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ORIGINAL ARTICLE
Hypertension

Impact of baseline blood pressure on adverse outcomes in Japanese patients with non-valvular atrial fibrillation: the J-RISK AF

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Aims This study aimed to investigate the impact of baseline blood pressure (BP) on adverse outcomes in patients with atrial fibrillation (AF), using a pooled analysis performed on data from J-RISK AF, a large-scale cohort of Japanese patients with AF.

Methods and results Of the 16 918 patients from five major AF registries including the J-RHYTHM Registry, Fushimi AF Registry, Shinken Database, Keio interhospital Cardiovascular Studies, and Hokuriku-Plus AF Registry, 15 019 non-valvular AF (NVAF) patients with baseline BP values (age, 70.0 ± 11.0 years; men, 69.1%) were analysed. Incidence rates of adverse events were evaluated between patients divided into baseline systolic BP quartiles or at 150 mmHg. During the follow-up period of 730 days, ischaemic stroke, major bleeding, all-cause death, and cardiovascular death occurred in 277, 319, 718, and 275 patients, respectively. Hazard ratios (HRs) for ischaemic stroke and major bleeding were comparable among the quartiles, whereas HRs for all-cause and cardiovascular deaths in the lowest quartile with systolic BP <114 mmHg were significantly higher [HR 1.43, 95% confidence interval (CI) 1.13–1.81; and HR 1.47, 95% CI 1.01–2.12, respectively] than in the third quartile, even after adjusting for known confounding factors. In patients with a systolic BP of ≥150 mmHg, adjusted HR for major bleeding was significantly higher than that of <150 mmHg (HR 1.64, 95% CI 1.12–2.40).

Conclusion In Japanese patients with NVAF, a baseline systolic BP <114 mmHg was significantly associated with higher all-cause and cardiovascular mortality. In contrast, a systolic BP ≥150 mmHg was an independent risk factor for major bleeding.

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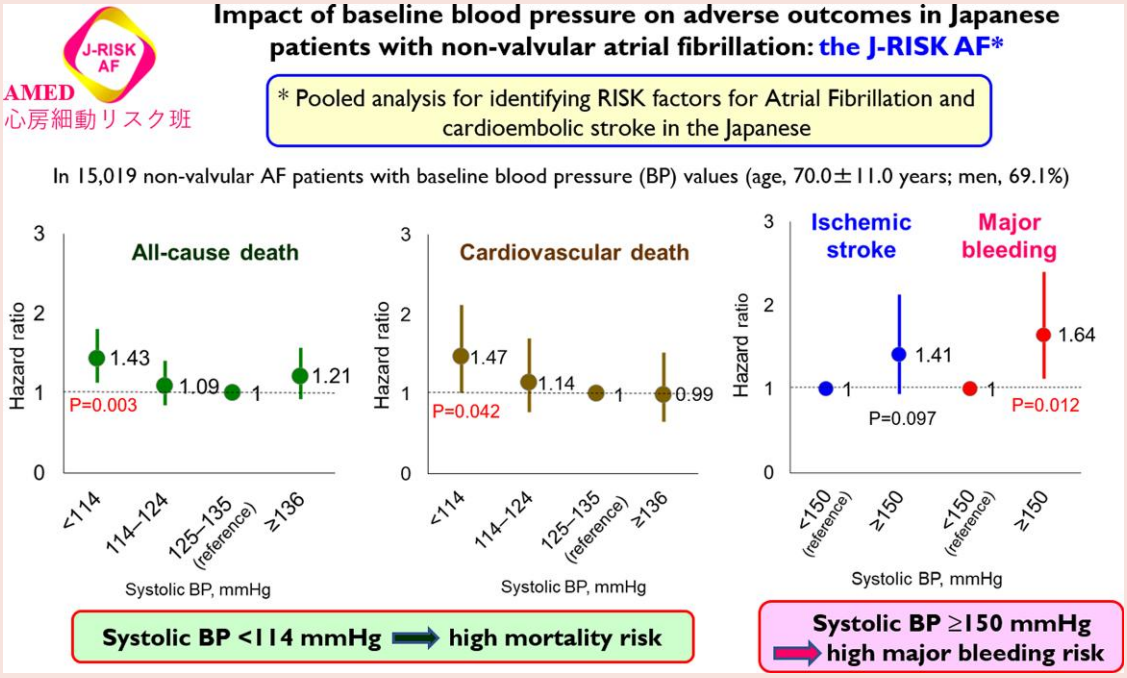
Graphical Abstract



Keywords Atrial fibrillation • Blood pressure • Thromboembolism • Major bleeding • Mortality

Introduction

Atrial fibrillation (AF) is a common arrhythmia known to be a risk factor for thrombo-embolism.[1,2] Hypertension is also a well-known risk factor for cardiovascular diseases[3–5] In patients with AF, hypertension is a risk factor for ischaemic stroke and major bleeding[6] and has been applied as a component of numerous conventional risk scores for patients with non-valvular AF (NVAF), such as $CHADS_2$,[7] CHA_2DS_2-VASc,[8] and HAS-BLED scores.[9] Although hypertension was a significant risk factor for ischaemic stroke in the primary analysis of the J-RISK AF,[10] it was not always identified as an independent predictor for ischaemic stroke.[11–15] Blood pressure (BP) control status may contribute to an increased risk of adverse events in patients with NVAF, rather than the prior diagnosis of hypertension. Indeed, in the J-RHYTHM Registry, hypertension or baseline BP quartile was not associated with thrombo-embolism, whereas a systolic BP ≥136 mmHg at the time closest to an event or at the end of follow-up (BP-end) was independently associated with a higher incidence of thromboembolism and major haemorrhage.[16] Furthermore, systolic BP visit-to-visit variability evaluated by standard deviation (SD) was also significantly associated with the incidence of thrombo-embolism, major haemorrhage, and all-cause death independent of BP-end.[17] In contrast, in the Fushimi AF Registry, a baseline systolic BP ≥150 mmHg was associated with a higher incidence of stroke/systemic embolism, haemorrhagic stroke, and major bleeding.[18]

Thus, we hypothesized that even baseline BP values may be associated with adverse outcomes in a larger number of study subjects. To investigate the impact of baseline BP values on adverse outcomes, a *post hoc* analysis was performed using pooled data from the J-RISK AF, a large-scale cohort of Japanese patients with AF.

Methods

Study design of the J-RISK AF

The J-RISK AF was a large-scale cohort study performed using pooled data from five major AF prospective registries in Japan: the J-RHYTHM Registry (7937 patients),[19] the Fushimi AF Registry (3749 patients),[20] the Shinken Database (2957 patients),[21] the Keio interhospital Cardiovascular Studies (783 patients),[22] and the Hokuriku-Plus AF Registry (1492 patients).[23] The study design and baseline patient characteristics have been reported elsewhere.[10,24] Briefly, the data from each registry were collected and integrated in March 2016, while those from the Keio Study were updated in April 2018. To balance the follow-up period among the registries, event data from individuals were collected for up to 730 days. After excluding patients with valvular AF (mitral stenosis and mechanical prosthetic valves) and those lacking complete data, 12 289 patients with NVAF were included in the main analysis.[10,24] This study was approved by the ethics committees of the Hirosaki University Graduate School of Medicine (2015-117, 2017-1051), the National Cerebral and Cardiovascular Center (M27-092-4), the National Hospital Organization Kyoto Medical Center (15-101), the Cardiovascular Institute (279), the Kanazawa University Graduate School of Medical Science (2035-1, 2460-1), and the Keio University School of Medicine (20120029) and was performed in accordance with ethics committee-approved research protocols in other institutes.

Seated brachial BP was measured in each patient at the time of enrolment using either the auscultatory method or an automated sphygmomanometer, as appropriate at each institution.

For the present *post hoc* analysis, patients with NVAF and baseline BP data were included. The primary endpoints were ischaemic stroke, major bleeding, all-cause death, and cardiovascular death. Among the cases with major bleeding, the number of intracranial haemorrhages was also counted. The diagnostic criteria for each event have been described elsewhere.[19–23]

Patients were divided into four groups according to the baseline systolic BP quartiles (lowest, <114; second, 114–124; third, 125–135, and highest, ≥136 mmHg), diastolic BP quartiles (lowest, <65; second, 65–71; third, 72–79, and highest, ≥80 mmHg) or two groups of baseline systolic BP <150 and ≥150 mmHg. The cut-off of systolic BP value of 150 mmHg was adopted based on a subanalysis of the Fushimi AF Registry.[18] In addition, the influence of baseline BP as a continuous variable on adverse events was evaluated. Furthermore, event rates and unadjusted hazard ratios (HRs) for adverse events were obtained by sex and anticoagulant use.

Statistical analyses

Data are presented as mean ± SD or number (percentage). To compare patient characteristics and 2-year event rates among the quartiles, a trend analysis was performed using the Cochran–Armitage test for categorical variables or the Jonckheere–Terpstra test for continuous variables, as appropriate. Differences in parameters between the two groups were analysed using Student's *t*-test for continuous variables and the χ^2 test or Fisher's exact test, as appropriate. Cumulative event-free rates were expressed by Kaplan–Meier curves and were compared among the quartiles using a log-rank test. Univariable and multivariable analyses with Cox proportional hazard models were performed to estimate the influence of baseline BP on adverse events. Hazard ratios and 95% confidence intervals for adverse events were calculated for each quartile compared with the third group (reference) or per 1 mmHg increase in baseline BP as a continuous variable. Explanatory variables for multivariable analysis were adopted from well-known risk factors including components of the CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or transient ischaemic attack (TIA), vascular disease (coronary artery disease), age 65–74 years, and female sex],[8] anticoagulant and antiplatelet use, and AF type (Model 1). An additional model (Model 2) was constructed using the variables of Model 1 plus cardiomyopathy, antihypertensive drug use, body mass index (BMI), estimated glomerular filtration rate (eGFR), and haemoglobin levels according to the difference in baseline patient characteristics (*Table 1*) and previous subanalyses of the J-RHYTHM Registry[25–27] and the Fushimi AF Registry.[28–30] Two-tailed *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using the SPSS software (version 23.0; IBM Corporation, Armonk, NY, USA).

Results

Of the 16 918 patients with AF initially enrolled in the J-RISK AF, 819 (4.8%) patients with valvular AF, 950 (5.6%) without baseline BP measurement, and 130 (0.8%) missing other essential variables were excluded. Consequently, a total of 15 019 patients (age, 70.0 ± 11.0 years; men, 69.1%) were included in this analysis.

Patient characteristics and medications

The characteristics of the 15 019 patients and their medications are listed in Supplementary material online, *Table S1*. Overall, 72% of the patients had hypertension, and the mean baseline systolic and diastolic BP values were 125.8 ± 17.5 and 73.1 ± 11.9 mmHg, respectively. Patient characteristics and medications in the baseline systolic BP quartiles are given in *Table 1*. Age, systolic and diastolic BP values, prevalence of woman, hypertension, and diabetes mellitus showed significant increasing trends across the quartiles, resulting in higher risk scores for the higher quartiles. In contrast, the prevalence of heart failure, coronary artery disease, and cardiomyopathy showed inverse trends across the quartiles. There was no significant trend in the prevalence of dyslipidemia, history of stroke, TIA, bleeding, or catheter ablation (*Table 1*).

Baseline systolic and diastolic blood pressure quartiles on adverse outcomes

During the 2-year follow-up period, ischaemic stroke, major bleeding, all-cause death, and cardiovascular death occurred in 277, 319, 718, and 275 patients, respectively. The corresponding incidence rates of these events were 1.0, 1.2, 2.7, and 1.0/100 person years, respectively, during a total follow-up period of 26 639 person years. Two-year event rates are summarized in *Table 2*. All-cause and cardiovascular mortality showed significant trends across systolic and diastolic BP quartiles. The Kaplan–Meier curves of the baseline systolic BP quartiles for each event are shown in *Figure 1*.

For baseline systolic BP, the HRs for ischaemic stroke and major bleeding were comparable among the quartiles, whereas the HRs for all-cause and cardiovascular deaths were significantly higher in the lowest quartile than in the third quartile in the unadjusted model (*Table 3*). This significance was consistent after adjusting for the confounding factors (*Table 4* and *Figure 2*). In contrast, for baseline diastolic BP, HRs for ischaemic stroke, all-cause death, and cardiovascular death were significantly higher in the lowest quartile than in the third quartile in the unadjusted model (*Table 3*), whereas only the HR for ischaemic stroke in the highest quartile was significantly higher in the fully adjusted model (*Table 5*).

When baseline BP values were analysed as a continuous variable, each 1 mmHg increase in systolic BP was significantly associated with an increased incidence of major bleeding in the fully adjusted model (*Table 4*). In contrast, diastolic BP was not associated with any events after adjusting for confounding factors (*Table 5*).

Baseline systolic blood pressure ≥150 mmHg on adverse outcomes

The patient characteristics and medications in the two groups with baseline systolic BP <150 and ≥150 mmHg are listed in Supplementary material online, *Table S1*. Age, systolic and diastolic BP values, prevalence of women, hypertension, history of stroke, or TIA were significantly higher in the systolic BP ≥150 mmHg group than in the systolic BP <150 mmHg group, resulting in higher risk scores for the systolic BP ≥150 mmHg group. In contrast, the prevalence of heart failure and cardiomyopathy was lower in the group with systolic BP ≥150 mmHg group than in the group with systolic BP <150 mmHg (see Supplementary material online, *Table S1*). The 2-year event rates of ischaemic stroke and major bleeding were significantly higher in the systolic BP ≥150 mmHg group than in the systolic BP <150 mmHg group (see Supplementary material online, *Table S2*). The Kaplan–Meier curves of the two groups for each event are shown in *Figure 3*. Unadjusted HRs for ischaemic stroke and major bleeding were significantly higher in the systolic BP ≥150 mmHg group than in the systolic BP <150 mmHg group, whereas only the HR for major bleeding was significantly higher after adjusting for confounding factors (*Table 6*).

Baseline systolic blood pressure and sex on adverse outcomes

All-cause and cardiovascular mortality showed significant inverse trends across baseline systolic BP quartiles in men but not in women. The 2-year event rate of major bleeding showed a significant increasing trend across systolic BP quartiles only in women (see Supplementary material online, *Table S3*). In contrast, there was no significant difference in any event rates between the groups of systolic BP <150 and ≥150 mmHg (see Supplementary material online, *Table S4*). Unadjusted HRs are summarized in Supplementary material online, *Table S5*. There were significant interactions between baseline systolic BP and sex for all-cause and cardiovascular deaths (see Supplementary material online, *Table S5*).

Baseline systolic blood pressure and anticoagulant use on adverse outcomes

The 2-year event rate of ischaemic stroke was significantly lower, while the rate of major bleeding was significantly higher, in patients receiving

Table 1 Patient characteristics in baseline systolic blood pressure quartiles

	Lowest quartile	Second quartile	Third quartile	Highest quartile	*P*-value for trend
Systolic BP range, mmHg	<114 (*n* = 3614)	114–124 (*n* = 3817)	125–135 (*n* = 3502)	≥136 (*n* = 4086)	
Age, years	69.6 ± 11.9	69.3 ± 11.3	69.9 ± 10.8	71.0 ± 10.0	<0.001
<65	1076 (29.8)	1161 (30.4)	988 (28.2)	989 (24.2)	
65–74	1190 (32.9)	1338 (35.1)	1221 (34.9)	1494 (36.6)	<0.001
≥75	1348 (37.3)	1318 (34.5)	1293 (36.9)	1603 (39.2)	
Sex, men	2535 (70.1)	2696 (70.6)	2452 (70.0)	2701 (66.1)	<0.001
Atrial fibrillation type					
Paroxysmal	1496 (41.4)	1725 (45.2)	1550 (44.3)	1970 (48.2)	<0.001
Persistent/permanent	2118 (58.6)	2092 (54.8)	1952 (55.7)	2116 (51.8)	
Comorbidities					
Heart failure	1188 (32.9)	970 (25.4)	803 (22.9)	813 (19.9)	<0.001
Hypertension	2188 (60.5)	2363 (61.9)	2419 (69.1)	3832 (93.8)	<0.001
Diabetes mellitus	671 (18.6)	709 (18.6)	720 (20.6)	853 (20.9)	0.002
Dyslipidaemia	1024 (31.3)	1118 (32.1)	1008 (31.7)	1207 (32.6)	0.333
Coronary artery disease	483 (13.4)	462 (12.1)	432 (12.3)	438 (10.7)	0.001
Cardiomyopathy	354 (10.1)	243 (6.6)	183 (5.5)	173 (4.4)	<0.001
History of stroke or TIA	511 (14.1)	520 (13.6)	501 (14.3)	550 (13.5)	0.568
History of bleeding	137 (3.9)	126 (3.4)	133 (3.9)	137 (3.4)	0.549
History of catheter ablation	106 (7.1)	92 (6.9)	88 (7.1)	89 (5.8)	0.178
$CHADS_2$ score	1.6 ± 1.3	1.6 ± 1.3	1.7 ± 1.3	1.9 ± 1.2	<0.001
CHA_2DS_2-VASc score	2.7 ± 1.7	2.7 ± 1.7	2.9 ± 1.7	3.1 ± 1.6	<0.001
Systolic BP, mmHg	103.9 ± 7.6	119.7 ± 3.1	129.9 ± 2.9	147.3 ± 11.1	<0.001
Diastolic BP, mmHg	63.7 ± 9.5	71.2 ± 9.0	75.5 ± 9.3	81.1 ± 11.7	<0.001
Body mass index, kg/m^2 (*n* = 13 371)	22.8 ± 3.7	23.5 ± 3.6	23.8 ± 3.5	23.9 ± 3.7	<0.001
eGFR, mL/min/1.73 m2 (*n* = 13 625)	61.3 ± 21.7	63.1 ± 19.9	63.5 ± 20.6	62.7 ± 20.3	<0.001
Haemoglobin, g/dL (*n* = 13 603)	13.3 ± 1.9	13.6 ± 1.8	13.6 ± 1.8	13.6 ± 1.9	<0.001
Medications					
Anticoagulant	2671 (73.9)	2789 (73.1)	2599 (74.2)	2929 (71.7)	0.071
Warfarin	2372 (65.6)	2462 (64.5)	2260 (64.5)	2532 (62.0)	0.002
PT-INR (*n* = 9337)	1.88 ± 0.53	1.86 ± 0.48	1.87 ± 0.51	1.82 ± 0.52	<0.001
DOAC	305 (8.4)	332 (8.7)	340 (9.7)	397 (9.7)	0.022
Antiplatelet	926 (25.6)	951 (24.9)	910 (26.0)	1064 (26.0)	0.453
Aspirin	812 (22.5)	831 (21.8)	786 (22.4)	894 (21.9)	0.711
Antihypertensive drugs	2178 (60.3)	2316 (60.7)	2308 (65.9)	2613 (64.0)	<0.001
Na channel blockers	622 (17.2)	756 (19.8)	801 (22.9)	890 (21.8)	<0.001
β-blockers	896 (24.8)	725 (19.0)	631 (18.0)	708 (17.3)	<0.001
K channel blockers	144 (4.0)	85 (2.2)	64 (1.8)	80 (2.0)	<0.001
Ca channel blockers	602 (16.7)	643 (16.8)	550 (15.7)	585 (14.3)	0.002
Digitalis	399 (11.0)	376 (9.9)	379 (10.8)	421 (10.3)	0.584
Statin	680 (20.8)	767 (22.0)	725 (22.8)	785 (21.2)	0.608

Data are the number of patients (%) or mean ± SD.
BP, blood pressure; TIA, transient ischaemic 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; eGFR, estimated glomerular filtration rate; PT-INR, prothrombin time international normalized ratio; DOAC, direct oral anticoagulant.

anticoagulant than in those not receiving anticoagulant only in the highest systolic BP quartile (≥136 mmHg) (*Figure 4*). In contrast, the rates of all-cause death were significantly higher in patients not receiving anticoagulant than in those receiving anticoagulant in all systolic BP quartiles (*Figure 4*). Crude HRs for events in baseline systolic BP quartiles and anticoagulant use are summarized in Supplementary material online, *Table S6*. There was no interaction between baseline systolic BP and anticoagulant use for all events (see Supplementary material online, *Table S6*).

Discussion

The major findings of this study are as follows. First, the lowest baseline systolic BP quartile (<114 mmHg) was associated with significantly higher

Table 2 Two-year event rates in baseline systolic and diastolic blood pressure quartiles

	Lowest quartile	Second quartile	Third quartile	Highest quartile	*P*-value for trend
Systolic BP range, mmHg	<114 (*n* = 3614)	114–124 (*n* = 3817)	125–135 (*n* = 3502)	≥136 (*n* = 4086)	
Ischaemic stroke	67 (1.9%)	64 (1.7%)	62 (1.8%)	84 (2.1%)	0.441
Major bleeding	70 (1.9%)	73 (1.9%)	77 (2.2%)	99 (2.4%)	0.090
Intracranial haemorrhage	22 (0.6%)	25 (0.7%)	25 (0.7%)	38 (0.9%)	0.090
All-cause death	249 (6.9%)	160 (4.2%)	131 (3.7%)	178 (4.4%)	<0.001
Cardiovascular death	97 (2.7%)	63 (1.7%)	49 (1.4%)	66 (1.6%)	0.001
Diastolic BP range, mmHg	<65 (*n* = 3548)	65–71 (*n* = 3368)	72–79 (*n* = 3297)	≥80 (*n* = 4793)	
Ischaemic stroke	77 (2.2%)	61 (1.8%)	46 (1.4%)	93 (1.9%)	0.365
Major bleeding	83 (2.3%)	76 (2.3%)	65 (2.0%)	94 (2.0%)	0.174
Intracranial haemorrhage	25 (0.7%)	31 (0.9%)	24 (0.7%)	30 (0.6%)	0.437
All-cause death	288 (8.1%)	136 (4.0%)	125 (3.8%)	169 (3.5%)	<0.001
Cardiovascular death	106 (3.0%)	58 (1.7%)	40 (1.2%)	71 (1.5%)	0.001

Data are the number of patients (%).
BP, blood pressure.

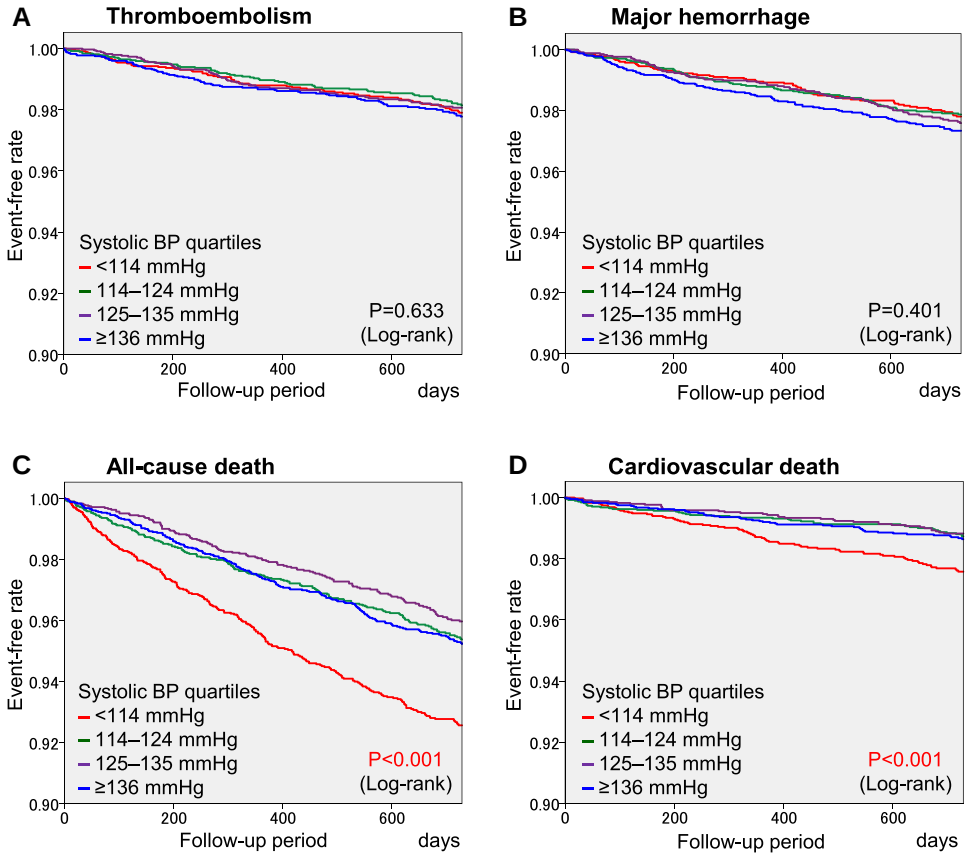


Figure 1 Kaplan–Meier curves of baseline systolic blood pressure quartiles for adverse events. (*A*) Ischaemic stroke, (*B*) major bleeding, (*C*) all-cause death, and (*D*) cardiovascular death. *P*-values: comparison among baseline systolic blood pressure quartiles using the log-rank test. BP, blood pressure.

Table 3 Hazard ratios for adverse events in baseline systolic and diastolic blood pressure quartiles (univariable analysis)

	Ischaemic stroke		Major bleeding		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 quartiles								
Lowest quartile (<114 mmHg)	1.07 (0.76–1.52)	0.684	0.90 (0.65–1.25)	0.534	1.89 (1.53–2.33)	<0.001	1.97 (1.40–2.78)	<0.001
Second quartile (114–124 mmHg)	0.96 (0.68–1.37)	0.830	0.88 (0.64–1.22)	0.449	1.14 (0.90–1.43)	0.272	1.20 (0.83–1.75)	0.335
Third quartile (125–135 mmHg)	Reference	—	Reference	—	Reference	—	Reference	—
Highest quartile (≥136 mmHg)	1.18 (0.85–1.63)	0.335	1.12 (0.83–1.50)	0.474	1.18 (0.94–1.47)	0.158	1.17 (0.81–1.69)	0.410
Systolic BP (per 1 mmHg increase)	1.004 (0.997–1.010)	0.283	1.007 (1.001–1.014)	0.022	0.990 (0.986–0.994)	<0.001	0.988 (0.981–0.995)	0.001
Diastolic BP quartiles								
Lowest quartile (<65 mmHg)	1.58 (0.10–2.28)	0.014	1.20 (0.87–1.67)	0.264	2.17 (1.76–2.67)	<0.001	2.50 (1.74–3.60)	<0.001
Second quartile (65–71 mmHg)	1.30 (0.89–1.90)	0.182	1.14 (0.82–1.59)	0.433	1.06 (0.84–1.36)	0.616	1.42 (0.95–2.12)	0.091
Third quartile (72–79 mmHg)	Reference	—	Reference	—	Reference	—	Reference	—
Highest quartile (≥80 mmHg)	1.39 (0.98–1.99)	0.065	0.99 (0.73–1.36)	0.972	0.93 (0.74–1.17)	0.541	1.22 (0.83–1.79)	0.323
Diastolic BP (per 1 mmHg increase)	0.993 (0.983–1.003)	0.184	0.992 (0.983–1.002)	0.104	0.968 (0.962–0.974)	<0.001	0.972 (0.962–0.982)	<0.001

BP, blood pressure; HR, hazard ratio; CI, confidence interval.

Table 4 Hazard ratios for adverse events in baseline systolic blood pressure quartiles (multivariable analysis)

	Ischaemic stroke		Major bleeding		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
Model 1								
Lowest quartile (<114 mmHg)	1.10 (0.78–1.56)	0.585	0.89 (0.64–1.23)	0.487	1.74 (1.40–2.15)	<0.001	1.74 (1.23–2.46)	0.002
Second quartile (114–124 mmHg)	1.02 (0.72–1.44)	0.930	0.91 (0.66–1.25)	0.550	1.15 (0.92–1.45)	0.227	1.19 (0.82–1.73)	0.355
Third quartile (125–135 mmHg)	Reference	—	Reference	—	Reference	—	Reference	—
Highest quartile (≥136 mmHg)	1.10 (0.79–1.54)	0.575	1.09 (0.81–1.48)	0.569	1.16 (0.92–1.46)	0.211	1.14 (0.78–1.65)	0.503
Systolic BP (per 1 mmHg increase)	1.001 (0.994–1.008)	0.734	1.007 (1.001–1.014)	0.030	0.992 (0.988–0.996)	<0.001	0.991 (0.984–0.998)	0.010
Model 2								
Lowest quartile (<114 mmHg)	0.97 (0.67–1.42)	0.893	0.81 (0.57–1.17)	0.814	1.43 (1.13–1.81)	0.003	1.47 (1.01–2.12)	0.042
Second quartile (114–124 mmHg)	1.03 (0.71–1.50)	0.877	0.91 (0.64–1.30)	0.617	1.09 (0.85–1.41)	0.508	1.14 (0.77–1.70)	0.512
Third quartile (125–135 mmHg)	Reference	—	Reference	—	Reference	—	Reference	—
Highest quartile (≥136 mmHg)	1.07 (0.73–1.56)	0.723	1.12 (0.79–1.60)	0.525	1.21 (0.93–1.57)	0.151	0.99 (0.65–1.52)	0.966
Systolic BP (per 1 mmHg increase)	1.002 (0.994–1.010)	0.615	1.010 (1.003–1.017)	0.009	0.997 (0.992–1.002)	0.218	0.993 (0.985–1.000)	0.054

BP, blood pressure; HR, hazard ratio; CI, confidence interval.
Model 1: adjusted for the components of CHA_2DS_2-VASc score, anticoagulant and antiplatelet use, atrial fibrillation type.
Model 2: adjusted for the variables of Model 1 plus cardiomyopathy, antihypertensive drug use, body mass index, estimated glomerular filtration rate, and haemoglobin levels ($n = 11\,827$).

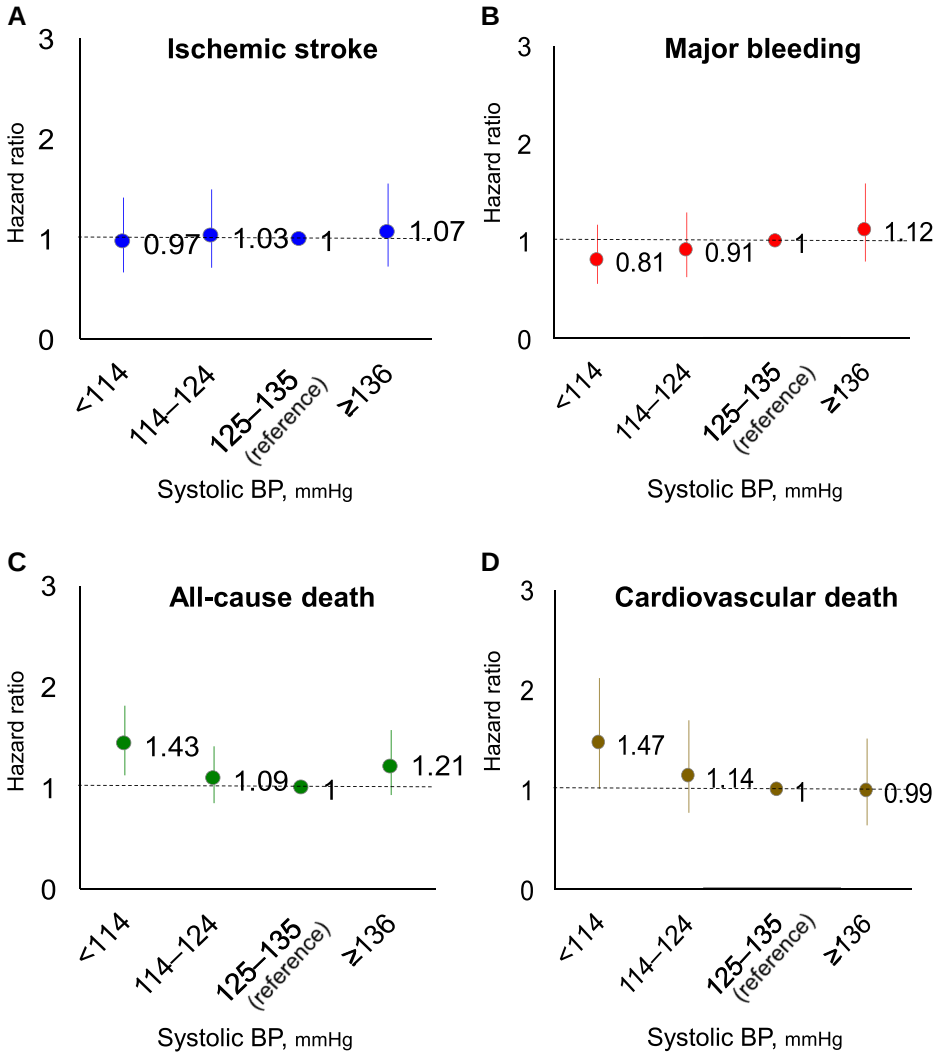


Figure 2 Hazard ratios for adverse events in baseline systolic blood pressure quartiles. (*A*) Ischaemic stroke, (*B*) major bleeding, (*C*) all-cause death, and (*D*) cardiovascular death, hazard ratios are adjusted for components of CHA_2DS_2-VASc score, anticoagulant and antiplatelet use, atrial fibrillation type, cardiomyopathy, antihypertensive drug use, body mass index, estimated glomerular filtration rate, and haemoglobin levels ($n = 11\,827$). BP, blood pressure.

all-cause and cardiovascular mortality. Second, a baseline systolic BP ≥150 mmHg was an independent risk factor for major bleeding. Third, a baseline diastolic BP ≥80 mmHg was significantly associated with an increased risk of ischaemic stroke in Japanese patients with NVAF.

Impact of low baseline blood pressure on mortality

In the present study, a baseline systolic BP <114 mmHg was independently associated with all-cause and cardiovascular deaths in Japanese patients with NVAF. This is a novel insight from this large cohort of Japanese patients with AF. Previous subanalyses of the J-RHYTHM Registry[16] and the Fushimi AF Registry,[18] component registries of the J-RISK AF, focused only on thrombo-embolism and major bleeding. Since several previous studies have suggested that a lower systolic BP is related to a higher risk of all-cause mortality in patients with AF,[31–34] we further evaluated the impact of a low BP on mortality. Although our results support those of previous studies, the association of low BP with a high risk of all-cause and cardiovascular deaths seems complicated. Most previous studies were conducted in patients with heart failure[32,33] and indicated that patients with a lower systolic BP tended to have heart failure, resulting in a worse prognosis.[34,35] In 187 106 patients with Type 2 diabetes and no previous cardiovascular disease from the Swedish national database, the lowest systolic BP group (110–119 mmHg) was associated with a significantly increased risk of heart failure and total mortality.[36] It was discussed that the association between low BP and increased mortality could be caused by concomitant diseases rather than antihypertensive treatment.[36] In a large-scale population-based study to estimate individual patient BP trajectories for 20 years before death,[37] systolic and diastolic BP values decreased from 10 to 3 years before death, with steeper decreases in the last 2 years of life. Decreases in BP values before death were present in individuals not treated for hypertension but were the steepest in patients

Table 5 Hazard ratios for adverse events in baseline diastolic blood pressure quartiles (multivariable analysis)

	Ischaemic stroke		Major bleeding		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
Model 1								
Lowest quartile (<65 mmHg)	1.35 (0.93–1.94)	0.116	1.01 (0.73–1.40)	0.969	1.52 (1.23–1.88)	<0.001	1.73 (1.20–2.50)	0.003
Second quartile (65–71 mmHg)	1.26 (0.86–1.84)	0.245	1.07 (0.76–1.48)	0.710	0.97 (0.76–1.23)	0.781	1.29 (0.86–1.93)	0.220
Third quartile (72–79 mmHg)	Reference	—	Reference	—	Reference	—	Reference	—
Highest quartile (≥80 mmHg)	1.45 (1.02–2.07)	0.040	1.02 (0.75–1.41)	0.882	1.09 (0.86–1.38)	0.465	1.42 (0.96–2.10)	0.077
Diastolic BP (per 1-mmHg increase)	1.000 (0.990–1.010)	0.991	0.999 (0.990–1.009)	0.905	0.986 (0.980–0.993)	<0.001	0.990 (0.980–1.000)	0.059
Model 2								
Lowest quartile (<65 mmHg)	1.42 (0.95–2.13)	0.091	0.85 (0.59–1.23)	0.377	1.20 (0.95–1.51)	0.137	1.38 (0.93–2.04)	0.113
Second quartile (65–71 mmHg)	1.28 (0.83–1.96)	0.261	1.07(0.74–1.55)	0.713	0.97 (0.75–1.27)	0.840	1.22 (0.80–1.88)	0.357
Third quartile (72–79 mmHg)	Reference	—	Reference	—	Reference	—	Reference	—
Highest quartile (≥80 mmHg)	1.57 (1.06–2.34)	0.026	1.11 (0.77–1.56)	0.584	1.29 (0.99–1.67)	0.059	1.47 (0.96–2.25)	0.076
Diastolic BP (per 1 mmHg increase)	0.999 (0.987–1.011)	0.838	1.007 (0.996–1.019)	0.207	0.999 (0.992–1.006)	0.760	0.997 (0.986–1.008)	0.624

BP, blood pressure; HR, hazard ratio; CI, confidence interval.
Model 1: adjusted for the components of CHA_2DS_2-VASc score, anticoagulant and antiplatelet use, atrial fibrillation type.
Model 2: adjusted for the variables of Model 1 plus cardiomyopathy, antihypertensive drug use, body mass index, estimated glomerular filtration rate, and haemoglobin levels ($n = 11\,818$).

with hypertension, dementia, heart failure, and late-life weight loss.[37] Accordingly, these clinical conditions may have become confounders for all-cause death.

In the present study, patients in the lower systolic BP quartiles were more likely to have poorer clinical conditions, such as older age, lower BMI, eGFR, and haemoglobin levels, and more prevalent coronary artery disease and cardiomyopathy (*Table 1*). However, even after adjusting for these factors in Model 2, the HRs for all-cause and cardiovascular deaths in the lowest quartile remained significantly higher. Therefore, a baseline systolic BP <114 mmHg could be an independent indicator of a high risk of mortality. A recent subanalysis of the J-RHYTHM Registry further demonstrated that an increase in systolic BP time in a subtarget range of <110 mmHg during the follow-up period tended to be associated with an increased risk of cardiovascular death.[38] These results suggested that a consistent low systolic BP may contribute to an increased risk of mortality. In addition, the impact of low baseline BP on mortality was stronger in men than in women (see Supplementary material online, *Table S6*).

In the present study, β-blocker use was more frequent in the lower baseline systolic BP quartiles. Although β-blocker use is known to contribute to a reduced risk of mortality in patients with heart failure, a protective effect of β-blockers on mortality was not observed in the present study. This is consistent with a previous meta-analysis of patients with heart failure and AF.[39] However, it is difficult to recommend that β-blocker use should be avoided in patients with low systolic BP values from this observational study because information regarding the degree and type of heart failure such as the New York Heart Association class and/or left ventricular ejection fraction was lacking in the J-RISK AF.

Lower diastolic BP is known to be associated with reduced coronary blood flow.[40] Therefore, lower diastolic BP values could be related to adverse outcomes, even in patients with AF. In the present study, the HRs for all-cause and cardiovascular deaths in the lowest diastolic BP quartile were significantly higher than those in the third quartile in the unadjusted model and adjusted Model 1 (*Tables 3* and *5*), as well as in systolic BP. However, this statistical significance disappeared after adjusting for BMI, eGFR, and haemoglobin levels in Model 2. Therefore, these factors may contribute to death more strongly than baseline diastolic BP values. In addition, unknown factors not evaluated in this study such as cancer might have affected mortality.

Impact of high baseline blood pressure on adverse events

In the present study, the highest baseline systolic BP quartile (≥136 mmHg) was not significantly associated with any adverse events. This is consistent with previous results of analyses of the J-RHYTHM Registry.[16] One of the reasons might be that the mean baseline systolic BP values were well-controlled to 125.8 mmHg in this study's subjects. Therefore, event risks in the subgroups of patients with an excessively high systolic BP of ≥150 mmHg other than quartiles were additionally evaluated. Consequently, a baseline systolic BP ≥150 mmHg was an independent risk factor for major bleeding but not for ischaemic stroke or mortality. This is consistent with previous results of the Fushimi AF Registry.[18] Baseline systolic BP per 1 mmHg increase also showed a significantly increased risk of major bleeding. Our results indicated that the patients with a baseline systolic BP ≥150 mmHg were at a higher risk of major bleeding (*Figure 3*) and the rate of major bleeding differed between patients with and without oral anticoagulant in the highest quartile (≥136 mmHg) (*Figure 4*). Another recent study from the Swedish Primary Care Cardiovascular Database of Skaraborg showed that the baseline systolic BP values between 145 and 180 represented a significantly higher risk for haemorrhagic stroke compared with a value of <130 mmHg in patients with AF and hypertension prior to the

Table 6 Hazard ratios for adverse events in baseline systolic blood pressure ≥150 mmHg

	Ischaemic stroke		Major bleeding		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
Univariable (unadjusted)								
Systolic BP <150 mmHg	Reference	—	Reference	—	Reference	—	Reference	—
Systolic BP ≥150 mmHg	1.62 (1.15–2.28)	0.006	1.51 (1.09–2.09)	0.014	1.13 (0.89–1.45)	0.308	0.98 (0.65–1.49)	0.927
Multivariable (Model 1)								
Systolic BP <150 mmHg	Reference	—	Reference	—	Reference	—	Reference	—
Systolic BP ≥150 mmHg	1.41 (0.99–2.00)	0.058	1.46 (1.04–2.04)	0.028	1.07 (0.83–1.37)	0.614	0.92 (0.60–1.41)	0.702
Multivariable (Model 2)								
Systolic BP <150 mmHg	Reference	—	Reference	—	Reference	—	Reference	—
Systolic BP ≥150 mmHg	1.41 (0.94–2.13)	0.097	1.64 (1.12–2.40)	0.012	1.17 (0.89–1.54)	0.309	0.82 (0.51–1.33)	0.430

BP, blood pressure; HR, hazard ratio; CI, confidence interval.
Model 1: adjusted for the components of CHA_2DS_2-VASc score, anticoagulant and antiplatelet use, atrial fibrillation type.
Model 2: adjusted for the variables of Model 1 plus cardiomyopathy, antihypertensive drug use, body mass index, estimated glomerular filtration rate, and haemoglobin levels ($n = 11\,827$).

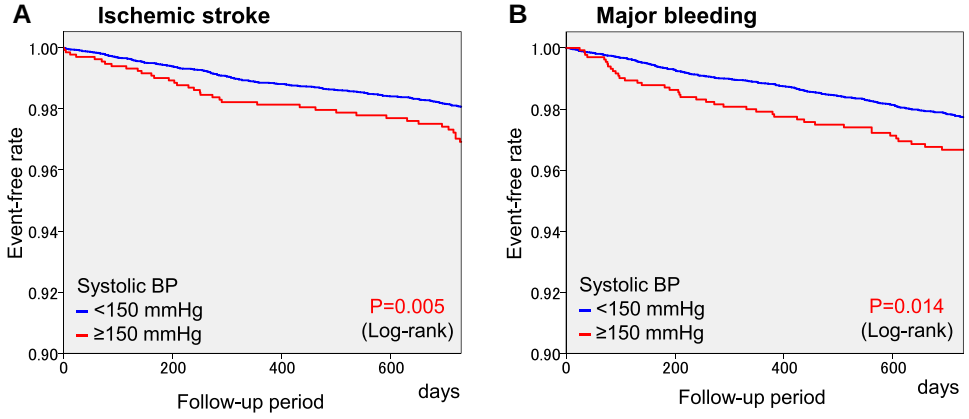


Figure 3 Kaplan–Meier curves of baseline systolic blood pressure groups for adverse events. (*A*) Ischaemic stroke and (*B*) major bleeding. *P*-values: comparison between baseline systolic blood pressure <150 and ≥150 mmHg using the log-rank test. BP, blood pressure.

initiation of anticoagulants.[41] Further prospective studies are needed to determine an optimal systolic BP target value for patients with AF before and during anticoagulation therapy.

In contrast, the highest baseline diastolic BP quartile (≥80 mmHg) was significantly associated with ischaemic stroke in the adjusted models. Moreover, HRs for ischaemic stroke and cardiovascular death followed a J-curve. This phenomenon of diastolic BP has often been observed in non-AF patient cohorts.[42–44]

Based on the present results, we propose that even baseline BP values can be used for risk evaluation in patients with NVAF, that is, lower systolic BP for mortality, higher systolic BP for major bleeding, and higher diastolic BP for ischaemic stroke.

Limitations

The present study has several limitations that should be mentioned. First, this was a *post hoc* analysis of data from the J-RIKS AF[10,24] and was therefore only hypothesis-generating in nature. Thus, the optimal target BP values could not be determined from the present analyses. Second, since all five registries were conducted in Japan, all study subjects in the J-RISK AF were Japanese, except a very small number of foreign people who live in Japan. Therefore, the present results may not be applicable to other racial/ethnic groups. Third, although HRs were fully adjusted for known confounding factors in the multivariable analysis, other unknown factors that were not measured in the present study could have affected the results. Fourth, the definition of hypertension was slightly different among the registries, as described in our previous paper.[10] The J-RHYTHM Registry[19] and the Keio interhospital Cardiovascular Studies[22] included a history of hypertension, but the other registries did not. However, the definition did not reflect the present results because only baseline BP values, not a diagnosis of hypertension, were used in this subanalysis. Fifth, BP measurement methods were not standardized. Blood pressure values were obtained using the auscultatory method or an automated sphygmomanometer, as appropriate for daily clinical practice in participant institutions in each registry. Blood pressure measurement timing (morning, afternoon, or exact time) was also unknown. Sixth, changes

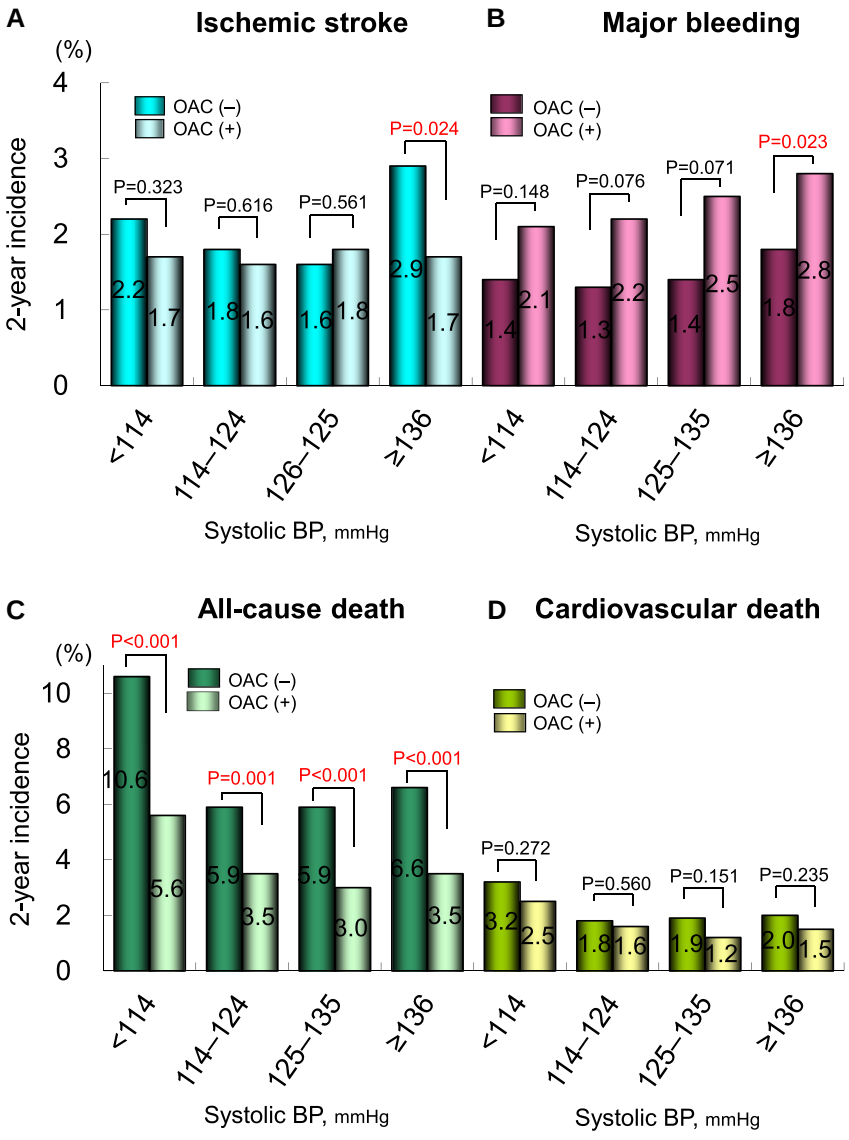


Figure 4 Two-year incidence of adverse events in baseline systolic blood pressure quartiles and anticoagulant use. (*A*) Ischaemic stroke, (*B*) major bleeding, (*C*) all-cause death, (*D*) cardiovascular death, *P*-values, comparison between OAC (–) and OAC (+). BP, blood pressure; OAC, oral anticoagulant.

in antihypertensive drug use, dosage, and adherence to drugs during the follow-up period were not considered in the analysis. Finally, only baseline BP values were available for the J-RISK AF. The impact of BP values at the time closest to an event, visit-to-visit BP variability, and BP consistency during the follow-up period was evaluated only in the J-RHYTHM Registry,[16,17,38] in which visit-to-visit BP values were collected.

Conclusions

In Japanese patients with NVAF, we found that a low baseline systolic BP <114 mmHg was significantly associated with higher all-cause and cardiovascular mortality. Furthermore, an excessively high systolic BP ≥150 mmHg was an independent risk factor for major bleeding.

Lead author biography

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Internal Medicine and Cardiology, NMS Tama Nagayama Hospital. His specialty and interests are pharmacotherapy and anticoagulation therapy in atrial fibrillation, ischaemic preconditioning and pharmacological cardioprotection, and hypertension and diabetes as risk factors of cardiac diseases.

Data availability

The data underlying this article will not be shared.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: E.K. received remuneration from Daiichi-Sankyo and Ono Pharmaceutical. H.T. received research funding from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Pfizer, and Speakers' Bureau/Honorarium from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. M.A. received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. S.S. received research funding from Daiichi-Sankyo and Mitsubishi-Tanabe, and Speakers' Bureau/Honorarium from Daiichi-Sankyo. K.H. received Speakers' Bureau/Honorarium from Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. M.S. received lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb, Astellas Pharma, Sanofi, and research funding from Takeda Pharmaceutical. M.G. received Speakers' Bureau/Honorarium from Daiichi-Sankyo, Abbott, and Japan Life Line. T.Y. received research funding from Daiichi-Sankyo, and Speakers' Bureau/Honorarium from Daiichi-Sankyo, Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Novartis Pharma, Otsuka Pharmaceutical, and Toa Eiyo. M.I. received Speakers' Bureau/Honorarium from Daiichi-Sankyo, Otsuka Pharmaceutical, Chugai Pharmaceutical, and Pfizer. K.T. received Speakers' Bureau/Honorarium from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb. T.O. received Speakers' Bureau/Honorarium from Bayer and Daiichi-Sankyo. K.O. received Speakers' Bureau/Honorarium from Boehringer Ingelheim, Bayer, Daiichi-Sankyo, Bristol-Myers Squibb, and Pfizer.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham tudy. *Stroke* 1991;**22**:983–988.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;**155**:469–473.
3. Kannel WB, Dawber TR, Friedman GD, Glennon WE, McNamara PM. Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease; the Framingham study. *Ann Intern Med* 1964;**61**:888–899.
4. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008;**371**:1513–1518.
5. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD III, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA III, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stockl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2224–2260.
6. Lip GY, Frison L, Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;**28**:752–759.
7. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
8. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;**137**:263–272.
9. 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.
10. Okumura K, Tomita H, Nakai M, Kodani E, Akao M, Suzuki S, Hayashi K, Sawano M, Goya M, Yamashita T, Fukuda K, Ogawa H, Tsuda T, Isobe M, Toyoda K, Miyamoto Y, Miyata H, Okamura T, Sasahara Y. Risk factors associated with ischemic stroke in Japanese patients with nonvalvular atrial fibrillation. *JAMA Netw Open* 2020;**3**:e202881.
11. The Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. *Arch Intern Med* 1996;**156**:409–416.
12. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. *Neurology* 1999;**53**:1319–1327.
13. 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.
14. 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.
15. 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. 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**:e002015.
16. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Otsuka T, Tomita H, Origasa H. Impact of blood pressure control on thromboembolism and major hemorrhage in patients with nonvalvular atrial fibrillation: a subanalysis of the J-RHYTHM Registry. *J Am Heart Assoc* 2016;**5**:e004075.
17. Kodani E, Inoue H, Atarashi H, Okumura K, Yamashita T, Otsuka T, Origasa H. Impact of blood pressure visit-to-visit variability on adverse events in patients with nonvalvular atrial fibrillation: subanalysis of the J-RHYTHM Registry. *J Am Heart Assoc* 2021;**10**:e018585.
18. Ishii M, Ogawa H, Unoki T, An Y, Iguchi M, Masunaga N, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Akao M. Relationship of hypertension and systolic blood pressure with the risk of stroke or bleeding in patients with atrial fibrillation: the Fushimi AF Registry. *Am J Hypertens* 2017;**30**:1073–1082.
19. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM Registry. *Circ J* 2011;**75**:1328–1333.
20. Akao M, Chun YH, Wada H, Esato M, Hashimoto T, Abe M, Hasegawa K, Tsuji H, Furuke K. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. *J Cardiol* 2013;**61**:260–266.
21. Suzuki S, Yamashita T, Otsuka T, Sagara K, Uejima T, Oikawa Y, Yajima J, Koike A, Nagashima K, Kirigaya H, Ogasawara K, Sawada H, Aizawa T. Recent mortality of Japanese patients with atrial fibrillation in an urban city of Tokyo. *J Cardiol* 2011;**58**:116–123.
22. Ikemura N, Kohsaka S, Kimura T, Ueda I, Katsumata Y, Nishiyama T, Aizawa Y, Tanimoto K, Momiyama Y, Akaishi M, Mitamura H, Fukuda K, Spertus JA, Takatsuki S. Assessment of sex differences in the initial symptom burden, applied treatment strategy,

and quality of life in Japanese patients with atrial fibrillation. *JAMA Netw Open* 2019;**2**: e191145.
23. Hayashi K, Tsuda T, Nomura A, Fujino N, Nohara A, Sakata K, Konno T, Nakanishi C, Tada H, Nagata Y, Teramoto R, Tanaka Y, Kawashiri MA, Yamagishi M. Impact of B-type natriuretic peptide level on risk stratification of thromboembolism and death in patients with nonvalvular atrial fibrillation - the Hokuriku-Plus AF Registry. *Circ J* 2018;**82**: 1271–1278.
24. Okumura K, Tomita H, Nakai M, Kodani E, Akao M, Suzuki S, Hayashi K, Sawano M, Goya M, Yamashita T, Fukuda K, Ogawa H, Tsuda T, Isobe M, Toyoda K, Miyamoto Y, Miyata H, Okamura T, Sasahara Y. A novel risk stratification system for ischemic stroke in Japanese patients with non-valvular atrial fibrillation. *Circ J* 2021;**85**: 1254–1262.
25. Inoue H, Kodani E, Atarashi H, Okumura K, Yamashita T, Origasa H. Impact of body mass index on the prognosis of Japanese patients with non-valvular atrial fibrillation. *Am J Cardiol* 2016;**118**:215–221.
26. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H. Impact of creatinine clearance on outcomes in patients with non-valvular atrial fibrillation: a subanalysis of the J-RHYTHM Registry. *Eur Heart J Qual Care Clin Outcomes* 2018;**4**:59–68.
27. Kodani E, Inoue H, Atarashi H, Okumura K, Yamashita T, Origasa H. Impact of hemoglobin concentration and platelet count on outcomes of patients with non-valvular atrial fibrillation: a subanalysis of the J-RHYTHM Registry. *Int J Cardiol* 2020;**302**:81–87.
28. Hamatani Y, Ogawa H, Uozumi R, Iguchi M, Yamashita Y, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Morita S, Akao M. Low body weight is associated with the incidence of stroke in atrial fibrillation patients - insight from the Fushimi AF Registry. *Circ J* 2015;**79**:1009–1017.
29. Abe M, Ogawa H, Ishii M, Masunaga N, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Lip GY, Akao M. Relation of stroke and major bleeding to creatinine clearance in patients with atrial fibrillation (from the Fushimi AF Registry). *Am J Cardiol* 2017;**119**: 1229–1237.
30. An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, Esato M, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M. Causes of death in Japanese patients with atrial fibrillation: the Fushimi Atrial Fibrillation Registry. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:35–42.
31. 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.
32. Tremblay-Gravel M, Khairy P, Roy D, Leduc H, Wyse DG, Cadrin-Tourigny J, Macle L, Dubuc M, Andrade J, Rivard L, Guerra PG, Thibault B, Ahmed A, Talajic M, Guertin MC, White M. Systolic blood pressure and mortality in patients with atrial fibrillation and heart failure: insights from the AFFIRM and AF-CHF studies. *Eur J Heart Fail* 2014;**16**: 1168–1174.
33. Mayer CC, Matschkal J, Sarafidis PA, Hagmair S, Lorenz G, Angermann S, Braunisch MC, Baumann M, Heemann U, Wassertheurer S, Schmaderer C. Association of ambulatory blood pressure with all-cause and cardiovascular mortality in hemodialysis patients: effects of heart failure and atrial fibrillation. *J Am Soc Nephrol* 2018;**29**:2409–2417.
34. Bohm M, Brueckmann M, Eikelboom JW, Ezekowitz M, Frassdorf M, Hijazi Z, Hohnloser SH, Mahfoud F, Schmieder RE, Schumacher H, Wallentin L, Yusuf S. Cardiovascular outcomes, bleeding risk, and achieved blood pressure in patients on long-term anticoagulation with the thrombin antagonist dabigatran or warfarin: data from the RE-LY trial. *Eur Heart J* 2020;**41**:2848–2859.
35. Lee SE, Lee HY, Cho HJ, Choe WS, Kim H, Choi JO, Jeon ES, Kim MS, Hwang KK, Chae SC, Baek SH, Kang SM, Choi DJ, Yoo BS, Kim KH, Cho MC, Kim JJ, Oh BH. Reverse J-curve relationship between on-treatment blood pressure and mortality in patients with heart failure. *JACC Heart Fail* 2017;**5**:810–819.
36. Adamsson Eryd S, Gudbjornsdottir S, Manhem K, Rosengren A, Svensson AM, Miftaraj M, Franzen S, Bjorck S. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. *BMJ* 2016;**354**:i4070.
37. Delgado J, Bowman K, Ble A, Masoli J, Han Y, Henley W, Welsh S, Kuchel GA, Ferrucci L, Melzer D. Blood pressure trajectories in the 20 years before death. *JAMA Intern Med* 2018;**178**:93–99.
38. Kodani E, Inoue H, Atarashi H, Okumura K, Suzuki S, Yamashita T, Origasa H. Impact of systolic blood pressure time in target range on adverse events in patients with nonvalvular atrial fibrillation (from the J-RHYTHM Registry). *Am J Cardiol* 2022;**180**:52–58.
39. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJS, Manzano L, Bohm M, van Veldhuisen DJ, Andersson B, Wedel H, von Lueder TG, Rigby AS, Hjalmarson A, Kjekshus J, Cleland JGF. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol* 2017;**69**:2885–2896.
40. Kannel WB, Wilson PW, Nam BH, D'Agostino RB, Li J. A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol* 2004;**94**:380–384.
41. Bager JE, Hjerpe P, Schioler L, Bengtsson Bostrom K, Kahan T, Odesjo H, Jood K, Hasselstrom J, Ljungman C, Manhem K, Mourtzinis G. Blood pressure levels and risk of haemorrhagic stroke in patients with atrial fibrillation and oral anticoagulants: results from the Swedish Primary Care Cardiovascular Database of Skaraborg. *J Hypertens* 2021;**39**:1670–1677.
42. Li J, Somers VK, Gao X, Chen Z, Ju J, Lin Q, Mohamed EA, Karim S, Xu H, Zhang L. Evaluation of optimal diastolic blood pressure range among adults with treated systolic blood pressure less than 130 mmHg. *JAMA Netw Open* 2021;**4**:e2037554.
43. Chen CL, Huang JY, Liu L, Yu YL, Shen G, Lo K, Huang YQ, Tang ST, Feng YQ. Relationship between diastolic blood pressure and the first ischaemic stroke in elderly patients with hypertension. *Postgrad Med J* 2020;**96**:525–529.
44. Bohm M, Schumacher H, Teo KK, Lonn E, Mahfoud F, Mann JFE, Mancia G, Redon J, Schmieder R, Weber M, Sliwa K, Williams B, Yusuf S. Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120–140 mmHg) and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Eur Heart J* 2018;**39**:3105–3114.