Systolic Blood Pressure Visit-to-Visit Variability and Major Adverse Outcomes in Atrial Fibrillation

The AFFIRM Study (Atrial Fibrillation Follow-Up Investigation of Rhythm Management)

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Abstract—Hypertension and atrial fibrillation predict major adverse events independently. Visit-to-visit variability (VVV) in systolic blood pressure (SBP) predicts outcomes beyond SBP itself, but risk associated with SBP-VVV in atrial fibrillation remains uncertain.We evaluated relationships between SBP-VVV, quality of oral anticoagulation control, and outcomes in patients with atrial fibrillation.Data from the AFFIRM trial (atrial fibrillation follow-up investigation of rhythm management) were analyzed. SBP-VVV was defined according to SD of SBP (SBP-SD) during follow-up. SBP-VVV was categorized by quartiles (1st, <10.09; 2nd, 10.09–13.85; 3rd, 13.86–17.33; and 4th, ≥17.34 mm Hg) and as a continuous variable.Among the original cohort, 3843 (94.7%) patients were eligible. Time in therapeutic range and percentage of international normalized ratio in range were progressively lower by quartiles (both $P<0.001$). An inverse linear association existed between SBP-SD and time in therapeutic range/percentage of international normalized ratio in range ($P<0.001$). After a median (interquartile range) follow-up of 3.6 (2.7–4.6) years, stroke and major bleeding rates progressively increased by SBP-VVV quartile (both $P<0.001$). Patients in the 4th quartile had the highest rate of cardiovascular and all-cause death ($P=0.005$ and $P<0.001$). A Cox multivariate analysis confirmed that 3rd and 4th quartiles were associated independently with a higher risk for stroke ($P=0.042$ and $P=0.004$) and major bleeding ($P=0.009$ and $P<0.001$). Patients in 4th quartile had also a higher risk for all-cause death ($P=0.048$). SBP-SD as a continuous variable was associated with increased risk for all outcomes. In conclusion, SBP-VVV is inversely associated with quality of anticoagulation control and independently predicts major adverse outcomes. Management of blood pressure variability may improve outcomes in atrial fibrillation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000556.

(*Hypertension*. 2017;70:949-958. DOI: 10.1161/HYPERTENSIONAHA.117.10106.)

Key Words: anticoagulant drugs ■ atrial fibrillation ■ hypertension ■ major bleeding ■ outcomes research ■ stroke

Systemic hypertension and atrial fibrillation (AF) are related.[1] Beyond sharing many similar epidemiological and pathophysiological features, hypertension is a major risk factor for developing AF,[1] whereas the history of hypertension in the context of AF is associated with an increased risk for thromboembolic events.[2] Furthermore, the presence of uncontrolled blood pressure in patients with AF is associated with an increased risk for hemorrhagic stroke,[3] major bleeding,[4,5] and intracranial hemorrhage.[5]

In the general population, greater blood pressure variability, defined as systolic blood pressure (SBP)–visit-to-visit variability (VVV), is related to a higher risk for cardiovascular and cerebrovascular events and with cardiovascular and all-cause death.[6,7] No specific data have been reported about the association between SBP-VVV and AF in determining major adverse clinical events (ie, stroke, major bleeding, and cardiovascular and all-cause death).

In addition, one of the strongest predictors of all major adverse events in anticoagulated patients with AF is quality of oral anticoagulation control, expressed as individual time in therapeutic range (TTR) or percentage of international normalized ratio (INR) in range (PINRR).[8–10] No reports have explored any relationship between SBP-VVV and quality of anticoagulation control.

The aims for this study were (1) to describe the relationship between SBP-VVV and quality of anticoagulation control, expressed as TTR and PINRR and (2) to analyze any association between SBP-VVV and major adverse clinical outcomes in patients with AF. These analyses were investigated as a post hoc ancillary study to the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management), which compared a rate-control versus a rhythm-control strategy for the clinical management of patients with AF.

Received July 31, 2017; first decision August 17, 2017; revision accepted August 30, 2017.

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Methods

The AFFIRM trial was a prospective randomized trial, conducted by the US National Heart, Lung, and Blood Institute. The study protocol and the principal trial results have been described in detail elsewhere.[11,12] The mean duration of follow-up was 3.5 years. Institutional review board for every institution approved study protocol. All patients entered the study after written informed consent. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

For the current analyses, all patients with available data on SBP at baseline and with at least 4 other measurements during follow-up were selected. Blood pressure measurement was performed at baseline visit and at every follow-up visit, according to the protocol-defined schedule (at 2, 4, 8, and 12 months and then every 4 months after enrollment[11]). SBP measurements were performed according to normal standard procedures, and no specific procedures were recommended from the study protocol. SBP was defined as controlled at baseline when ≤140 mm Hg. SBP-VVV was defined according to the SD of mean SBP during follow-up for every patient. According to the SBP-SD, patients were categorized in quartiles (1st, <10.09; 2nd, 10.09–13.85; 3rd, 13.86–17.33; and 4th, ≥17.34 mm Hg).

Thromboembolic risk was defined according to the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) risk score.[13] Low-risk patients were defined as those men with a CHA_2DS_2-VASc score =0 or women with a CHA_2DS_2-VASc =1; moderate risk was defined as male patients with a CHA_2DS_2-VASc score =1; high risk was defined as patients with a CHA_2DS_2-VASc score ≥2.[14]

Quality of Anticoagulation Control

Quality of anticoagulation control was assessed according TTR and PINRR calculated from INR values retrieved from the follow-up forms filled by any physician during the planned follow-up visits at 2, 4, 8, and 12 months and then every 4 months, after enrollment.[11]

TTR was calculated according to Rosendaal interpolation method.[15] TTR was calculated for all the patients who qualified for the following conditions: (1) at least 1 year of INR observations; (2) at least 4 available INR measurements; (3) interval between 2 observations ≤1 year; (4) in case of 2 INR observation periods of at least 1 year, separated each other >1 year, the longest one was considered for calculation; and (5) in the case that 2 INR observation periods occurred for the same time length, the closest one to the end of study was considered for calculation. PINRR was calculated, for all patients qualifying for TTR calculation, as the overall percentage of INR measurements found during the entire follow-up within the TTR between 2 and 3.

Outcomes

Based on the study design, all investigators reported major adverse event occurrence at site level, through the follow-up form, providing all available clinical details.[11] Outcomes of interest were (1) stroke, (2) major bleeding, (3) cardiovascular death, (4) all-cause death, and (5) a composite outcome of stroke/major bleeding/cardiovascular death. A central adjudication committee originally evaluated all the recorded events and classified all the death events.

Statistical Analysis

All continuous variables were expressed as mean and SD or median and interquartile range (IQR) and compared accordingly with 1-way ANOVA or Kruskal–Wallis 1-way ANOVA test. Categorical variables, expressed as counts and percentages, were compared with the χ^2 test. A linear regression model was performed to establish the relationship of continuous SBP-SD with TTR and PINRR. A regression model was performed and adjusted for congestive heart failure, hypertension, age, sex, diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, peripheral arterial disease. A logistic regression model was also drafted to establish the relationship between SBP-SD as a continuous variable and SBP-SD quartiles with TTR and PINRR at progressively lower cut-offs (>70%, ≤65%, and ≤60%). The logistic model was adjusted for the same variables as above.

Kaplan–Meier curves for all major adverse clinical outcomes considered, according to SBP-SD quartiles, were drafted. Survival distributions were compared using the log-rank test. A Cox regression analysis was performed to establish whether SBP quartiles and SBP-SD as a continuous variable were independently associated with increased risk for all major adverse clinical outcomes considered. For every outcome, for SBP quartiles and continuous SBP-SD, 2 distinct Cox models were performed. In the first model, the analysis was adjusted for use of warfarin, TTR, hepatic/renal disease, pulmonary disease, randomized treatment, and CHA_2DS_2-VASc. In the second model, the analysis was adjusted for use of warfarin, TTR, hepatic/renal disease, pulmonary disease, randomized treatment, congestive heart failure, hypertension, age, sex, diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, and peripheral arterial disease. Several sensitivity analyses evaluated association between SBP quartiles and the composite outcome for (1) patients with no history of hypertension at baseline; (2) patients with SBP controlled, defined as <140 mm Hg, at baseline; (3) elderly patients (ie, ≥75 years); and (4) patients with high thromboembolic risk. A 2-sided P value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 24.0 (IBM, NY).

Results

Among 4060 patients enrolled in the original cohort, 3843 (94.7%) were available for the current analysis. Median (IQR) age was 71 (65–76) years, with 1496 (38.9%) women. Overall, median (IQR) CHA_2DS_2-VASc was 3 (2–4). At baseline median (IQR) SBP was 132 (120–150) mm Hg, whereas median (IQR) diastolic blood pressure was 78 (70–84) mm Hg. SBP was controlled in 2532 (65.9%) patients. During the entire follow-up period, median (IQR) SBP was 135.14 (125.86–144.44) mm Hg, whereas median (IQR) SBP-SD was 14.49 (±4.90) mm Hg. TTR and PINRR were available for 3169 (82.5%) patients. Median (IQR) TTR was 67.9% (51.5–81.0), whereas median (IQR) PINRR was 62.5% (50.0–76.9).

Baseline characteristics according to SBP-SD quartiles are reported in Table 1. Across the quartiles, the median age and the proportion of female patients was progressively higher (both P<0.001). Baseline SBP and diastolic blood pressure were progressively higher with increasing quartiles (P=0.001 and P<0.001, respectively). The main cardiovascular risk factors (hypertension and diabetes mellitus) were progressively more prevalent across the quartiles (P<0.001 and P=0.013, respectively). Patients in 3rd and 4th quartiles had more coronary artery disease (P=0.010), whereas patients in the 4th quartile were more likely diagnosed with peripheral arterial disease (8.9%) and congestive heart failure (25.3%; P=0.014 and P<0.001, respectively). CHA_2DS_2-VASc score was progressively higher from the 1st to 4th quartile (P<0.001), as was the proportion at higher thromboembolic risk (P<0.001).

Despite no difference in use of aspirin and warfarin across quartiles, patients in the 4th quartile reported a higher prevalence of polypharmacy (45.8%; P<0.001). Both median (IQR) TTR and PINRR were progressively lower across quartiles, being lowest in the 4th quartile (P<0.001 for both).

SBP-VVV and Quality of Anticoagulation Control

The final adjusted linear regression model found that SBP-SD was inversely associated with TTR (standardized beta, −0.073; t, −4.142; P<0.001). Indeed, SBP-SD was progressively lower according to increasing TTR (P<0.001; Figure 1,

Table 1. Baseline Characteristics According to Systolic Blood Pressure SD Quartiles

Characteristics	1st Quartile (<10.09*) N=963	2nd Quartile (10.09–13.85*) N=959	3rd Quartile (13.86–17.33*) N=962	4th Quartile (≥17.34*) N=959	*P* Value
Age, y, median (IQR)	70 (64–75)	71 (65–76)	71 (65–76)	71 (66–77)	<0.001
BMI, kg/m^2, median (IQR) 2387	28.2 (24.8–31.9)	27.9 (24.7–31.9)	28.7 (25.4–32.1)	27.7 (24.7–31.5)	0.136
Baseline SBP, mm Hg, median (IQR)	130 (120–140)	132 (120–148)	138 (121–150)	140 (122–156)	0.001
Baseline DBP, mm Hg, median (IQR)	76 (70–80)	78 (70–82)	79 (70–84)	80 (70–86)	<0.001
Female sex, n (%)	329 (34.2)	353 (36.8)	387 (40.2)	427 (44.5)	<0.001
Minority, n (%)	83 (8.6)	92 (9.6)	114 (11.9)	131 (13.7)	0.002
Hypertension, n (%)	578 (60.0)	646 (67.4)	732 (76.1)	776 (80.9)	<0.001
Diabetes mellitus, n (%)	169 (17.5)	177 (18.5)	198 (20.6)	221 (23.0)	0.013
Smoking habit, n (%)	116 (12.0)	102 (10.6)	126 (13.1)	122 (12.7)	0.365
Coronary artery disease, n (%)	345 (35.8)	337 (35.1)	376 (39.1)	400 (41.7)	0.010
Myocardial infarction, n (%)	156 (16.2)	149 (15.5)	172 (17.9)	183 (19.1)	0.155
Peripheral arterial disease, n (%)	52 (5.4)	57 (5.9)	64 (6.7)	85 (8.9)	0.014
Stroke/TIA, n (%)	130 (13.5)	115 (12.0)	130 (13.5)	128 (13.3)	0.713
Congestive heart failure, n (%)	214 (22.2)	170 (17.7)	234 (24.3)	243 (25.3)	<0.001
Valvular heart disease, n (%)	124 (12.9)	104 (10.8)	115 (12.0)	126 (13.1)	0.408
Hepatic/renal disease, n (%)	44 (4.6)	40 (4.2)	60 (6.2)	62 (6.5)	0.054
Pulmonary disease, n (%)	143 (14.8)	118 (12.3)	150 (15.6)	139 (14.5)	0.196
First AF episode, n (%)	340 (36.2)	302 (32.7)	312 (33.6)	347 (37.5)	0.107
Randomized treatment, n (%)					<0.001
Rate control	533 (55.3)	514 (53.6)	477 (49.6)	396 (41.3)	
Rhythm control	430 (44.7)	445 (46.4)	485 (50.4)	563 (58.7)	
Use of aspirin, n (%)	262 (27.2)	240 (25.0)	240 (24.9)	269 (28.1)	0.304
Use of warfarin, n (%)	824 (85.6)	811 (84.6)	827 (86.0)	801 (83.5)	0.443
TTR%, median (IQR) 3169	69.3 (54.2–81.3)	70.2 (55.2–82.8)	66.7 (50.9–80.9)	63.6 (46.4–79.0)	<0.001
PINRR%, median (IQR) 3169	64.3 (50.0–77.8)	66.7 (50.0–77.8)	62.5 (50.0–75.0)	60.0 (45.5–73.8)	<0.001
Polypharmacy, n (%)	358 (37.3)	318 (33.2)	409 (42.6)	439 (45.8)	<0.001
CHA_2DS_2-VASc, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	<0.001
CHA_2DS_2-VASc, mean (SD)	2.71 (1.40)	2.80 (1.33)	3.04 (1.32)	3.30 (1.41)	<0.001
Thromboembolic risk, n (%)					<0.001
Low risk	22 (2.3)	8 (0.8)	2 (0.2)	5 (0.5)	
Moderate risk	187 (19.4)	152 (15.8)	118 (12.3)	87 (9.1)	
High risk	754 (78.3)	799 (83.3)	842 (87.5)	867 (90.4)	

AF indicates atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category; DBP, diastolic blood pressure; IQR, interquartile range; PINRR, percentage of international normalized ratio range; SBP, systolic blood pressure; TIA, transient ischemic attack; and TTR, time in therapeutic range.

*Expressed as mm Hg.

top) and with increasing TTR deciles (*P*<0.001; Figure 1, bottom). Similarly, SBP-SD was found to be inversely associated with PINRR (standardized beta, –0.070; t, –3.959; *P*<0.001).

In the final logistic regression model (Tables 2 and 3) compared with patients in the 1st quartile, those in 4th quartile had a significant inverse association with TTR >70% (odds ratio, 0.75; 95% confidence interval [CI], 0.61–0.92), whereas patients in the 3rd and 4th quartiles were significantly associated with TTR ≤65% (*P*=0.014 and *P*<0.001, respectively, for 3rd and 4th quartiles) and TTR ≤60% (both *P*<0.001). Continuous SBP-SD was inversely associated with TTR >70% (odds ratio, 0.98; 95% CI, 0.96–0.99 per mm Hg) and directly associated with TTR ≤65% and TTR ≤60% (both *P*<0.001). Similar results were found for PINRR (Tables 2 and 3).

Follow-Up and Survival Analysis

After a median (IQR) follow-up of 3.6 (2.7–4.6) years, there were 149 (3.9%) strokes, 248 (6.5%) major bleeds, 258

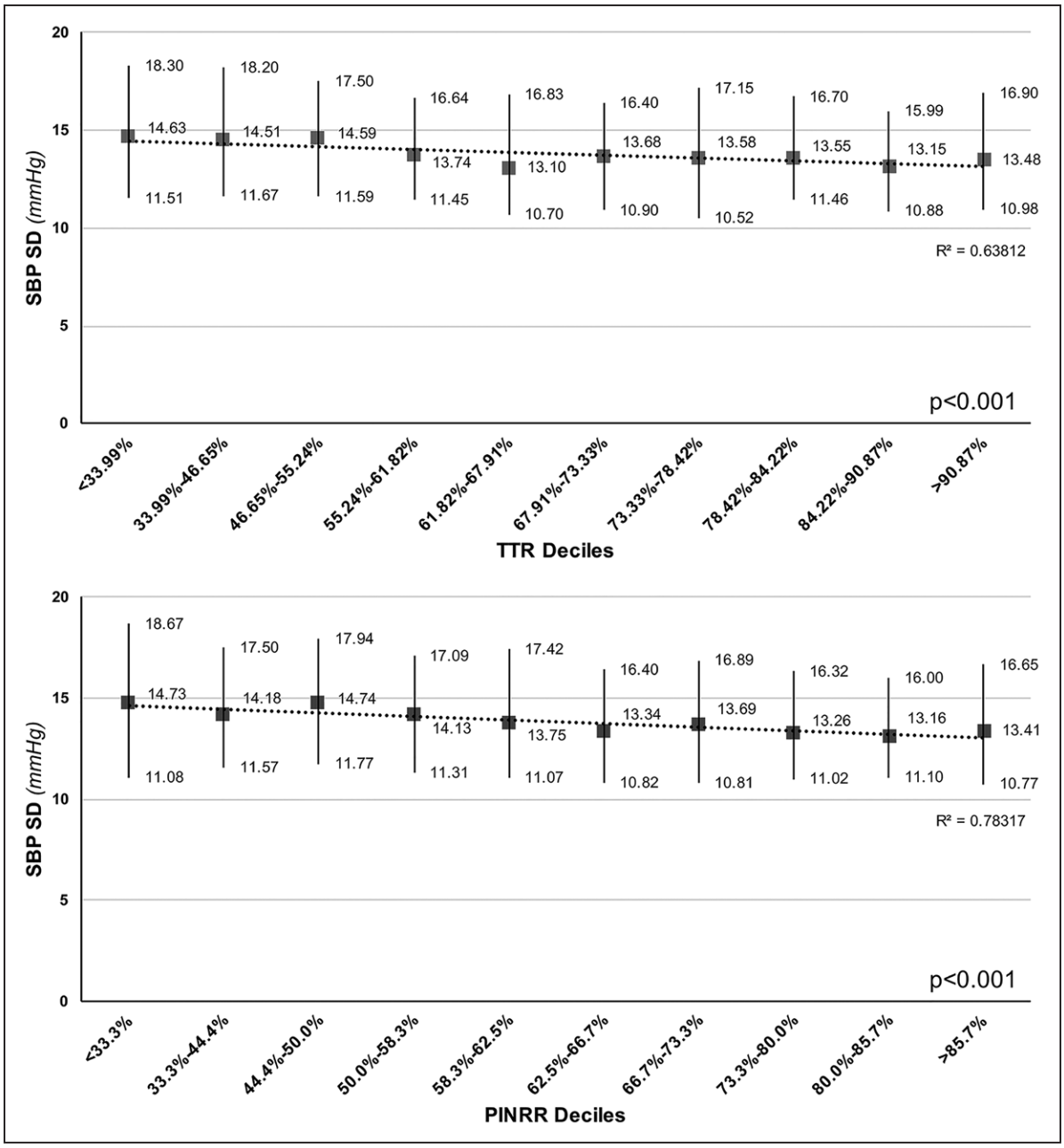

Figure 1. Systolic blood pressure (SBP)-SD according to quality of anticoagulation control indexes. Values are expressed as median (interquartile range). **Top**, Time in therapeutic range (TTR); **bottom**, percentage of international normalized ratio in range (PINRR).

(6.7%) cardiovascular deaths, and 495 (12.9%) all-cause deaths. Accordingly, 560 (14.6%) composite outcome events were recorded.

According to SBP-SD quartiles (Table 4), rates of stroke and major bleeding progressively increased from the 1st to 4th quartile (both $P<0.001$). Also, patients in the 3rd and 4th quartiles had the highest rate for cardiovascular death ($P=0.005$) and all-cause death ($P<0.001$). The composite outcome of stroke/major bleeding/cardiovascular death progressively increased from the 1st (10.8%) to 4th quartile (20.8%; $P<0.001$).

Kaplan–Meier curves (Figure 2) demonstrated that patients in 3rd and 4th quartiles had progressively higher risk for stroke (log-rank, 20.024; $P<0.001$), major bleeding (log-rank, 48.322; $P<0.001$), and cardiovascular death (log-rank, 11.985; $P=0.007$; Figure 2A through 2C). Patients in the 4th quartile had the highest risk for all-cause death (log-rank, 21.333; $P<0.001$; Figure 2D). For the occurrence of the composite outcome, patients in 3rd and 4th quartiles had the highest risk (log-rank, 49.929; $P<0.001$; Figure 3).

Multivariate Analyses

A final forward Cox multivariate regression (Table 5) confirmed that patients in the 3rd and 4th quartiles had an independent increase in risk for stroke (hazard ratio [HR], 1.85; 95% CI, 1.02–3.35 and HR, 2.33; 95% CI, 1.30–4.16, respectively) and major bleeding (HR, 1.92; 95% CI, 1.18–3.15 and HR, 2.88; 95% CI, 1.79–4.61, respectively). SBP-SD as a continuous variable was associated with an increased

Table 2. Logistic Regression Analysis for Quality of Anticoagulation Control Indexes

	Time in Therapeutic Range								
	TTR>70%*			TTR≤65%*			TTR≤60%*		
SBP-VVV	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
1st quartile (ref)	…	…	…	…	…	…	…	…	…
2nd quartile	1.07	0.88–1.31	0.481	0.96	0.78–1.17	0.679	0.95	0.77–1.18	0.660
3rd quartile	0.86	0.71–1.05	0.145	1.28	1.05–1.57	0.014	1.25	1.01–1.53	0.036
4th quartile	0.75	0.61–0.92	0.006	1.54	1.26–1.89	<0.001	1.54	1.25–1.90	<0.001
SBP-SD (per mm Hg)	0.98	0.96–0.99	0.001	1.04	1.02–1.05	<0.001	1.04	1.02–1.05	<0.001

CI indicates confidence interval; INR, international normalized ratio; OR, odds ratio; PINRR, percentage of INR in range; SBP, systolic blood pressure; TTR, time in therapeutic range, and VVV, visit-to-visit variability.

*Adjusted for congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, peripheral arterial disease, and sex.

risk for both outcomes (*P*=0.002 for stroke and *P*<0.001 for major bleeding).

Despite an increase in risk of cardiovascular death for SBP-SD as a continuous variable (*P*=0.010), SBP-SD quartiles were not independently associated with cardiovascular death (Table 5). Conversely, patients in 4th quartile had an independent increase in risk for all-cause death (HR, 1.38; 95% CI, 1.00–1.91), which was also evident for SBP-SD as a continuous variable (*P*<0.001). The risk of the composite outcome was increased for patients in 3rd and 4th quartiles (HR, 1.55; 95% CI, 1.15–2.09 and HR, 1.94; 95% CI, 1.45–2.60). An increased risk was confirmed for SBP-SD as a continuous variable (*P*<0.001).

Sensitivity Analyses

The 4th quartile of SBP-SD was associated with an increased risk of stroke/major bleeding/cardiovascular death, in patients with no history of hypertension (*P*=0.010) and in elderly patients (*P*=0.005; Figure 4). The 3rd and 4th quartiles of SBP-SD were associated with an increased risk of composite outcome in patients with controlled SBP at baseline (*P*=0.014 and *P*<0.001, respectively) and in those at high thromboembolic risk (*P*=0.009 and *P*<0.001, respectively).

We performed sensitivity analyses with a logistic regression analysis for quality of anticoagulation control indexes, and second, a Cox regression analysis for major adverse outcomes, including the use of aspirin and polypharmacy as covariates. These did not affect significantly our results (data not shown).

Discussion

In this post hoc subgroup analysis from the AFFIRM trial, we demonstrate for the first time in patients with AF that SBP-VVV (expressed as SBP-SD) is associated with quality of anticoagulation control and with major adverse clinical events.

Specifically, we show an inverse linear association between increasing SBP-SD and TTR, as well as PINRR. Second, increasing SBP-VVV was independently associated with an increased risk for stroke, major bleeding, and the composite outcome of stroke/major bleeding/cardiovascular death. Third, increasing SBP-SD quartiles were associated with increased risk for the composite outcome even in specific subgroups, such as patients with no history of hypertension, elderly patients, patients with controlled SBP at baseline, and patients at high thromboembolic risk.

As far as we are aware, no previous data linked SBP-VVV and quality of anticoagulation control. Quality of anticoagulation control is a key determinant of major adverse clinical events in patients with AF.[8] There is an inverse independent association between TTR and both thromboembolic, as well as bleeding outcomes.[8] Indeed, several studies have reported that TTR is significantly associated with adverse outcomes in specific subgroups, including patients with chronic kidney

Table 3. Logistic Regression Analysis for Quality of Anticoagulation Control Indexes

	Percentage of INR in Range								
	PINRR>70%*			PINRR≤65%*			PINRR≤60%*		
SBP-VVV	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
1st quartile (ref)	…	…	…	…	…	…	…	…	…
2nd quartile	1.09	0.89–1.34	0.386	0.942	0.77–1.15	0.552	0.98	0.80–1.20	0.864
3rd quartile	0.81	0.66–0.99	0.042	1.24	1.02–1.51	0.033	1.33	1.09–1.62	0.005
4th quartile	0.72	0.58–0.89	0.003	1.44	1.17–1.76	0.001	1.54	1.26–1.89	<0.001
SBP-SD (per mm Hg)	0.97	0.95–0.98	<0.001	1.03	1.02–1.05	<0.001	1.04	1.02–1.06	<0.001

CI indicates confidence interval; INR, international normalized ratio; OR, odds ratio; PINRR, percentage of INR in range; SBP, systolic blood pressure; TTR, time in therapeutic range, and VVV, visit-to-visit variability.

*Adjusted for congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, peripheral arterial disease, and sex.

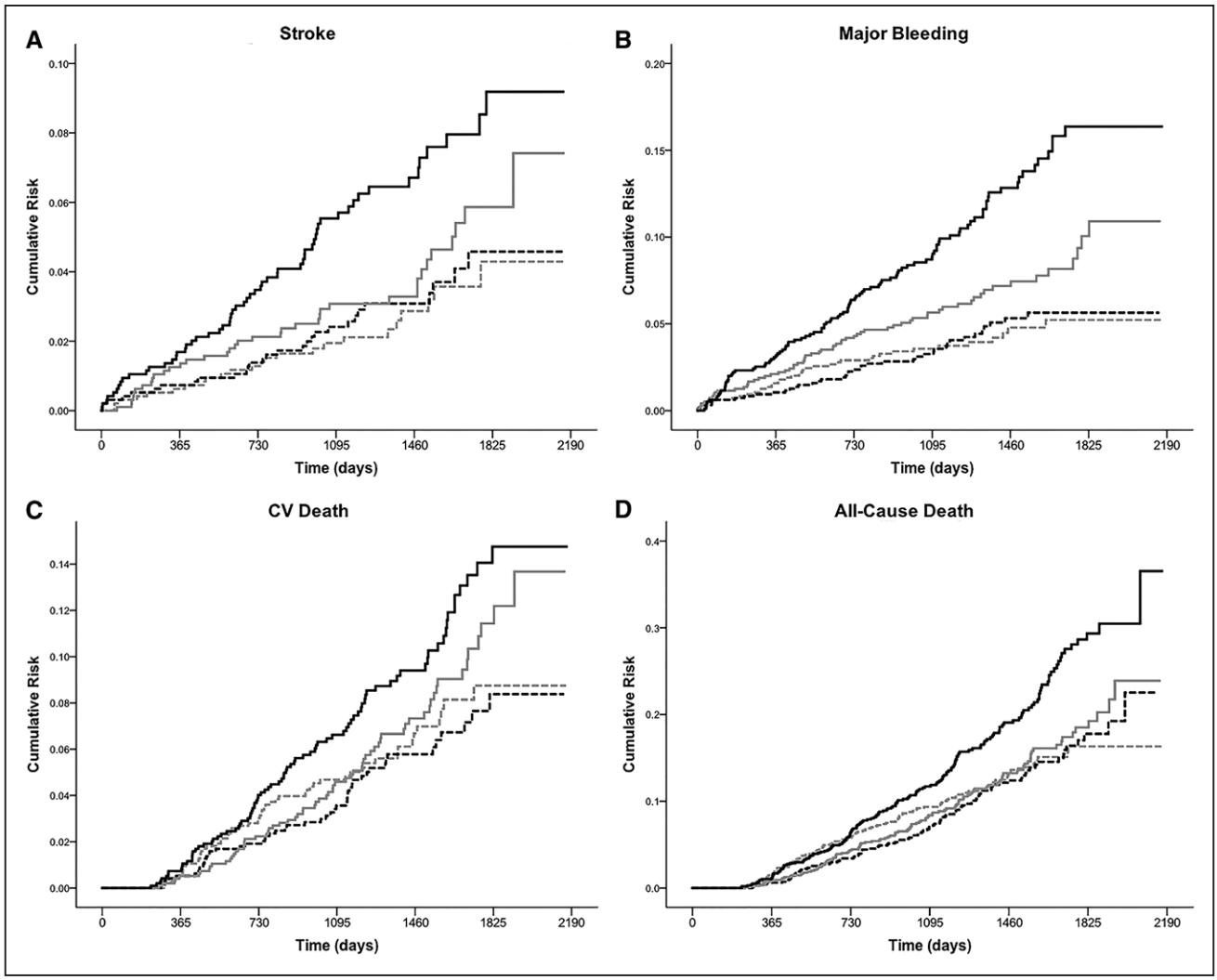

Figure 2. Kaplan–Meier curves for major clinical adverse events. **A**, Stroke; (**B**) major bleeding; (**C**) cardiovascular (CV) death; (**D**) all-cause death; grey dashed line: 1st quartile; black dashed line, 2nd quartile; grey solid line, 3rd quartile; black solid line, 4th quartile.

disease[16] or obesity,[17] even independently of sex.[18] Similarly, PINRR is a strong and independent predictor of outcomes on long-term follow-up.[10]

We could hypothesize that the strong relationship between SBP-SD and measures of quality of anticoagulation control in our study could be an indirect expression of overall patients' adherence to therapy. Indeed, the ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) showed that patients nonadherent to blood pressure pharmacological treatments had higher blood pressure VVV[19]; furthermore, those patients who improved adherence throughout follow-up had a significant reduction of blood pressure VVV, whereas nonadherent patients reported an increase in blood pressure VVV.[19] In an observational cohort of AF anticoagulated patients, poor adherence to medications, reported as a visual self-reported scale, was associated with poor anticoagulation control based on TTR.[20] Also, the use of educational programmes designed to improve patient adherence to prescription medication is associated with improved TTR levels.[21] We can also speculate that strategies aimed to improve patients' adherence and management of medications, enabling patients to understand, share, and follow physicians' recommendations could improve both SBP variability and the quality of anticoagulation control. In addition, we could hypothesize that relationship between SBP-VVV and quality of anticoagulation control could simply reflect an overall better quality of care, both related to physicians and healthcare systems. Given that our data were derived from a randomized controlled trial, this confounding aspect should be limited.

Hypertension, defined as history of hypertension at the beginning of observation, is associated with an increased risk of adverse events in patients with AF.[1,2] A subgroup analysis from the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) found that clinical history of hypertension was associated with an increased risk of thromboembolic events (HR, 1.24; 95% CI, 1.03–1.49),[3] whereas an analysis from the RE-LY (Randomized Evaluation of Long-Term) anticoagulation therapy trial documented an increased risk for major bleeding (HR, 1.25; 95% CI, 1.06–1.46).[4]

Beyond history of hypertension per se, blood pressure VVV is a potent predictor of outcomes in several clinical scenarios. Despite a wide variability in assessment and reporting, blood pressure VVV results in a relative risk increase ranging from 12% to 34% for incident cardiovascular disease, stroke,

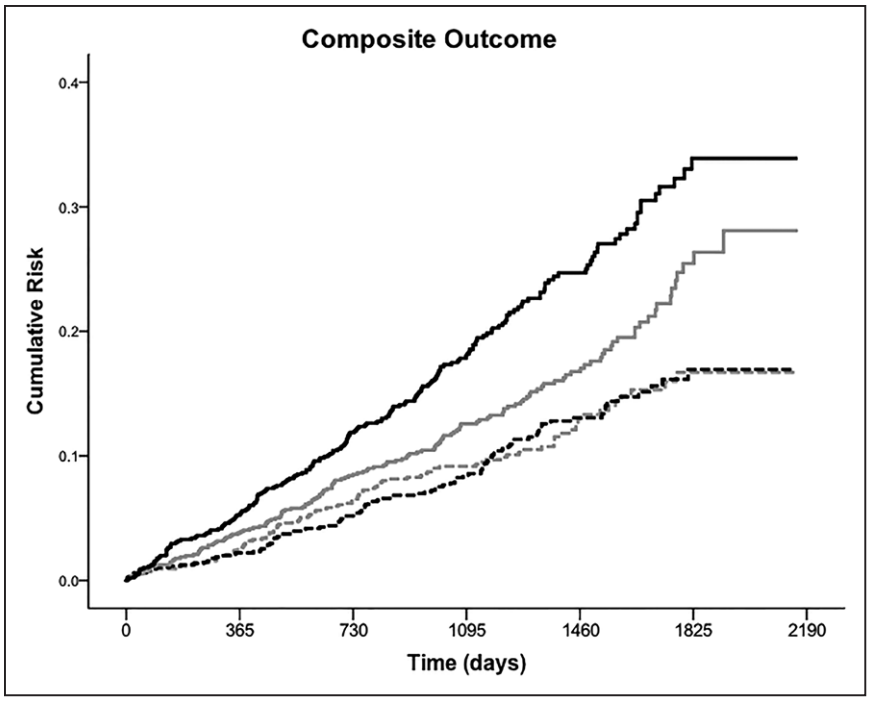

Figure 3. Kaplan–Meier curves for composite outcome. Grey dashed line, 1st quartile; black dashed line, 2nd quartile; grey solid line, 3rd quartile; black solid line, 4th quartile.

cardiovascular death, and all-cause death.[7] Recently, a large study of >2.5 million subjects conducted among US veterans reported that increasing quartiles of SBD-SD were associated with increasing risk for incident cardiovascular disease, stroke, all-cause death, and incident end-stage renal disease.[6] Our data confirm that higher SBP-VVV is a strong predictor of stroke and death even in AF subjects. In the context of AF, SBP-VVV is also a powerful predictor of major bleeding, irrespective of oral anticoagulation treatment and quality of anticoagulation control.

Beyond adherence to medications, possible mechanistic reasons for the association between SBP-VVV and major adverse events have been proposed. For example, subclinical atherosclerosis,[22–24] increased intima-media thickness,[23] and endothelial dysfunction[25–27] have been associated with SBP variability. These relationships are evident, even in high-risk (eg, diabetic) patients,[24] the elderly,[23] and nonhypertensive subjects.[26]

In patients with AF, no data thus far have been reported about the relationship between SBP-VVB and outcomes, but some proxy measures of blood pressure long-term control have been studied in relation to outcomes. In a substudy from an observational Japanese registry, blood pressure measured at the time of outcome occurrence or at the end of observation was taken as a measure of blood pressure control over time.[5] In this cohort, patients among the 4th quartile of SBP had an increased risk for both thromboembolic (odds ratio, 2.88; 95% CI, 1.75–4.74) and major bleeding (odds ratio, 1.61; 95% CI, 1.02–2.53) events, compared with the 1st quartile.[5] A further refined model, adjusted according to predicted risk of bleeding, demonstrated that patients in the 4th quartile of SBP had an increased risk for intracranial hemorrhage but not major bleeding.[5] In the study by Rao et al,[3] uncontrolled blood pressure over time, defined as a SBP ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at any time during follow-up observation was associated with an increased risk for thromboembolic events (HR, 1.53; 95% CI, 1.25–1.86) and major/clinically relevant nonmajor bleeding (HR, 1.14; 95% CI, 1.01–1.28). Our study reports for the first time that a reliable direct measure of SBP-VVV is strongly associated with stroke, major bleeding, and mortality outcomes. Moreover, we show that an association between SBP-VVV and risk of the adverse outcomes is consistent irrespective of elderly age, blood pressure history, blood pressure control, and thromboembolic risk strata.

Our data suggest that strict and consistent SBP control is highly desirable in patients with AF. Further, more intensive

Table 4. Major Adverse Clinical Outcomes According to Systolic Blood Pressure SD Quartiles

Outcomes	1st Quartile (<10.09*) N=963	2nd Quartile (10.09–13.85*) N=959	3rd Quartile (13.86–17.33*) N=962	4th Quartile (≥17.34*) N=959	*P* Value
Stroke, n (%)	24 (2.5)	29 (3.0)	37 (3.8)	59 (6.2)	<0.001
Major bleeding, n (%)	38 (3.9)	41 (4.3)	65 (6.8)	104 (10.8)	<0.001
CV death, n (%)	55 (5.7)	50 (5.2)	67 (7.0)	86 (9.0)	0.005
All-cause death, n (%)	106 (11.0)	105 (10.9)	117 (12.2)	167 (17.4)	<0.001
Stroke/major bleeding/CV death, n (%)	104 (10.8)	107 (11.2)	150 (15.6)	199 (20.8)	<0.001

CV indicates cardiovascular.
*Expressed as mm Hg.

Table 5. Cox Regression Analysis for Major Adverse Events

	Model 1*			Model 2†		
Outcomes	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Stroke						
SBP-SD quartiles						
1st quartile (ref)	…	…	…	…	…	…
2nd quartile	1.42	0.76–2.67	0.272	1.42	0.76–2.66	0.276
3rd quartile	1.80	1.00–3.26	0.052	1.85	1.02–3.35	0.042
4th quartile	2.21	1.23–3.97	0.008	2.33	1.30–4.16	0.004
SBP-SD (per mm Hg)	1.06	1.02–1.09	0.004	1.06	1.02–1.10	0.002
Major bleeding						
SBP-SD quartiles						
1st quartile (ref)	…	…	…	…	…	…
2nd quartile	1.35	0.79–2.28	0.273	1.34	0.79–2.28	0.278
3rd quartile	1.90	1.16–3.11	0.011	1.92	1.18–3.15	0.009
4th quartile	2.82	1.75–4.53	<0.001	2.88	1.79–4.61	<0.001
SBP-SD (per mm Hg)	1.07	1.04–1.10	<0.001	1.08	1.05–1.11	<0.001
CV death						
SBP-SD quartiles						
1st quartile (ref)	…	…	…	…	…	…
2nd quartile	0.94	0.60–1.47	0.936	1.00	0.64–1.57	0.996
3rd quartile	1.01	0.66–1.55	0.965	1.05	0.68–1.60	0.840
4th quartile	1.12	0.74–1.71	0.585	1.22	0.80–1.87	0.349
SBP-SD (per mm Hg)	1.03	1.00–1.06	0.034	1.04	1.01–1.07	0.010
All-cause death						
SBP-SD quartiles						
1st quartile (ref)	…	…	…	…	…	…
2nd quartile	1.12	0.80–1.57	0.497	1.18	0.85–1.66	0.322
3rd quartile	1.02	0.73–1.42	0.911	1.08	0.78–1.50	0.650
4th quartile	1.25	0.91–1.73	0.166	1.38	1.00–1.91	0.048
SBP-SD (per mm Hg)	1.04	1.02–1.06	<0.001	1.05	1.02–1.07	<0.001
Stroke/major bleeding/CV death						
SBP-SD quartiles						
1st quartile (ref)	…	…	…	…	…	…
2nd quartile	1.18	0.86–1.63	0.305	1.22	0.89–1.68	0.225
3rd quartile	1.52	1.12–2.04	0.006	1.55	1.15–2.09	0.004
4th quartile	1.87	1.39–2.50	<0.001	1.94	1.45–2.60	<0.001
SBP-SD (per mm Hg)	1.05	1.03–1.07	<0.001	1.06	1.04–1.08	<0.001

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; and SBP, systolic blood pressure.

*Adjusted for use of warfarin, time in therapeutic range, hepatic/renal disease, pulmonary disease, randomized treatment, and CHA_2DS_2-VASc.

†Adjusted for use of warfarin, time in therapeutic range, hepatic/renal disease, pulmonary disease, randomized treatment, congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack, myocardial infarction, peripheral arterial disease, and sex.

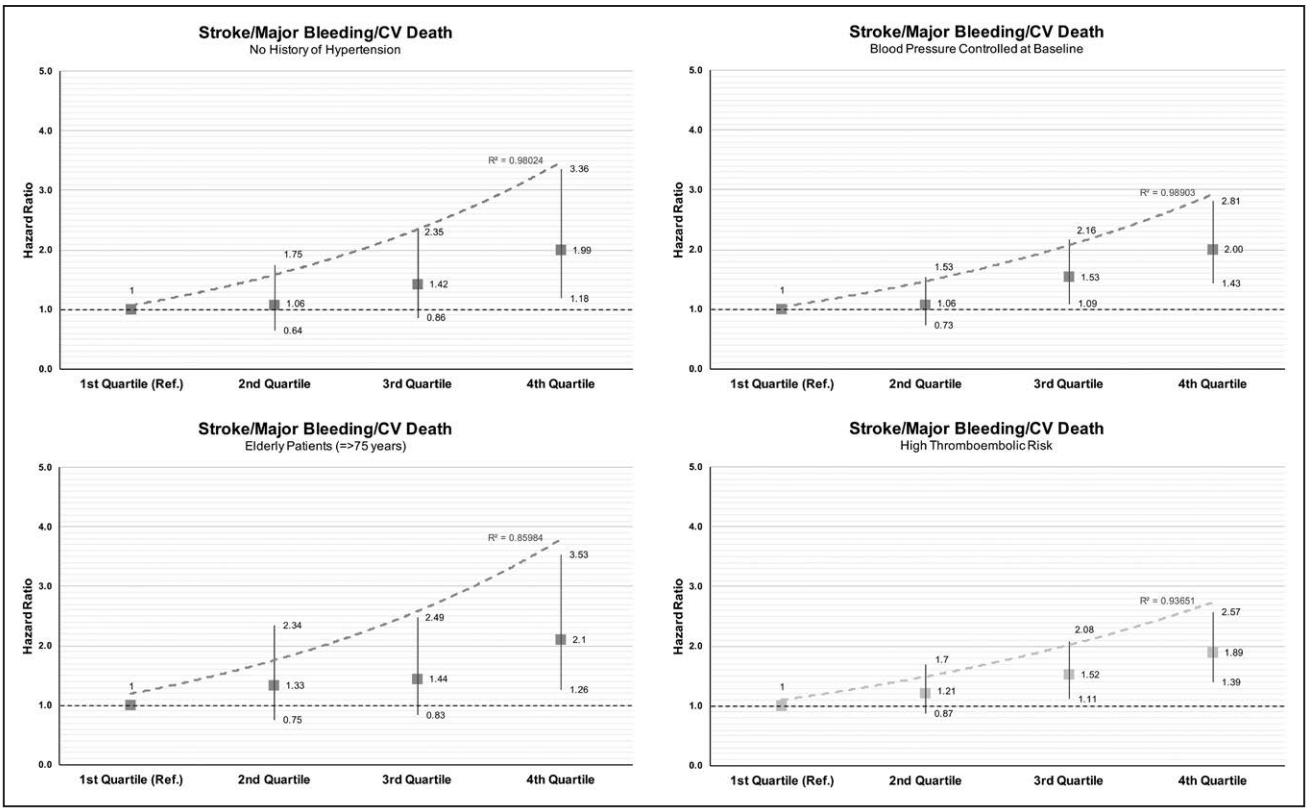

Figure 4. Sensitivity analyses for composite outcome risk. Values are expressed as hazard ratios and 95% confidence intervals. CV indicates cardiovascular.

treatment aimed to achieve lower blood pressure and SBP levels is associated with better outcomes during long-term follow-up.[28] In a recent network meta-analysis of hypertensive subjects, the lowest mean achieved SBP (120–124 mm Hg) versus the highest (≥160 mm Hg) is associated with a larger reduction of cardiovascular disease and all-cause death.[29] Also, in a post hoc analysis from 2 large randomized controlled trials of antihypertensive medications, the highest mean achieved SBP was associated with the highest risk of a composite outcome of cardiovascular death, myocardial infarction, stroke, and hospital admission for heart failure and for all-cause death.[30]

Limitations

The main limitation of this study is related to the post hoc design. Similarly, another major limitation lies in the nonstandardized measurement of blood pressure, which could have affected the reproducibility of SBP-VVV measurements and has to be considered when interpreting our data. We also cannot account for differences in paroxysmal and permanent AF because type of AF was not available for this analysis. Furthermore, we could not account for medication adherence throughout the follow-up period. Also, we could not define whether blood pressure measurements accounted for the irregularity in rhythm at the precise time of actual measurement. Conversely, the AFFIRM study is largely known to be a well-controlled reliable study with adjudicated outcomes.

Perspectives

In a large cohort of patients with AF derived from a randomized controlled trial, SBP-VVV is inversely associated with anticoagulation control, whereas increasing SBP-VVV is associated with a higher of major adverse outcomes. Strategies to reduce SBP-VVV, as well as to improve oral anticoagulation control, are needed among patients with AF and would help reduce major adverse clinical outcomes in patients with AF.

Sources of Funding

The AFFIRM study (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) was funded by the United States National Heart, Lung, and Blood Institute. No specific funding has been received for this work.

Disclosures

M. Proietti is a consultant for Boehringer Ingelheim; B. Olshansky for Lundbeck, Amarin, and Boehringer Ingelheim; and G.Y.H. Lip for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. G.Y.H. Lip is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo.

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Novelty and Significance

What Is New?

- Systolic blood pressure (SBP)–visit-to-visit variability (VVV) was found associated with a worse quality of anticoagulation control.
- A higher SBP-VVV identified patients with a higher risk of major adverse events in a large atrial fibrillation cohort.

What Is Relevant?

- A better management of SBP during a long-term clinical follow-up would help improving outcomes in patients with atrial fibrillation.

Summary

SBP-VVV in a large cohort of patients with atrial fibrillation, derived from a randomized controlled trial, was found to be associated with worse quality of anticoagulation control. An increased SBP-VVV was also independently associated with an increased risk of stroke, major bleeding, cardiovascular death, and all-cause death during a long-term follow-up, beyond advanced age, hypertension history, blood pressure control at baseline, and increased thromboembolic risk. Interventions to achieve better management of blood pressure to obtain a lower SBP-VVV would improve quality of anticoagulation control and minimize major clinical outcomes.