Impact of Systolic Blood Pressure Time in Target Range on Adverse Events in Patients With Nonvalvular Atrial Fibrillation (from the J-RHYTHM Registry)

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Although time in target range (TTR) of systolic blood pressure (BP), an index of consistency of BP control, is reportedly associated with major cardiovascular outcomes, the impact of BP-TTR on adverse events in patients with nonvalvular atrial fibrillation (NVAF) has not been thoroughly investigated. Thus, we performed a post hoc analysis to clarify it in patients with NVAF using data of the J-RHYTHM registry. Of 7,406 outpatients with NVAF, 7,226 (age, 70 ± 10 years; men, 71%), in whom BP was measured 4 times or more (15 ± 5 times) during the 2-year follow-up period or until occurrence of an event, constituted the study group. Systolic BP-TTR, with a target range of 110 to 130 mm Hg, was calculated by Rosendaal linear interpolation method. Overall systolic BP-TTR was 50 ± 28%. Thromboembolism, major hemorrhage, all-cause death, and cardiovascular death occurred in 110 (1.5%), 121 (1.7%), 168 (2.3%), and 60 patients (0.8%), respectively. Each 1% increase in systolic BP-TTR was significantly associated with a decreased incidence of all adverse events in the unadjusted model; whereas, significant association was observed only for cardiovascular death (adjusted hazard ratio 0.983, 95% confidence interval 0.971 to 0.995, p = 0.006) after adjusting for known confounders and systolic BP at the time closest to an event. In contrast, each 1% increase in systolic BP time in subtarget range of <110 mm Hg was significantly associated with an increased risk of thromboembolism (hazard ratio 1.014, 95% confidence interval 1.005 to 1.024, p = 0.002). In conclusion, systolic BP-TTR and BP time in subtarget range would be useful for risk evaluation of cardiovascular death and thromboembolism, respectively, in patients with NVAF. **(Am J Cardiol 2022;00:1−7)**

Introduction

Hypertension is an established risk factor for several cardiovascular diseases,[1−3] including atrial fibrillation (AF).[4,5] Because hypertension is also a risk factor for thromboembolic and hemorrhagic complications in patients with AF,[6,7] it has been adapted as a component of traditional risk scores for patients with nonvalvular AF (NVAF).[8−10] However, hypertension is not always identified as an independent risk factor for thromboembolism or major hemorrhage.[11−15] One of reasons might be that the consistency of blood pressure (BP) control during the follow-up period is not necessarily considered. Time in target range (TTR) of systolic BP, an index of consistency of BP control, is reportedly associated with major cardiovascular outcomes in a post hoc analysis of the SPRINT (Systolic Blood Pressure Intervention Trial),[16] which was not focused on patients with NVAF. We hypothesized that the TTR of BP values (BP-TTR) could be associated with adverse events in patients with NVAF. Therefore, we performed a post hoc analysis to test this hypothesis in patients with NVAF, using data of the J-RHYTHM registry.

Methods

The J-RHYTHM registry was conducted as a nationwide prospective observational study to investigate the status of anticoagulation therapy and the optimal anticoagulation therapy in Japanese patients with AF.[17] The study protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of each participating institution. Written informed consent was obtained from all participants at the time of enrollment. The study design and patient characteristics at the time of enrollment have been reported elsewhere.[17,18] Briefly, a consecutive series of outpatients with AF of any type was enrolled from 158 institutions in 2009, regardless of antihypertensive drug use. All drugs and their dosages were selected at the discretion of

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the treating physicians. Patients with valvular AF (mechanical heart valve and mitral stenosis) were excluded from this subanalysis. Seated brachial BP was measured in each patient at the time of enrollment and at each follow-up visit by either the auscultatory method or an automated sphygmomanometer, as appropriate at each institution.[7,19]

For the present post hoc analysis, patients with NVAF, in whom BP was measured at least 4 times during the 2-year follow-up period or until occurrence of an event, were included. The primary end points were as follows: thromboembolism, including symptomatic ischemic stroke, transient ischemic attack, and systemic embolism; major hemorrhage, including intracranial hemorrhage, gastrointestinal hemorrhage, and other hemorrhages requiring hospitalization; and all-cause and cardiovascular death. The diagnostic criteria for each event have been described elsewhere.[17,18]

The overall consistency of BP control during the follow-up period was evaluated using systolic BP-TTR calculated by a linear interpolation method by Rosendaal,[20] which was analogous to the time in therapeutic range of prothrombin time international normalized ratio (PT-INR) in patients receiving warfarin.[21] In this study, the target systolic BP range was set at 110 to 130 mm Hg or 120 to 140 mm Hg, according to the post hoc analysis of the SPRINT.[16] The impact of systolic BP-TTR on adverse events was evaluated as a continuous variable and also as categorical one. For the latter, patients were categorized into the 4 systolic BP-TTR groups (<25%, 25% to 49.9%, 50% to 74.9%, and ≥75%), following a previous study.[16] These groups were named the lowest, second, third, and highest, in ascending order from the lowest.

Systolic BP time in subtarget range (BP-TSubTR) and supratarget range (BP-TSupraTR) were defined as the time in systolic BP values of <110 and >130, or <120 and >140 mm Hg, respectively, depending on the target systolic BP selected. The impact of systolic BP-TSubTR and BP-TSupraTR on adverse events was also evaluated.

Data are presented as mean ± SD or number (percentage). For comparison of patient characteristics and 2-year event rates among the groups, trend analysis was performed using the Cochran-Armitage test for categorical variables or the Jonckheere-Terpstra test for continuous variables, as appropriate. Univariable and multivariable analyses using the Cox proportional hazards models were performed to investigate the influence of systolic BP-TTR on adverse events. Cox proportional hazards assumption was verified by the log-log survival curve in all of the study outcomes. Risks of systolic BP-TTR for each adverse event were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs) per 1% increase in systolic BP-TTR as a continuous variable or those of each systolic BP-TTR group compared with the highest group as a reference. Explanatory variables for multivariable analysis were adopted from well-known risk factors used in our previous subanalyses for hypertension and BP,[7,19] including components of the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or transient ischemic attack, vascular disease [coronary artery disease], age 65 to 74 years, female gender),[9] warfarin and antiplatelet use, type of AF, BP measurement times, and BP values at the time closest to an event or at the end of follow-up (BP-end) (model 1).[7,19] An additional model included variables of model 1 plus creatinine clearance, body mass index, and hemoglobin levels as explanatory variables based on the results of our previous subanalyses (model 2).[19,22] In patients receiving warfarin, time therapeutic range of PT-INR was added as a covariate in the extra model. A 2-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software version 23.0 (IBM Corporation, Armonk, New York).

Results

Of the 7,937 entire patients with AF enrolled in the J-RHYTHM registry,[18] 421 with valvular AF (5.3%) were excluded and 110 were lost to follow-up (1.5%). Of the remaining 7,406 patients with NVAF,[7,23] 180 patients (2.4%) with BP measurements <4 times during the follow-up period were excluded. Consequently, 7,226 patients (age, 70 ± 10 years; men, 71%) were included in this subanalysis.

Clinical characteristics and medications of 7,226 patients are listed in Table 1. A total of 60% of the patients had hypertension, and BP was measured 15 ± 5 times during the follow-up period. Both systolic BP-TTRs of 110 to 130 mm Hg and 120 to 140 mm Hg were around 50% (Table 1). Patient characteristics and medications in systolic BP-TTR groups for 110 to 130 mm Hg and 120 to 140 mm Hg are shown in Supplementary Table 1A, B. Age, systolic and diastolic BP, and prevalence of women, hypertension, age ≥75 years, and diabetes mellitus showed significant decreasing trends across the 4 groups (Supplementary Table 1A). In contrast, prevalence of heart failure and hypertension showed inverse trends across the 4 groups and there was no significant trend in age across the systolic BP-TTR groups for 120 to 140 mm Hg (Supplementary Table 1B). Consequently, risk scores for thromboembolism ($CHADS_2$ and CHA_2DS_2-VASc scores) and hemorrhage (HAS-BLED score) showed significant trends across the 4 systolic BP-TTR groups for 110 to 130 mm Hg, but not for 120 to 140 mm Hg (Supplementary Table 1A, B).

During the 2-year follow-up period, thromboembolism, major hemorrhage, all-cause death, and cardiovascular death occurred in 110 (1.5%), 121 (1.7%), 168 (2.3%), and 60 (0.8%) patients, respectively. Corresponding incidence rates of these events were 0.8, 0.8, 1.2, and 0.4 /100 person-years, respectively, during the follow-up period of 14,580 person-years.

When BP-TTR was analyzed as a continuous variable, each 1% increase in systolic BP-TTR of 110 to 130 mm Hg was significantly associated with a decreased incidence of all adverse events in the unadjusted model; whereas, a significant association was observed only for cardiovascular death in adjusted model 2 (Table 2). Each 1% increase in systolic BP-TTR of 120 to 140 mm Hg was significantly associated with a decreased incidence of all-cause and cardiovascular death in the unadjusted model; whereas, the significant association disappeared in adjusted models (Table 2). When BP-TTR was analyzed as a categorical variable, 2-year event rates and unadjusted HRs for adverse

Table 1
Patient characteristics and medications (n = 7226)

Age (years)	70±10
Men	5108 (71%)
Body mass index (kg/m^2) (n=6242)	24±4
Type of atrial fibrillation	
Paroxysmal	2762 (38%)
Persistent	1056 (15%)
Permanent	3408 (47%)
Coronary artery disease	755 (10%)
Cardiomyopathy	620 (9%)
Hypertrophic cardiomyopathy	258 (4%)
Dilated cardiomyopathy	362 (5%)
Congenital heart disease	96 (1%)
Chronic obstructive pulmonary disease	124 (2%)
Hyperthyroidism	129 (2%)
Risk factors for stroke	
Heart failure	1998 (28%)
Hypertension	4378 (61%)
Age (≥75 years)	2483 (34%)
Diabetes mellitus	1326 (18%)
Stroke/TIA	991 (14%)
$CHADS_2$ score	1.7±1.2
CHA_2DS_2-VASc score	2.8±1.6
HAS-BLED score (n=6846)	1.5±1.0
BP measurement times	15±5
Systolic BP (mmHg)	126±16
BP-TTR (110−130 mmHg) (%)	50±28
BP-TSubTR (<110 mmHg) (%)	14±24
BP-TSupraTR (>130 mmHg) (%)	37±33
BP-TTR (120−140 mmHg) (%)	51±29
BP-TSubTR (<120 mmHg) (%)	34±33
BP-TSupraTR (>140 mmHg) (%)	15±23
Diastolic BP (mmHg)	73±11
Heart rate (beats/min)	72±13
Creatinine clearance (mL/min) (n=5925)	69±28
Hemoglobin (g/dL) (n=6398)	13.7±1.7
Medications	
Warfarin	6269 (87%)
PT-INR (n=6269)	1.9±0.5
Time in therapeutic range (%) (n=5934)	60±29
Antiplatelet	1882 (26%)
Aspirin	1928 (23%)
Other antiplatelets	420 (6%)
Warfarin+antiplatelet	1329 (18%)
ARB/ACE-I	3850 (53%)
Other antihypertensive drugs	3456 (48%)
Statins	1757 (24%)

Data are number of patients (%) or mean±SD.

TIA = transient ischemic attack; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and history of stroke or TIA; CHA_2DS_2-VASc = additionally, vascular disease (coronary artery disease), age 65−74 years, and female sex; HAS-BLED = hypertension (systolic BP ≥140 mmHg), abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (episodes of INR ≥3.5), elderly (age >65 years), drugs (use of antiplatelets)/alcohol concomitantly; BP = blood pressure; TTR = time in target range; TSubTR = time in subtarget range; TSupraTR = time in supratarget range; PT-INR = prothrombin time international normalized ratio; ARB = angiotensin II receptor blocker; ACE-I = angiotensin converting enzyme inhibitor.

events in systolic BP-TTR groups are summarized in Supplementary Tables 2 and 3. In the adjusted model 2, systolic BP-TTR was not significantly association with any adverse event across the 4 groups, except for thromboembolism in the third BP-TTR group and all-cause death in the second BP-TTR group for 120 to 140 mm Hg (Table 3).

Each 1% increase in systolic BP-TSubTR of <110 mm Hg was significantly associated with an increase incidence of all-cause and cardiovascular death in the unadjusted model; whereas, a significant association was observed for thromboembolism in the adjusted model 2. Each 1% increase in systolic BP-TSupraTR of >130 mm Hg was significantly associated with an increased risk of major hemorrhage and a decreased risk of all-cause and cardiovascular death in the unadjusted model; whereas, a significant association was observed only for thromboembolism in the adjusted model 2 (Table 4). Similarly, systolic BP-TSubTR of <120 mm Hg and BP-TSupraTR of >140 mm Hg were significantly associated with thromboembolism in the adjusted model 2 (Table 4). The significant association between BP-TSubTR, BP-TSupraTR, and thromboembolism was consistent in patients receiving warfarin, even after adjusting for the time in therapeutic range of PT-INR in addition to variables of the model 2 (Supplementary Table 4).

When upper systolic BP limit was set at 160 mm Hg, according to the HAS-BLED score,[10] each 1% increase in systolic BP-TSupraTR (>160 mm Hg) was significantly associated with an increased incidence of thromboembolism and major hemorrhage in the unadjusted model; whereas, the significant association disappeared in the adjusted models. In contrast, systolic BP-TSupraTR (>160 mm Hg) was significantly associated with an increased risk of cardiovascular death in adjusted models (Supplementary Table 5).

Discussion

The major findings of this study were as follows. First, an increase in systolic BP-TTR of 110 to 130 mm Hg was significantly associated with a decreased risk of cardiovascular death in patients with NVAF, independent of BP-end and other conventional risk factors. Second, systolic BP-TTR of 110 to 130 mm Hg was slightly better for predicting adverse events than 120 to 140 mm Hg. Third, an increase in systolic BP-TSubTR, irrespective of target systolic BP of <110 or <120 mm Hg, was significantly associated with an increased risk of thromboembolism.

Using data of approximately 70,000 veterans with hypertension, Doumas et al determined usefulness of consistent control of systolic BP between 120 and 140 mm Hg.[24] They indicated that consistency of BP control over 10 years was a strong determinant of all-cause mortality. In the post hoc analysis of the SPRINT,[16] each 1-SD increase in systolic BP-TTR was significantly associated with a decreased risk of major cardiovascular events (HR 0.85, 95% CI 0.74 to 0.96, p = 0.011), independent of mean systolic BP values. However, the usefulness of systolic BP-TTR in major cardiovascular events was not evaluated separately for each target systolic BP range (110 to 130 mm Hg vs 120 to 140 mm Hg).[16] Therefore, in the present subanalysis, we investigated the impact of systolic BP-TTR on adverse events separately for both target systolic BP range of 110 to 130 mm Hg and 120 to 140 mm Hg. Our results indicated that the target systolic BP of 110 to 130 mm Hg would be

Table 2
Influence of systolic BP-TTR on adverse events (Cox proportional hazards analysis)

	Thromboembolism		Major hemorrhage		All-cause death		Cardiovascular death	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Systolic BP-TTR (110–130 mmHg)								
Univariable	0.993 (0.986–1.000)	0.038	0.993 (0.987–0.999)	0.034	0.993 (0.987–0.998)	0.009	0.984 (0.975–0.993)	0.001
Multivariable (model 1)	1.003 (0.996–1.009)	0.442	0.998 (0.992–1.005)	0.580	0.993 (0.987–0.998)	0.011	0.983 (0.974–0.993)	0.001
Multivariable (model 2)	1.005 (0.997–1.012)	0.229	1.000 (0.992–1.007)	0.905	0.994 (0.987–1.001)	0.070	0.983 (0.971–0.995)	0.006
Systolic BP-TTR (120–140 mmHg)								
Univariable	0.996 (0.990–1.003)	0.286	0.998 (0.992–1.005)	0.620	0.985 (0.979–0.990)	<0.001	0.978 (0.969–0.987)	<0.001
Multivariable (model 1)	0.998 (0.991–1.005)	0.602	0.999 (0.993–1.006)	0.817	0.994 (0.983–1.000)	0.050	0.990 (0.980–1.000)	0.060
Multivariable (model 2)	1.000(0.992–1.007)	0.905	0.998 (0.991–1.005)	0.576	0.998 (0.991–1.005)	0.582	0.995 (0.983–1.007)	0.423

Model 1: adjusted for components of CHA_2DS_2-VASc score, warfarin and antiplatelet use, type of atrial fibrillation, BP measurement times, and systolic BP at the time closest to an event or at the end of follow-up. Model 2: adjusted for variables of model 1 plus creatinine clearance, body mass index, and hemoglobin (n=5596).
BP = blood pressure; TTR = time in target range; HR = hazard ratio (/1% increase); CI = confidence interval.

better for the risk evaluation of adverse events than 120 to 140 mm Hg. However, it is difficult to refer from only this study for the optimal target systolic BP range for preventing thromboembolism and major hemorrhage because the significance of systolic BP-TTR of 110 to 130 mm Hg for thromboembolism and major hemorrhage disappeared in the adjusted models (Table 2). In 298,374 Korean patients with NVAF who were oral anticoagulant-naive, who underwent hypertension treatment, patients with BP ≥130 or <120/80 mm Hg were at significantly higher risks of major cardiovascular events, including all-cause death, than those with BP of 120 to 129/<80 mm Hg.[25] That study indicated that there was the J-curve on events and BP of 120 to 129/<80 mm Hg would be the optimal BP treatment target for patients with AF who underwent hypertension treatment. Given that an increase in systolic BP-TTR of 110 to 130 mm Hg was associated with a decreased risk of cardiovascular death in this study (Table 2), systolic BP-TTR of 110 to 130 mm Hg could be useful for predicting cardiovascular mortality.

We also evaluated the impact of systolic BP-TSubTR and BP-TSupraTR on adverse events in this study, as we previously investigated for time in therapeutic range of PT-INR.[21] Our results suggested that consistent low-BP state caused by any reasons could be associated with an increased risk of thromboembolic events and cardiovascular death compared with consistent high-BP state. In a large-scale population-based study to estimate clinically measured BP trajectories for 20 years before death,[26] systolic and diastolic BPs decreased gradually for 14 to 18 years, with steeper decreases in the last 2 years of life. Decreases in BP values were observed in patients not treated for hypertension but were steepest in patients with hypertension, dementia, heart failure, and late-life weight loss.[26] These facts might explain our results as well. In contrast, although an increase in systolic BP-TSupraTR of both >130 and >140 mm Hg was significantly associated with an increased risk of major hemorrhage in the unadjusted model, the significant association disappeared after adjusting for BP-end (Table 4). Therefore, BP-end, itself, would be more critical for the onset of hemorrhagic events than BP-TSupraTR.[7]

This study has several limitations. First, it was a post hoc analysis of data from the J-RHYTHM registry[18,23] and was, therefore, hypothesis-generating in nature. Second, study subjects were recruited from only 158 institutions in Japan in 2009 and most of the participating physicians specialized in cardiology and in the management of cardiac arrhythmias. Oral anticoagulant used was only warfarin. Therefore, these results may not be generalizable to the contemporary overall Japanese population with NVAF in the era of nonvitamin K antagonist oral anticoagulants. In addition, because all study subjects were Japanese in this study, these data may not necessarily be applicable to other racial/ethnic populations. Third, BP measurement methods were not standardized. BP values were obtained by auscultatory method or an automated sphygmomanometer, as appropriate for daily clinical practice in each institution. Fourth, changes in antihypertensive drugs and dosage and adherence to drugs during the follow-up period were not considered in the analysis. Finally, because the study design was

Table 3
Influence of systolic BP-TTR on adverse events (multivariable Cox proportional hazards analysis)

	Thromboembolism		Major hemorrhage		All-cause death		Cardiovascular death	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Systolic BP-TTR (110−130 mmHg)								
Model 1								
Lowest (<25%)	0.80 (0.45−1.44)	0.246	1.07 (0.62−1.84)	0.814	1.68 (1.03−2.76)	0.040	3.23 (1.37−7.64)	0.008
Second (25−49.9%)	0.97 (0.54−1.77)	0.925	1.29 (0.75−2.22)	0.355	1.93 (1.17−3.17)	0.010	2.62 (1.05−6.50)	0.038
Third (50−74.9%)	0.87 (0.48−1.59)	0.652	0.98 (0.56−1.71)	0.940	1.21 (0.71−2.08)	0.482	1.37 (0.50−3.73)	0.537
Highest (≥75%)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Model 2								
Lowest (<25%)	0.66 (0.35−1.23)	0.187	0.81 (0.44−1.48)	0.491	1.36 (0.77−2.40)	0.291	2.37 (0.85−6.66)	0.101
Second (25−49.9%)	0.99 (0.53−1.83)	0.967	1.18 (0.67−2.09)	0.565	1.66 (0.95−2.90)	0.074	2.02 (0.70−5.86)	0.194
Third (50−74.9%)	0.68 (0.35−1.32)	0.249	0.75 (0.40−1.39)	0.358	1.07 (0.59−1.94)	0.835	0.94 (0.28−3.13)	0.919
Highest (≥75%)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Systolic BP-TTR (120−140 mmHg)								
Model 1								
Lowest (<25%)	1.53 (0.82−2.84)	0.179	1.02 (0.60−1.73)	0.956	1.62 (0.89−2.96)	0.116	1.41 (0.56−3.57)	0.464
Second (25−49.9%)	1.21 (0.65−2.26)	0.554	1.10 (0.67−1.82)	0.703	2.13 (1.19−3.81)	0.011	1.98 (0.81−4.80)	0.133
Third (50−74.9%)	1.75 (0.99−3.09)	0.055	0.81 (0.49−1.37)	0.434	1.56 (0.85−2.85)	0.149	0.71 (0.25−2.04)	0.523
Highest (≥75%)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Model 2								
Lowest (<25%)	1.38 (0.69−2.76)	0.365	1.17 (0.64−2.12)	0.608	1.31 (0.65−2.63)	0.447	1.15 (0.35−3.83)	0.818
Second (25−49.9%)	1.31 (0.67−2.57)	0.433	1.12 (0.63−2.00)	0.694	2.05 (1.05−4.02)	0.035	2.13 (0.68−6.63)	0.193
Third (50−74.9%)	1.90 (1.02−3.54)	0.042	0.89 (0.49−1.60)	0.696	1.87 (0.94−3.73)	0.074	1.01 (0.28−3.63)	0.991
Highest (≥75%)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	

Model 1: adjusted for components of CHA_2DS_2-VASc score, warfarin and antiplatelet use, type of atrial fibrillation, BP measurement times, and systolic BP at the time closest to an event or at the end of follow-up. Model 2: adjusted for variables of model 1 plus creatinine clearance, body mass index, and hemoglobin (n=5596).

BP = blood pressure; TTR = time in target range; HR = hazard ratio; CI = confidence interval.

Table 4
Influence of systolic BP-TSubTR and TSupraTR on adverse events (Cox proportional hazards analysis)

	Thromboembolism		Major hemorrhage		All-cause death		Cardiovascular death	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Systolic BP-TSubTR (<110 mmHg)								
Univariable	1.004 (0.997−1.011)	0.257	0.996 (0.988−1.005)	0.371	1.019 (1.015−1.024)	<0.001	1.026 (1.019−1.033)	<0.001
Multivariable (model 1)	1.018 (1.010−1.026)	<0.001	1.004 (0.996−1.013)	0.319	1.012 (1.007−1.017)	<0.001	1.018 (1.009−1.026)	<0.001
Multivariable (model 2)	1.014 (1.005−1.024)	0.002	1.003 (0.994−1.013)	0.495	1.004 (1.998−1.011)	0.222	1.010 (0.999−1.021)	0.077
Systolic BP-TSupraTR (>130 mmHg)								
Univariable	1.003 (0.997−1.009)	0.327	1.007 (1.001−1.007)	0.013	0.989 (0.984−0.994)	<0.001	0.998 (0.979−0.997)	0.008
Multivariable (model 1)	0.989 (0.983−0.996)	0.002	1.000 (0.994−1.007)	0.924	0.999 (0.993−1.004)	0.623	1.002 (0.993−1.012)	0.639
Multivariable (model 2)	0.989 (0.982−0.996)	0.003	0.999 (0.992−1.006)	0.722	1.003 (0.995−1.010)	0.473	1.008 (0.995−1.021)	0.237
Systolic BP-TSubTR (<120 mmHg)								
Univariable	0.999 (0.993−1.005)	0.734	0.994 (0.988−1.000)	0.044	1.014 (1.010−1.018)	<0.001	1.018 (1.011−1.025)	<0.001
Multivariable (model 1)	1.011 (1.004−1.018)	0.001	0.999 (0.993−1.006)	0.868	1.004 (0.999−1.009)	0.114	1.005 (0.997−1.014)	0.236
Multivariable (model 2)	1.010 (1.003−1.017)	0.007	1.0000(0.993−1.008)	0.986	0.999 (0.993−1.006)	0.863	1.001 (0.990−1.012)	0.903
Systolic BP-TSupraTR (>140 mmHg)								
Univariable	1.007 (0.999−1.014)	0.070	1.011 (1.005−1.018)	0.001	0.991 (0.983−0.989)	0.029	0.992(0.979−1.005)	0.227
Multivariable (model 1)	0.987(0.978−0.996)	0.004	1.002 (0.994−1.010)	0.619	1.001 (0.992−1.009)	0.852	1.005 (0.992−1.019)	0.427
Multivariable (model 2)	0.986(0.976−0.986)	0.005	1.003 (0.994−1.012)	0.479	1.007 (0.997−1.018)	0.188	1.011 (0.993−1.030)	0.228

Model 1: adjusted for components of CHA_2DS_2-VASc score, warfarin and antiplatelet use, type of atrial fibrillation, BP measurement times, and systolic BP at the time closest to an event or at the end of follow-up. Model 2: adjusted for variables of model 1 plus creatinine clearance, body mass index, and hemoglobin (n=5596).

BP = blood pressure; TSubTR = time in subtarget range; TSupraTR = time in supratarget range; HR, hazard ratio (/1% increase); CI = confidence interval.

not a randomized controlled trial, a causal relation between systolic BP-TTR and adverse events could not be determined. Thus, precise optimal systolic BP target in patients with NVAF remains uncertain from this study.

In conclusion, the present results suggest that systolic BP-TTR of 110 to 130 mm Hg and BP-TSubTR, irrespective of target systolic BP of <110 or <120 mm Hg, would be useful for risk evaluation of cardiovascular death and thromboembolism, respectively, in patients with NVAF, independent of systolic BP-end.

Disclosures

Dr. Kodani received remuneration from Daiichi-Sankyo and Ono Pharmaceutical; Dr. Inoue received remuneration from Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi-Sankyo; Dr. Atarashi received remuneration from Daiichi-Sankyo; Dr. Okumura received remuneration from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, and Medtronic; Dr. Suzuki received research funding from Daiichi-Sankyo and Mitsubishi-Tanabe and remuneration from Bristol-Myers Squibb and Daiichi-Sankyo; and Dr. Yamashita received research funding from Bayer Healthcare, Bristol-Meyers Squibb, and Daiichi-Sankyo and remuneration from Bayer Healthcare-Myers Squibb, Daiichi-Sankyo, Novartis, Ono Pharmaceutical, Otsuka Pharmaceutical, and Toa Eiyo. The remining authors have no conflicts of interest to declare.

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A list of the participating physicians has been shown in References.[7,17–19] The J-RHYTHM registry is registered at the University Hospital Medicine Information Network Clinical Trials Registry (UMIN000001569).

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.06.045.

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