%	5.0%	6.7%	
Hispanic	4.2%	3.4%	4.3%	4.5%	
College education	22.6%	27.8%	21.8%	20.5%	<0.001
Blood pressure (systolic)	126 (16.8)	121 (15.2)	121 (11.3)	150 (10.9)	<0.0001
Blood pressure (diastolic)	73.1 (10.6)	72.0 (9.8)	71.2 (9.7)	79.8 (11.2)	<0.0001
Body mass index (kg/m^2)	30.5 (7.7)	28.7 (7.1)	30.8 (7.8)	31.0 (7.7)	<0.0001
Smoking (Current or former)	48.4%	45.4%	50.0%	45.9%	<0.0001
Obstructive sleep apnea	18.2%	13.4%	19.6%	17.9%	<0.0001
Chronic obstructive pulmonary disease	16.4%	11.3%	17.8%	16.1%	<0.0001
Diabetes mellitus	29.4%	14.3%	31.7%	35.0%	<0.0001
Hyperlipidemia	71.9%	53.9%	76.0%	74.3%	<0.0001
History of coronary artery disease	36.0%	26.3%	39.2%	34.2%	<0.0001
Peripheral vascular disease	13.4%	8.0%	14.1%	15.5%	<0.0001
Congestive heart failure	32.3%	24.0%	35.7%	28.8%	<0.0001
Stroke or transient ischemic attack	15.1%	11.2%	15.3%	17.8%	<0.0001
Estimated glomerular filtration Rate <30 ml/min/1.73 m^2 or dialysis	34.5%	23.0%	37.2%	35.7%	<0.0001
Type of Atrial Fibrillation					
New Onset	4.3%	5.6%	4.2%	5.7%	<0.0001
Paroxysmal	50.6%	56.0%	48.4%	52.7%	
Persistent	16.8%	16.2%	17.4%	15.7%	
Permanent	27.9%	22.2%	30.0%	25.9%	
Left ventricular ejection fraction					<0.0001
>50%	70.2%	70.2%	68.9%	74.4%	
30%−50%	15.1%	12.6%	16.6%	12.6%	
<30%	4.2%	5.3%	4.5%	2.3%	
Posterior Wall Thickness >1.0 cm	39.9%	32.8%	41.3%	41.5%	<0.0001
Estimated glomerular filtration mg/min/1.73 m^2	68.5 (23.4)	74.4 (23.5)	67.0 (23.2)	68.2 (23.1)	<0.0001
Aldosterone antagonist	5.5%	3.7%	6.5%	4.0%	<0.0001
Angiotensin receptor blocker	17.8%	4.6%	19.7%	22.6%	<0.0001
Beta blockers	64.1%	54.8%	66.6%	63.9%	<0.0001
Statin	55.1%	41.5%	58.1%	57.1%	<0.0001
Diuretic	49.1%	28.4%	54.2%	50.4%	<0.0001
Renin-angiotensin system inhibitors	30.2%	13.8%	32.7%	36.3%	<0.0001
Calcium channel blockers	16.7%	12.0%	17.5%	18.0%	<0.0001
Antithrombotic therapy	44.2%	42.9%	44.5%	44.2%	0.6802
Oral anticoagulation	76.1%	67.9%	78.4%	75.8%	<0.0001
Currently taking warfarin	71.2%	62.7%	73.4%	71.4%	<0.0001
Median time in therapeutic range for warfarin alone (Interquartile range)	67% (45%−86%)	69% (46%−89%)	67% (45%−86%)	66% (42%−86%)	0.24
Median time in therapeutic range for warfarin + antiplatelet (Interquartile range)	66% (45%−84%)	65% (45% - 86%)	66% (47%−84%)	66% (41%−84%)	0.83
Dabigatran or rivaroxaban only	335 (3.3%)	69 (4.0%)	202 (3.2%)	64 (3.2%)	<0.0001
Dabigatran or Rivaroxaban and antiplatelet	159 (1.6%)	20 (1.2%)	114 (1.8%)	25 (1.2%)	<0.0001
Stroke and bleeding risk					
CHADS VASC Risk Score	3.9 (1.8)	2.4 (1.6)	4.2 (1.6)	4.3 (1.6)	<0.0001
CHADS VASC Risk Score					<0.0001
0	2.2%	13.1%	0%	0%	
1	7.0%	18.8%	4.8%	3.8%	
2−4	54.2%	58.3%	53.7%	52.3%	
5−6	29.1%	8.9%	32.8%	41.1%	

(*continued*)

Table 1 (***Continued***)

Variable	Overall (n = 10,098)	Baseline values			p Value
		No hypertension (n = 1,715) (17.0%)	Hypertension & controlled systolic Blood pressure (n = 6,351) (62.9%)	Hypertension & uncontrolled systolic blood pressure (n = 2,032) (16.2%)	
7−9	7.5%	0.9%	8.7%	2.8%	
ATRIA Score					<0.0001
0−3	73.7%	87.7%	70.5%	72.1%	
4	8.9%	0.5%	10.9%	9.8%	
>=5	17.3%	11.8%	18.6%	18.2%	

Unless otherwise specified, values are means (standard deviations).

associated with at least one uncontrolled SBP over 2 years of follow-up suggests that patients with greater risk factors for stroke in AF are also more likely to have uncontrolled SBP.

Previous post-hoc analyses verifying the relation between SBP and stroke have generally been limited by use of cutoff-values[4−6,20] or have been based on a single BP.[21] A single post-hoc analysis based on average BPs in anticoagulated patients from the Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials suggested a nonlinear increase in stroke risk with an inflection point at an SBP >140 mm Hg.[22] Conversely, a post-hoc analysis from the RELY trial did not reveal a relation between a diagnosis of hypertension and stroke risk[23] whereas an analysis from the ARISTOTLE trial found a relation between categories of follow-up hypertension and

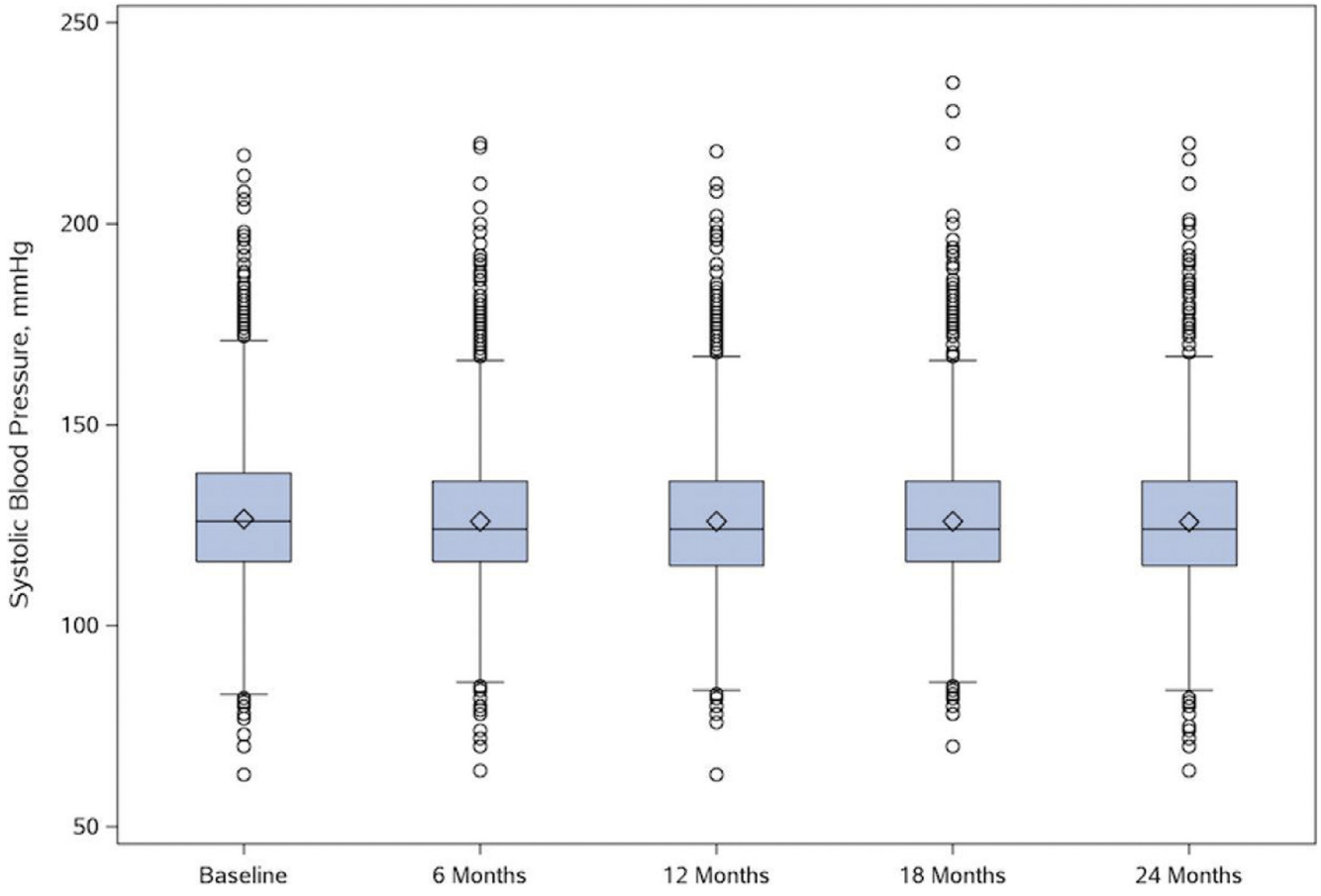

Figure 1. Longitudinal trends in systolic blood pressure control in the entire study cohort.

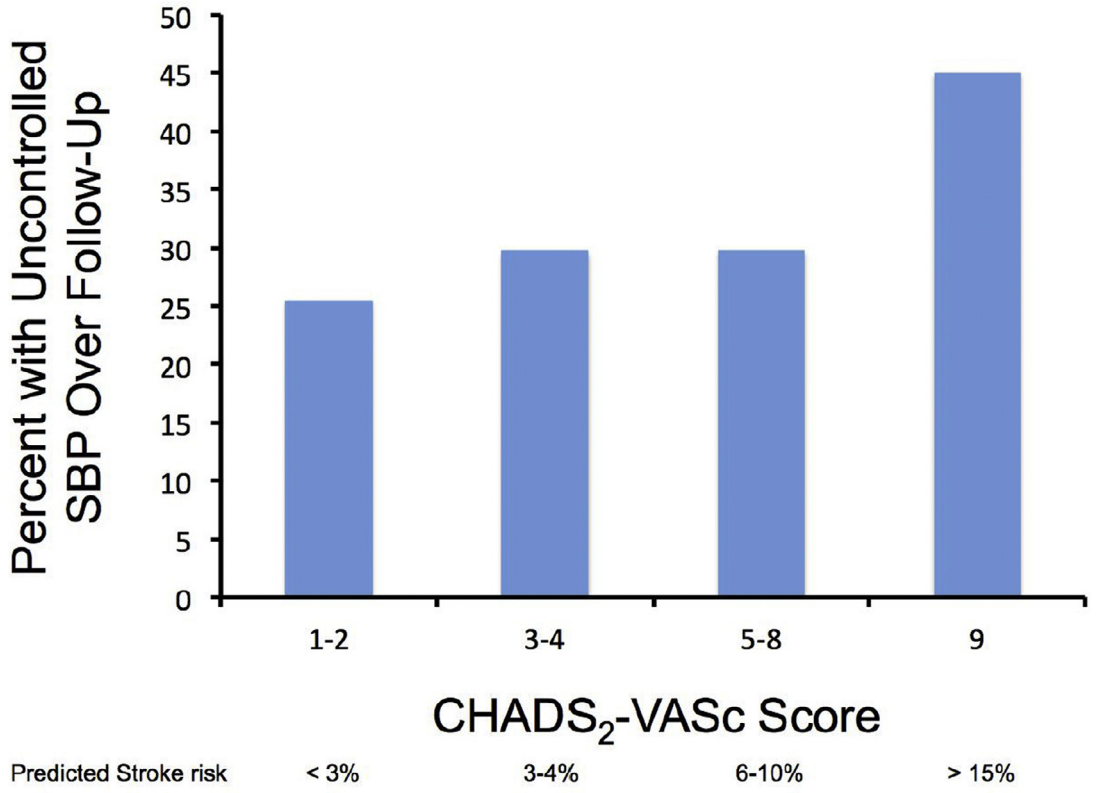

Figure 2. Failure to achieve SBP control on at least one follow-up and baseline $CHADS_2$-VASc Score. SBP = systolic blood pressure.

stroke.[12] Our finding in a "real world" cohort of patients with AF that the heart rate for stroke or systemic embolism is linearly related to continuous, time-dependent SBP suggests that SBP remains an important predictor of stroke in clinical practice, regardless of the cutoff value used to define SBP "control."

Previous clinical practice data indicate that patients with hypertension usually require close monitoring of anticoagulation and optimal BP control to diminish the risk of bleeding complications.[23] These recommendations have been bolstered by contemporary bleeding risk scores such as $HEMORR_2HAGES$,[24] HAS-BLED,[14] and ATRIA[25]. However, data from previous clinical trial analyses have been split on confirming the relation between hypertension and bleeding,[10,21,22] with the single confirmatory analysis relying on a single BP measurement.[21] Ours is the first study to assess multiple BP measurements as a time dependent variable and demonstrate a relation between continuous SBP and major bleeding as well as bleeding hospitalizations. Our findings serve to confirm and extend the importance of SBP in AF related major bleeding beyond the previously identified cut point of 160 mm Hg.[26,27]

There are multiple limitations to the present analysis. First, this analysis is based on an observational cohort of patients in clinical practice and is thus subject to sampling bias, reporting bias, and residual and/or unmeasured confounding despite our extensive covariate adjustment. Second, although the ORBIT-AF registry was designed to be inclusive, the population is older, overwhelmingly white (~90%), and the primary AF caregiver was most often a cardiologist (80.5%), thus, the results may not be generalizable to the entire population of AF patients. Third, our analysis relies on nonstandardized, clinic-obtained BPs that may be prone to measurement error and may not accurately reflect the patient's home or out of office SBP. Though we have attempted to address this deficiency by treating SBP as a time dependent variable, future analyses of SBP control may need to take into account ambulatory BP data. Furthermore, because we assessed SBP as a time dependent variable, we could not assess the impact of time in therapeutic range, itself a time dependent variable, on the relation between SBP and outcomes. Fourth, the 2017 American College of Cardiology/American Heart Association BP guideline lowered the BP threshold for hypertension from 140/90 mm Hg or more to 130/80 mm Hg or more.[28] But, given the study period from 2010 to 2014, JNC 7 was used as the threshold for hypertension in this present study. Lastly, the ORBIT-AF registry does not contain complete data on patients' reasons for being or not being on certain antihypertensive agents. Thus a detailed analysis of antihypertensive medication choices is not possible.

In this large, observational registry of outpatients with AF, 1 in 4 patients with AF have uncontrolled BP, a percentage that did not improve substantially over 2 years of follow-up. Patients at the highest risk of stroke were also the most likely to have one or more high SBP readings in clinic over follow-up. In patients with persistent uncontrolled BP, use of guideline recommended antihypertensive therapy was suboptimal. Increasing SBP was associated with stroke or systemic embolism or TIA, MI, major

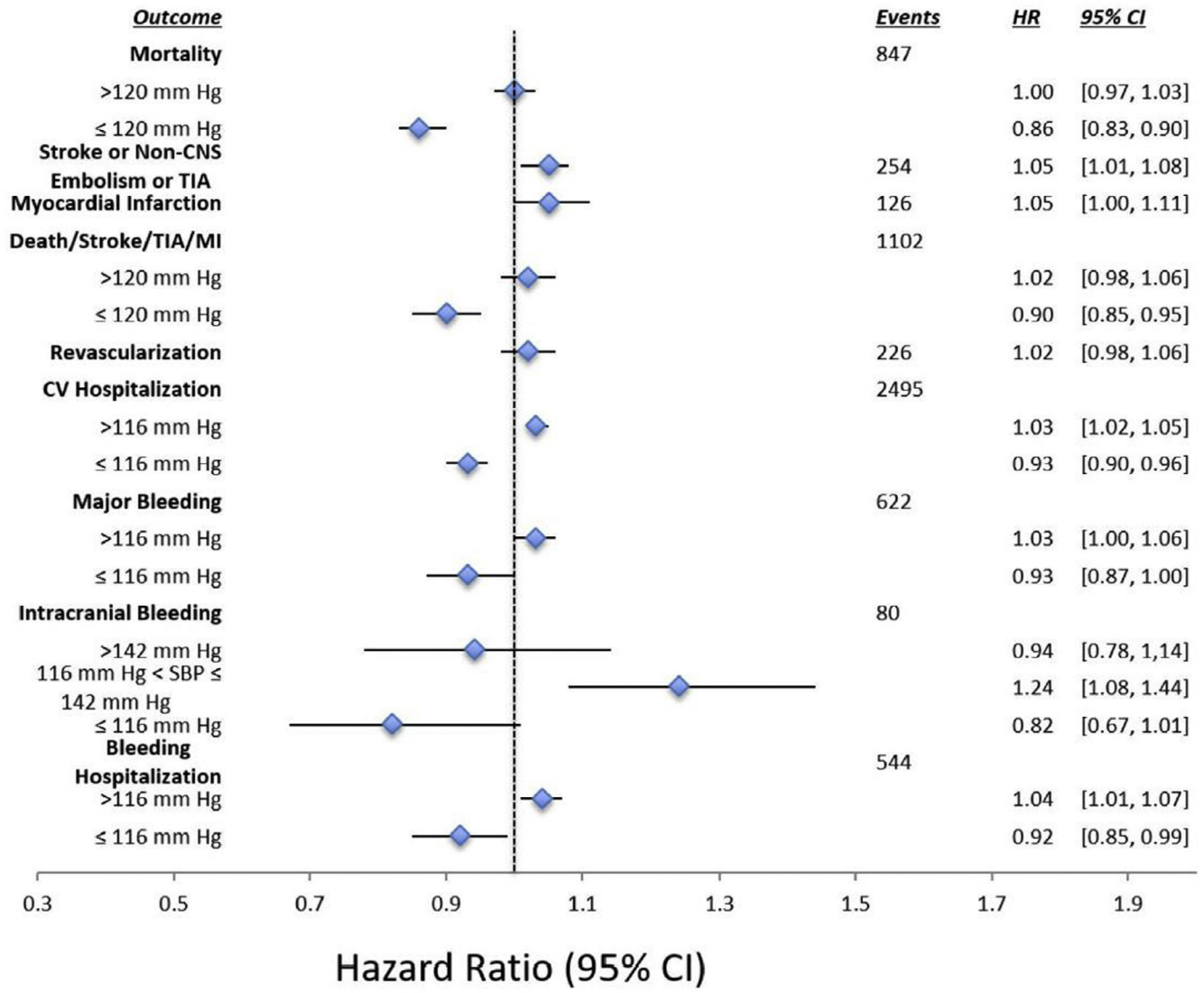

Figure 3. Cardiovascular outcomes by time dependent continuous SBP. SBP = systolic blood pressure; TIA = transient ischemic attack. Cut points were chosen based on inflection points in the SBP − outcome relationship as determined by linear splines.

bleeding, and bleeding hospitalization Together these data suggest that opportunities remain to improve SBP control in outpatients with AF.

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Supplementary materials

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1. Manolis AJ, Rosei EA, Coca A, Cifkova R, Erdine SE, Kjeldsen S, Lip GY, Narkiewicz K, Parati G, Redon J, Schmieder R, Tsioufis C, Mancia G. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension. *J Hypertens* 2012;30:239–252.
2. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014;114:1453–1468.
3. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;82:2N–9N.
4. Stroke Prevention in Atrial Fibrillation Investigators. Risk Factors for thromboembolism during aspirin therapy in patients with atrial fibrillation. J Stroke Cerebrovasc Dis 1995:147−157.
5. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke* 1999;30:1223–1229.
6. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;35:183–187.
7. Wang Z, Whiteside SPH, Sim L, Farah W, Morrow AS, Alsawas M, Barrionuevo P, Tello M, Asi N, Beuschel B, Daraz L, Almasri J, Zaiem F, Larrea-Mantilla L, Ponce OJ, LeBlanc A, Prokop LJ, Murad MH. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049–1056.
8. Badheka AO, Patel NJ, Grover PM, Shah N, Patel N, Singh V, Deshmukh AJ, Mehta K, Chothani A, Savani GT, Arora S, Rathod A, Marzouka GR, Lafferty J, Mehta JL, Mitrani RD. Optimal blood pressure in patients with atrial fibrillation (from the AFFIRM Trial). *Am J Cardiol* 2014;114:727–736.
9. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J* 2012;76:2289–2304.
10. Rao MP, Halvorsen S, Wojdyla D, Thomas L, Alexander JH, Hylek EM, Hanna M, Bahit MC, Lopes RD, De Caterina R, Erol C, Goto S, Lanas F, Lewis BS, Husted S, Gersh BJ, Wallentin L, Granger CB. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Steering Committee and Investigators. Blood pressure control and risk of stroke or systemic embolism in patients with atrial fibrillation: results From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *J Am Heart Assoc* 2015: 4. pii: e002015.
11. Dekker FW, de Mutsert R, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time-dependent effects and time-varying risk factors. *Kidney Int* 2008;74:994–997.
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572.
13. SPRINT Research GroupWright JT Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;373:2103–2116.
14. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CV, Cohen DL, Cadet JC, Jean-Charles RR, Taler S, Kountz D, Townsend R, Chalmers J, Ramirez AJ, Bakris GL, Wang J, Schutte AE, Bisognano JD, Touyz RM, Sica D, Harrap SB. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens* 2014;32:3–15.
15. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;117:e510–e526.
16. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159–2219.
17. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr., Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr., Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–520.
18. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major

bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–1100.
19. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol* 2011;57:173–180.
20. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost* 2011;9:39–48.
21. Nagarakanti R, Wallentin L, Noack H, Brueckmann M, Reilly P, Clemens A, Connolly SJ, Yusuf S, Ezekowitz MD. Comparison of characteristics and outcomes of dabigatran versus warfarin in hypertensive patients with atrial fibrillation (from the RE-LY Trial). *Am J Cardiol* 2015;116:1204–1209.
22. Lip GY, Frison L, Grind M. SPORTIF Invetigators. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;28:752–759.
23. Berwaerts J, Webster J. Analysis of risk factors involved in oral-anticoagulant-related intracranial haemorrhages. *QJM* 2000;93:513–521.
24. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;151:713–719.
25. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;58:395–401.
26. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - who is at risk, and how best to identify such patients. *Thromb Haemost* 2009;102:268–278.
27. Hughes M, Lip GY. Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation in primary and secondary care. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM* 2007;100:599–607.
28. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr., Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13–e115.