의학박사 학위논문

비판막성 심방세동에서 고혈압 조절 정도의 혈전색전증 발생에 대한 영향

Clinical implication of controlled blood pressure level on risk of thromboembolic event in patients with non-valvular atrial fibrillation

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이 논문을 의학박사 학위 논문으로 제출함

2020 년 2 월

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Abstract

Background: Hypertension is common comorbidity and independent risk factor for stroke in patients with nonvalvular atrial fibrillation (AF). However, proper target of blood pressure (BP) control for patients with nonvalvular AF and hypertension is not well-known.

Methods: A 12,453 consecutive patients with hypertension and nonvalvular AF were enrolled from Asan Medical center (a tertiary referral center in South Korea) between 2006 and 2017. Mean BP measurement at out-patient clinic was calculated with linear interpolation method. Primary outcome was ischemic stroke and systemic embolism.

Results: Among 12,453 patients, mean systolic BP was over 140mmHg in 1,352 patients, between 120 to 140mmHg in 6,641 patients, and under 120mmHg in 4,460 patients. The mean age was 67.3±11.2 years, mean follow up duration was 949.0±1001.4 days, and mean BP measurement interval was 49.4±55.3 days. Event rate per year for ischemic stroke and systemic embolism was higher with increased systolic BP (2.5% for < 120mmHg group, 3.0% for 120-140mmHg group, and 3.3% for ≥ 140mmHg group). Compared with systolic BP 120-140mmHg group, systolic BP < 120mmHg group showed significantly lower risk of ischemic stroke and systemic embolism (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.72-0.96, p-value = 0.01), and systolic BP ≥ 140mmHg group showed no significant difference in risk of ischemic stroke and systemic embolism (HR 1.09, 95% CI 0.88-1.35, p-value = 0.433). There was no significant difference on risk of ischemic stroke and systemic embolism regarding the diastolic BP. High variation of both systolic and diastolic visit-to-visit BP within each patient significantly increase the risk of ischemic stroke and systemic embolism. Treated hypertension patients were in higher risk of ischemic stroke or systemic embolism than patients without history of hypertension regardless of controlled BP level.

Conclusion: Control of systolic BP to under 120 mmHg and low variation of systolic and diastolic BP showed lower risk of thromboembolism in patients with hypertension and

nonvalvular AF. History of hypertension itself is a risk factor of thromboembolism regardless of controlled BP level.

Key words: Nonvalvular atrial fibrillation, hypertension, blood pressure control, ischemic stroke, systemic embolism

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Introduction

Atrial fibrillation (AF) represents the most common cardiac arrhythmia affecting millions of patients in USA [1]. In Korea, prevalence of AF was 0.67% among adult population aged over 20 years old and was more than 1% for aged over 60 years old [2]. In these studies, hypertension was common comorbidity with prevalence rate of approximately 50 to 70% in AF patients. The presence of hypertension in patients with AF is an independent risk factor for stroke, which such patients were at 1.5 to 3.6 fold increased risk compared to AF patients without hypertension [3, 4].

Currently, the CHA_2DS_2-VASc (congestive heart failure, hypertension, age 65 to 74 years and over 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, sex category) score is widely used by most guidelines for stroke prevention in AF [5, 6]. However, AF [5, 6] and hypertension [7, 8] guidelines do not have specific recommendations regarding the optimal blood pressure (BP) treatment goals for patients with AF and hypertension, particularly for stroke prevention.

Recently, DH Kim et al have suggested the optimal BP target in patients with AF as systolic BP between 120 to 129 mmHg and diastolic BP under 80 mmHg, which may lower the risk of ischemic stroke as well as cardiovascular event or death [9]. However, BP control status was assessed by BP measurement only once at baseline.

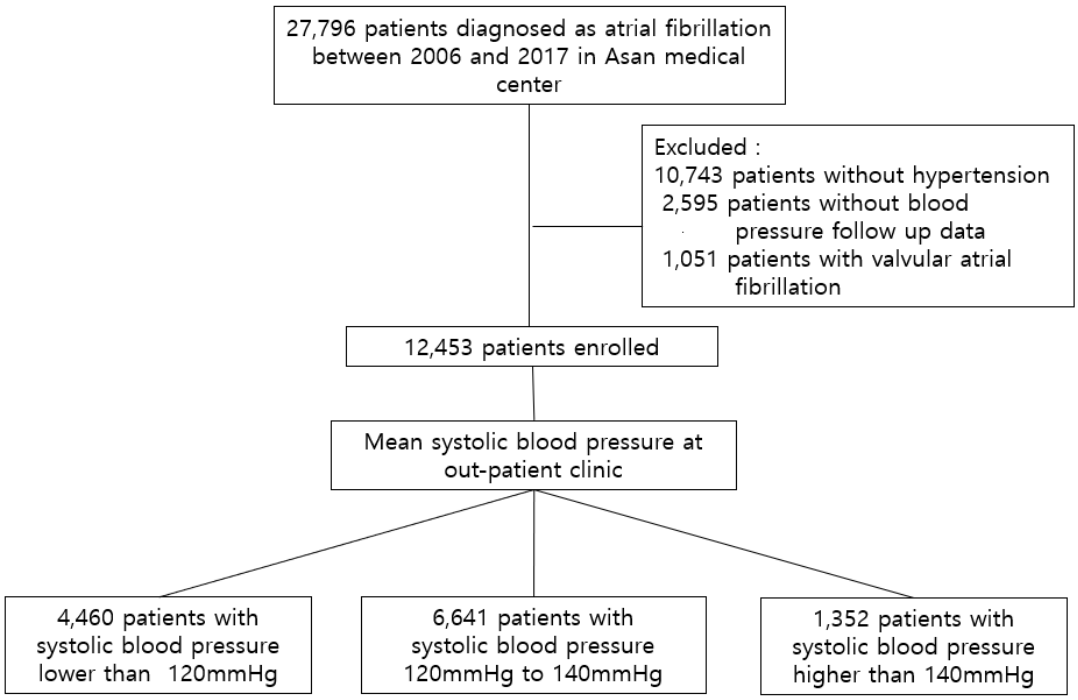
Further studies to reveal the proper target systolic and diastolic BP for patients with nonvalvular AF and hypertension are needed. We investigate the optimal target of systolic and diastolic BP to prevent the ischemic stroke and systemic embolism based on multiple out-patient clinic BP measurement.

Methods

Study subjects

The present study is a retrospective observational review of consecutive nonvalvular AF patients. A total of 27,796 patients were diagnosed with AF from 2006 to 2017 in Asan Medical Center, Seoul, Korea. Among them, 17,053 patients diagnosed as hypertension. Patients with (1) prosthetic valve (1,063 patients) or (2) mitral stenosis more than moderate degree (354 patients) and (3) who do not have follow-up BP measurements (2,595 patients) were excluded from this analysis. Finally, 12,453 patients were enrolled, and divided into 3 groups according to the controlled systolic BP level (lower than 120mmHg, between 120 to 140mmHg, and higher than 140mmHg) (Figure 1). The study was approved by the institutional review board of Asan Medical Center, which waived the need for informed consent from patients based on the retrospective nature of the study.

Figure 1. Study flow chart



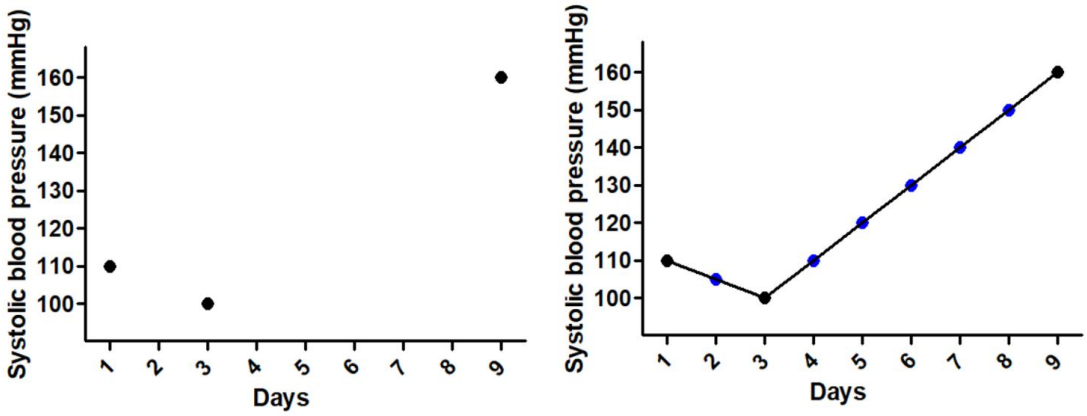
Data collection

Data on the study subjects were extracted from the Asan BiomedicaL research Environment (ABLE) system, which included demographic characteristics, baseline thromboembolic risks, medication, and blood pressure data collected from out-patient clinic. Baseline thromboembolic risk was calculated using the CHA_2DS_2-VASc scoring system [10].

Blood pressure measurements

BP measurements were taken at out-patient clinic in our center. After 5 minutes of rest with the patient in the sitting position, brachial BP was measured by automatic oscillometric device (BP210, ACCUNIQ, Korea). If BP was measured repeatedly, lower BP was counted for analysis, because repeated measurement was usually because of relatively high clinic BP than home BP. Linear interpolation was used to calculate the mean of the measured BP for each patient (Figure 2). The unknown BP values between dates of measurement were interpolated using a linear function so measured and estimated BP can cover the entire days within the observation period. Patients were divided into 3 groups by systolic BP and diastolic BP separately. Cut off value of 120mmHg and 140mmHg for systolic BP was used regarding the SPRINT trial [11], and cut off value of 80mmHg and 90mmHg for diastolic BP was used regarding the medication threshold and target of BP on current guidelines [7),8)].

Figure 2. Example of linear interpolation of systolic blood pressure



Black dots are measured systolic blood pressure and blue dots are calculated systolic blood pressure by linear interpolation. Simple mean ((110+100+160)/3=123.3mmHg) and linearly interpolated mean ((110+105+100+110+120+130+140+150+160)/9=125mmHg) is different.

Clinical outcome events and assessments

The primary outcome was the incidence of new-onset ischemic stroke or systemic embolism during follow-up. Ischemic stroke was diagnosed primarily based on imaging findings and clinical presentations[12]. An ischemic stroke event was diagnosed by an independent neurologist. Systemic embolism was defined as a sudden loss of perfusion in a limb or organ, assessed using vascular imaging, ankle-brachial index, procedural findings, and laboratory findings along with clinical presentation [13].

Statistical analyses

Categorical variables are shown as frequencies with percentages, and continuous variables as mean and standard deviation or median and interquartile range. Categorical variables were compared using the chi-square test, and continuous variables were compared using analysis of variance with post-hoc analysis with Tukey's method or Wilcoxon rank-sum test as appropriate. The Kaplan-Meier method was used to calculate the unadjusted event rates, which were then compared using log-rank test. The Cox proportional hazards model was used to assess the relative risk of each variable on study outcomes. CHA_2DS_2-VASc score and usage of oral anticoagulants were included in the multivariable model. All statistical analyses were performed using R software version 3.6.1. All p values were 2-sided, and p values <0.05 were considered statistically significant.

Results

Baseline characteristics

Among 12,453 enrolled patients, patients were divided into 3 groups regarding the controlled systolic and diastolic BP level separately (systolic BP < 120mmHg, n=4460; systolic BP 120-140mmHg, n=6641; systolic BP ≥ 140mmHg, n=1352) (diastolic BP < 80mmHg, n=10939; diastolic BP 80-90mmHg, n=1334; diastolic BP ≥ 90mmHg, n=180). Baseline characteristics of the patients are summarized in Table 1 (systolic BP) and Table 2 (diastolic BP).

The mean patient age was 67.3 years, with a preponderance of men (62.5%). Paroxysmal AF patients were 5,735 (46.1%). Ischemic stroke or systemic embolism occurred in 927 (7.4%) patients during mean follow-up of 2.6 ± 2.7 years. Among CHA_2DS_2-VASc score components, patients with systolic BP ≥ 140mmHg had more diabetes, prior history of stroke/transient ischemic attack(TIA). Patients with systolic BP < 120mmHg had more heart failure. Numerically, CHA_2DS_2-VASc score was similar between the groups divided by systolic BP. Usage of oral anticoagulant was less prevalent and usage of calcium channel blocker was more prevalent in patients with systolic BP ≥ 140mmHg.

Risk of ischemic stroke and systemic embolism according to components of CHA_2DS_2-VASc score and paroxysmal AF is shown in Table 3. All variables except heart failure were related to the risk of thromboembolism.

Table 1. Baseline characteristics of patients according to controlled systolic blood pressure level

	All patients (N=12453)	SBP<120 (N=4460)	SBP 120-140 (N=6641)	SBP≥140 (N=1352)	P-value
Age (years)	67.3 ±11.2	67.2 ±11.4	67.3 ±11.0	67.8 ±11.5	0.112
Male	7786 (62.5)	2778 (62.3)	4180 (62.9)	828 (61.2)	0.461
Paroxysmal atrial fibrillation	5735 (46.1)	1863 (41.8)	3231 (48.7)	641 (47.4)	<0.001
Diabetes	3396 (27.3)	1097 (24.6)	1841 (27.7)	458 (33.9)	<0.001
Vascular disease	1106 (8.9)	406 (9.1)	576 (8.7)	124 (9.2)	0.682
Peripheral artery disease	454 (3.6)	138 (3.1)	256 (3.9)	60 (4.4)	0.029
Aortic plaque	365 (2.9)	98 (2.2)	215 (3.2)	52 (3.8)	0.001
Prior myocardial infarction	716 (5.7)	288 (6.5)	356 (5.4)	72 (5.3)	0.04
Prior stroke/TIA	1798 (14.4)	487 (10.9)	1057 (15.9)	254 (18.8)	<0.001
Heart failure	2477 (19.9)	1258 (28.2)	1027 (15.5)	192 (14.2)	<0.001
LVEF	54.6 ± 12.4	51.2 ± 14.3	56.4 ± 10.9	57.4 ± 10.2	<0.001
CHA_2DS_2VASc	3.1 ± 1.5	3.1 ± 1.4	3.1 ± 1.6	3.3 ± 1.7	0.011
Chronic renal disease	3850 (40.8)	1550 (44.6)	1877 (37.7)	423 (43.4)	<0.001
Left atrial size (mm)	45.4 ± 8.5	46.1 ± 9.2	45.0 ± 8.1	45.2 ± 7.5	<0.001
ACEI/ARB	8371 (67.2)	2924 (65.6)	4501 (67.8)	946 (70.0)	0.004
Beta blocker	5195 (41.7)	1838 (41.2)	2816 (42.4)	541 (40.0)	0.186
Calcium channel blocker	6067 (48.7)	1519 (34.1)	3700 (55.7)	848 (62.7)	<0.001
Thizide	2617 (21.0)	838 (18.8)	1455 (21.9)	324 (24.0)	<0.001
Oral anticoagulation	7540 (60.5)	2704 (60.6)	4114 (61.9)	722 (53.4)	<0.001
Follow up duration (days)	949.0 ±1001.4	943.8 ±1003.7	990.8 ±1014.6	761.0 ±903.0	0.001
BP measurements	19.2 ±18.1	16.9 ±16.5	21.5 ±19.2	15.3 ±16.1	<0.001
BP interval (days)	49.4 ± 55.3	55.9 ± 60.8	46 ± 52.8	49.7 ± 56.1	<0.001
BP SD within patients	15.3 ± 6.4	14.7 ± 6.8	15.2 ± 5.8	17.4 ± 7.6	<0.001

Data are reported as means ± standard deviation or numbers ().

Blood pressure is reported as mmHg

SBP=systolic blood pressure; TIA=transient ischemic attact; LVEF=left ventricular ejection fraction; ACEI=angiotensin converting enzyme inhibitor; ARB=antiotensin II receptor blocker; BP=blood pressure; SD=standard deviation

Table 2. Baseline characteristics of patients according to controlled diastolic blood pressure level

	All patients (N=12453)	DBP<80 (N=10939)	DBP 80-90 (N=1334)	DBP≥90 (N=180)	P-value
Age (years)	67.3 ±11.2	68.0 ±11.0	62.6 ±11.6	59.9 ±13.8	<0.001
Male	7786 (62.5)	6712 (61.4)	942 (70.6)	132 (73.3)	<0.001
Paroxysmal atrial fibrillation	5735 (46.1)	5056 (46.2)	606 (45.4)	73 (40.6)	0.283
Diabetes	3396 (27.3)	3097 (28.3)	271 (20.3)	28 (15.6)	<0.001
Vascular disease	1106 (8.9)	1025 (9.4)	70 (5.2)	11 (6.1)	<0.001
Peripheral artery disease	454 (3.6)	417 (3.8)	31 (2.3)	6 (3.3)	0.023
Aortic plaque	365 (2.9)	336 (3.1)	24 (1.8)	5 (2.8)	0.034
Prior myocardial infarction	716 (5.7)	671 (6.1)	39 (2.9)	6 (3.3)	<0.001
Prior stroke/TIA	1798 (14.4)	1595 (14.6)	181 (13.6)	22 (12.2)	0.425
Heart failure	2477 (19.9)	2256 (20.6)	200 (15.0)	21 (11.7)	<0.001
LVEF	54.6 ± 12.4	54.5 ± 12.5	55.9 ± 11.1	54.2 ± 12.0	0.003
CHA_2DS_2VASc	3.1 ± 1.5	3.2 ± 1.5	2.6 ± 1.5	2.4 ± 1.5	<0.001
Chronic renal disease	3850 (40.8)	3533 (42.4)	276 (28.6)	41 (30.4)	<0.001
Left atrial size (mm)	45.4 ± 8.5	45.5 ± 8.5	44.8 ± 8.1	45.4 ± 8.0	0.02
ACEI/ARB	8371 (67.2)	7369 (67.4)	891 (66.8)	111 (61.7)	0.255
Beta blocker	5195 (41.7)	4540 (41.5)	580 (43.5)	75 (41.7)	0.385
Calcium channel blocker	6067 (48.7)	5248 (48.0)	727 (54.5)	92 (51.1)	<0.001
Thizide	2617 (21.0)	2317 (21.2)	270 (20.2)	30 (16.7)	0.257
Oral anticoagulation	7540 (60.5)	6691 (61.2)	766 (57.4)	83 (46.1)	<0.001
Follow up duration (days)	949.0 ±1001.4	965.2 ±1005.1	855.0 ±972.9	661.8 ±906.5	<0.001
BP measurements	19.2 ±18.1	19.8 ±18.4	15.0 ±15.2	11.0 ±18.0	<0.001
BP interval (days)	49.4 ± 55.3	48.7 ± 54.6	57.0 ± 64.0	60.2 ± 50.3	<0.001
BP SD within patients	15.3 ± 6.4	9.9 ± 4.3	9.8 ± 3.6	10.7 ± 4.6	<0.001

Data are reported as means ± standard deviation or numbers ().

Blood pressure is reported as mmHg

DBP=diastolic blood pressure; TIA=transient ischemic attact; LVEF=left ventricular ejection fraction; ACEI=angiotensin converting enzyme inhibitor; ARB=antiotensin II receptor blocker; BP=blood pressure; SD=standard deviation

Table 3. Risk of ischemic stroke and systemic embolism according to components of CHA_2DS_2-VASc score and paroxysmal AF

Univariate analysis	HR (95% CI)	P-value
Age (years)	1.05 (1.04-1.06)	<0.001
Male	0.7 (0.62-0.8)	<0.001
Diabetes	1.45 (1.26-1.67)	<0.001
Vascular disease	2.3 (1.92-2.74)	<0.001
Prior stroke/TIA	2.57 (2.22-2.97)	<0.001
Heart failure	0.91 (0.77-1.08)	0.28
Paroxysmal atrial fibrillation	0.73 (0.64-0.83)	<0.001

HR=hazard ratio; TIA=transient ischemic attack

Blood pressure measurement

The mean interval of BP measurement was 49.4 ± 55.3 days with follow up duration 949.0±1001.4 days and BP measurement 19.2±18.1 times. For systolic BP, simple mean was 123.4 ± 13.1 mmHg and lineally interpolated mean was 124.2 ± 13.7 mmHg with difference of 0.8 ± 0.8 mmHg (P<0.001). For diastolic BP, simple mean was 69.9 ± 8.0 mmHg and lineally interpolated mean was 70.3 ± 8.5 mmHg with difference of 0.4 ± 0.1 mmHg (P<0.001).

Controlled blood pressure level and risk of ischemic stroke and systemic embolism

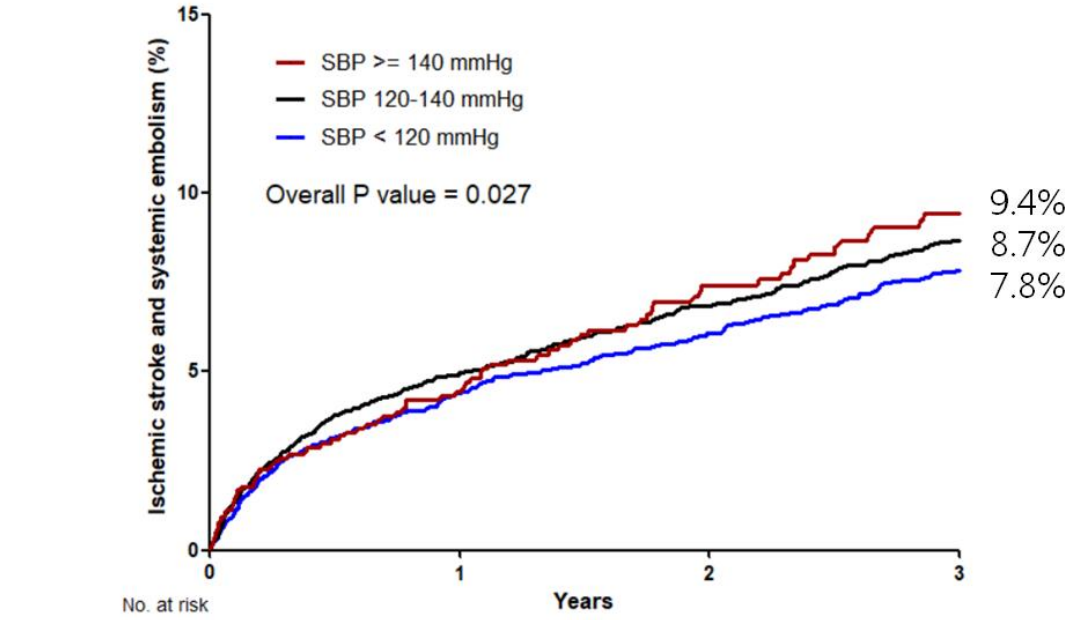
The crude incidence of subsequent ischemic stroke or systemic embolism following a nonvalvular AF diagnosis is depicted in Figure 3 (systolic BP) and Figure 4 (diastolic BP). Event rate per year for ischemic stroke or systemic embolism regarding controlled BP level is shown in Figure 5 (systolic BP) and Figure 6 (diastolic BP). Rate of thromboembolic events become higher as controlled systolic BP level is higher. However, for diastolic BP, between 80 to 90 mmHg showed lowest rate of thromboembolic event and over 90 mmHg showed highest rate of thromboembolic event.

The relative risk of ischemic stroke or systemic embolism for controlled BP level is summarized in Table 4, Figure 7 and 8. Higher and lower level of controlled BP was compared with middle level of controlled BP. After adjustment with CHA_2DS_2-VASc score and oral anticoagulants, systolic BP lower than 120mmHg showed significantly decreased risk of thromboembolism (HR 0.83, 95% CI 0.72-0.96, p =0.01) compared with systolic BP between 120 and 140 mmHg. However, systolic BP higher than 140mmHg did not significantly increase the risk of thromboembolism compared with systolic BP between 120 and 140 mmHg (HR 1.09, 95% CI 0.88-1.35, p =0.433). Controlled level of diastolic BP did not significantly influence the risk of thromboembolism (lower than 80mmHg, HR 1.04, 95% CI 0.83-1.31, p =0.726; higher than 90mmHg, HR 1.58, 95% CI 0.89-2.80, p =0.116; both compared with controlled diastolic BP between 80 and 90mmHg).

The receiver operating characteristic (ROC) curve for prediction of ischemic stroke and systemic embolism was 0.5198 for controlled systolic BP level (Figure 9) and 0.5244 for controlled diastolic BP level (Figure 10).

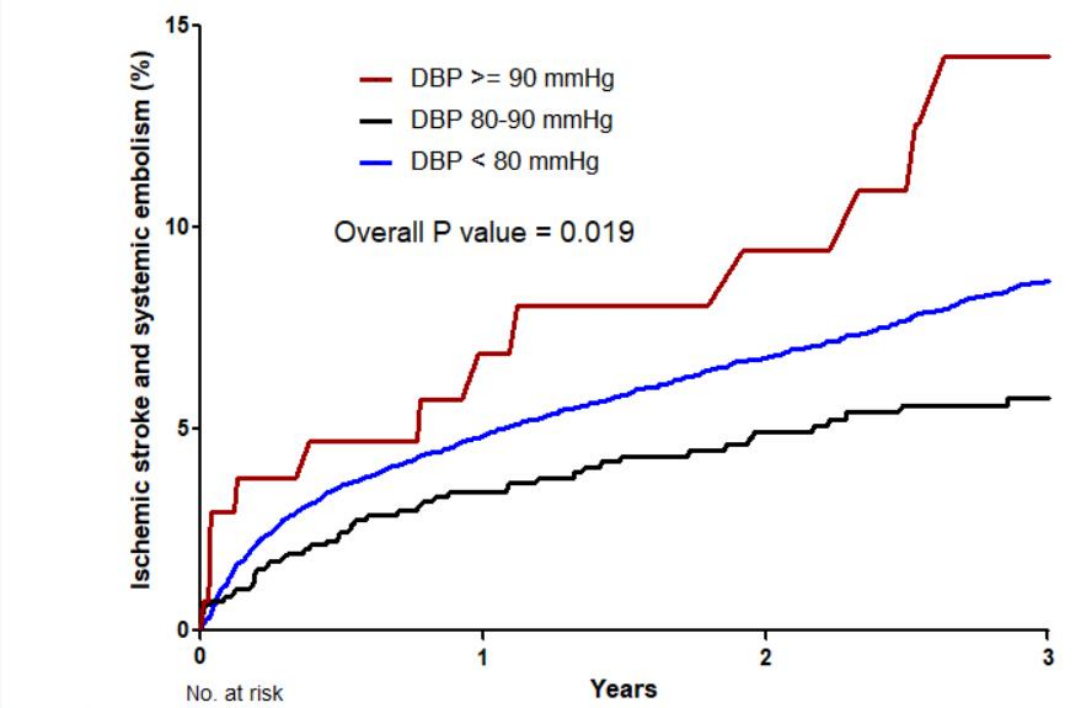
Analysis with simple mean of controlled BP was similar to analysis with interpolated mean. Systolic BP lower than 120mmHg showed significantly decreased risk of thromboembolism (HR 0.80, 95% CI 0.70-0.92, p =0.002) compared with systolic BP between 120 and 140 mmHg. However, systolic BP higher than 140mmHg did not significantly increase the risk of thromboembolism compared with systolic BP between 120 and 140 mmHg (HR 1.08, 95% CI 0.85-1.37, p =0.55).

Figure 3. Incidience of ischemic stroke or systemic embolism according to controlled systolic blood pressure level



SBP=systolic blood pressure

Figure 4. Incidience of ischemic stroke or systemic embolism according to controlled diastolic blood pressure level



DBP=diastolic blood pressure

Figure 5. Event rate per year of ischemic stroke and systemic embolism according to systolic blood pressure

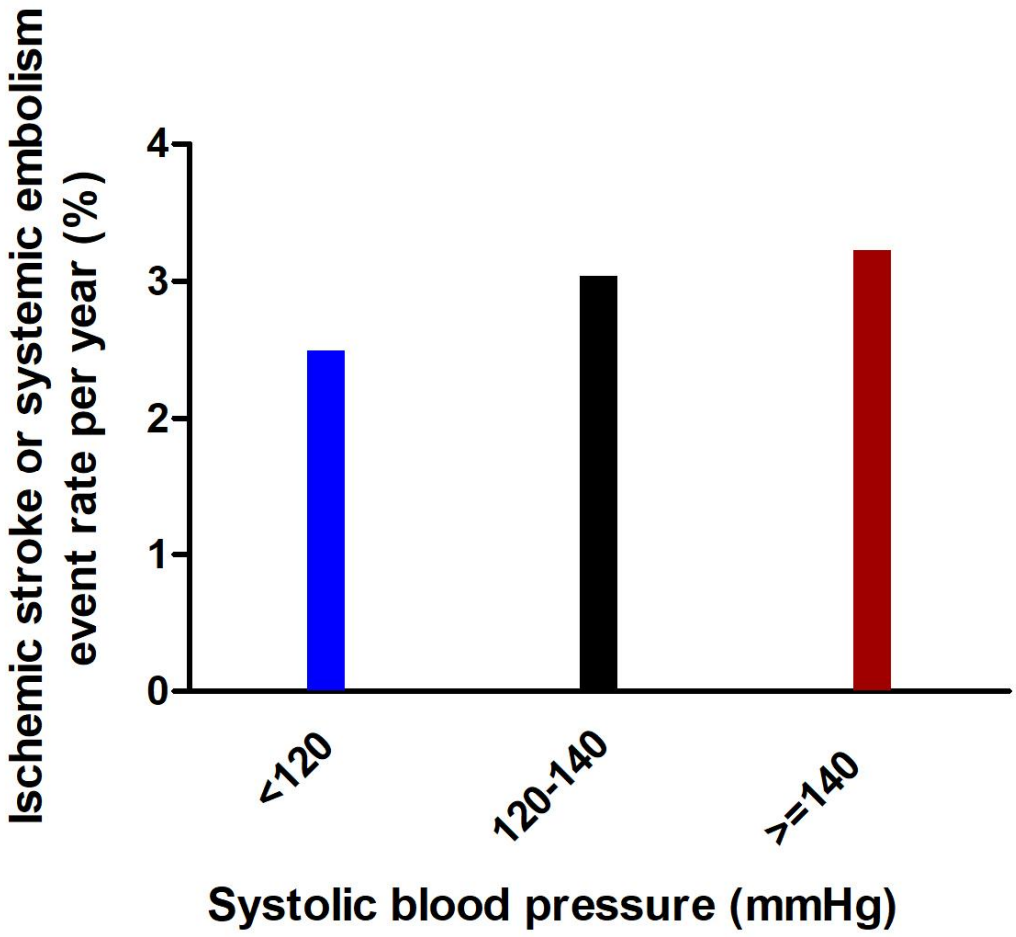


Figure 6. Event rate per year of ischemic stroke and systemic embolism according to diastolic blood pressure

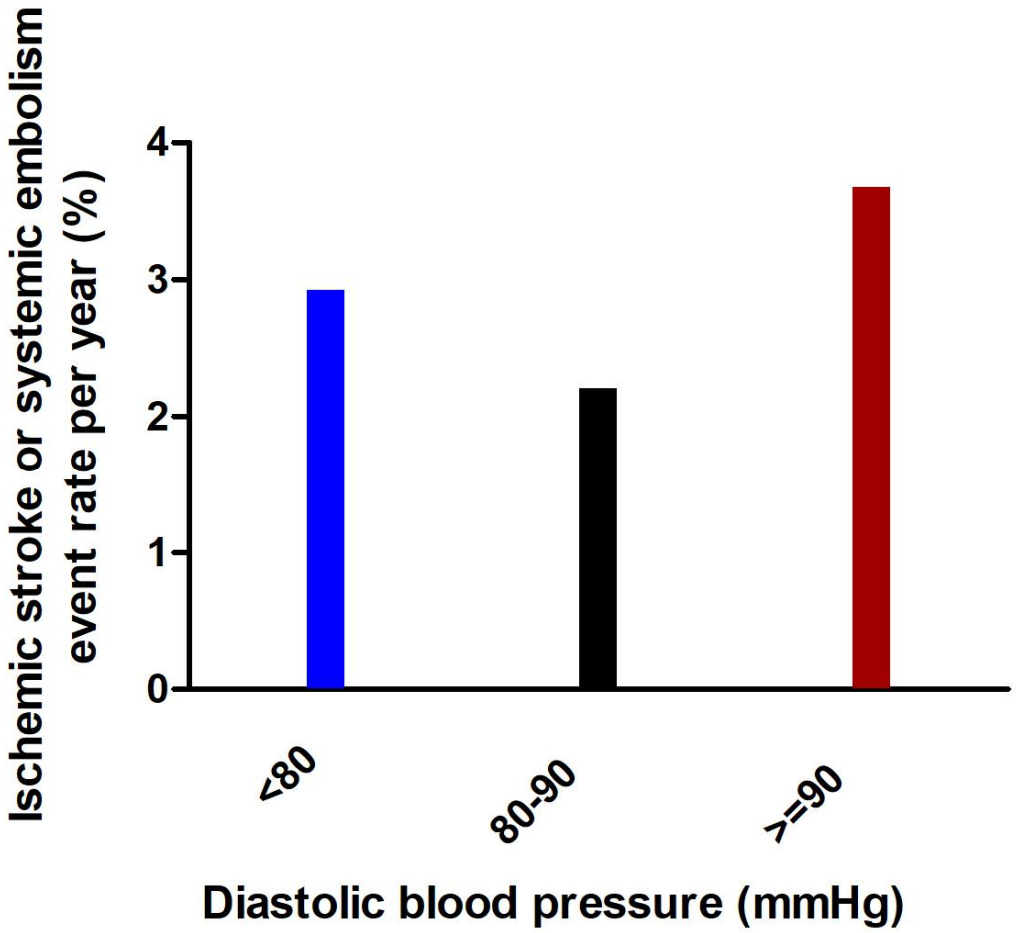


Table 4. Risk of ischemic stroke and systemic embolism according to controlled blood pressure level

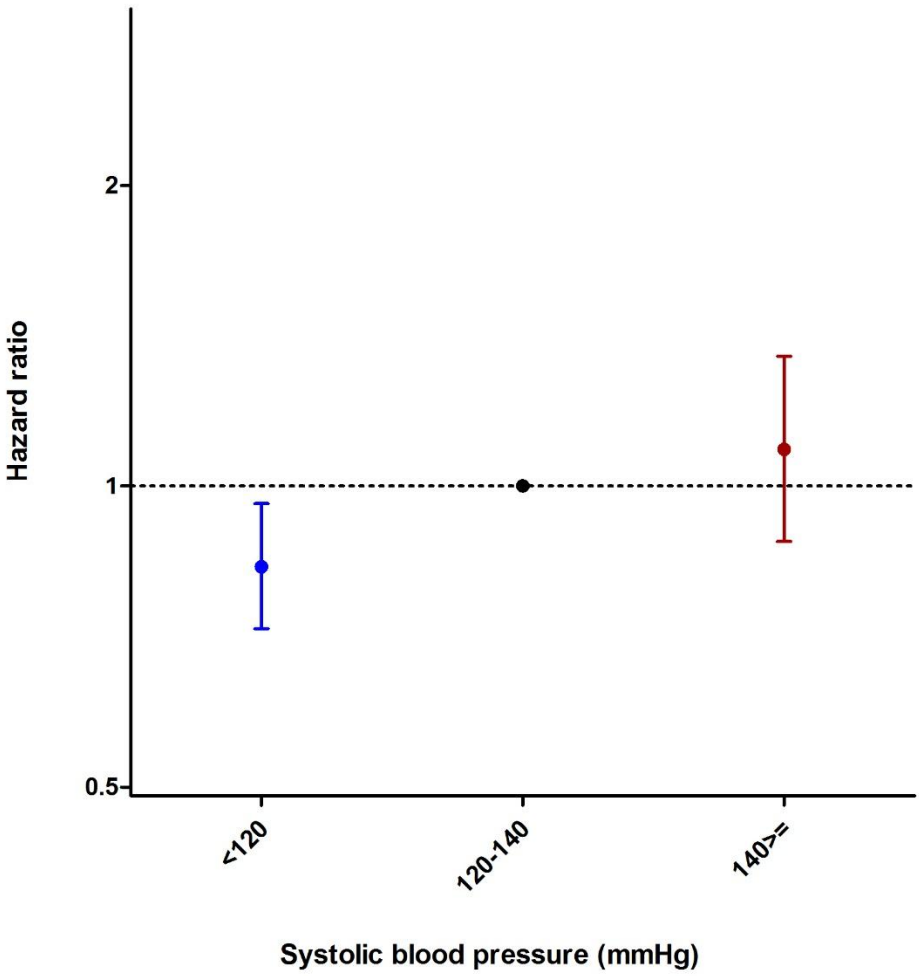
	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
120 ≤ SBP < 140	Ref.		Ref.	
SBP < 120	0.82 (0.71-0.94)	0.005	0.83 (0.72-0.96)	0.01
SBP ≥ 140	1.10 (0.89-1.37)	0.376	1.09 (0.88-1.35)	0.433
80 ≤ DBP < 90	Ref.		Ref.	
DBP < 80	1.30 (1.03-1.63)	0.026	1.04 (0.83-1.31)	0.726
DBP ≥ 90	1.24 (0.70-2.19)	0.465	1.58 (0.89-2.80)	0.116

Blood pressure is reported as mmHg

Adjusted for CHA_2DS_2-VASc score and oral anticoagulant

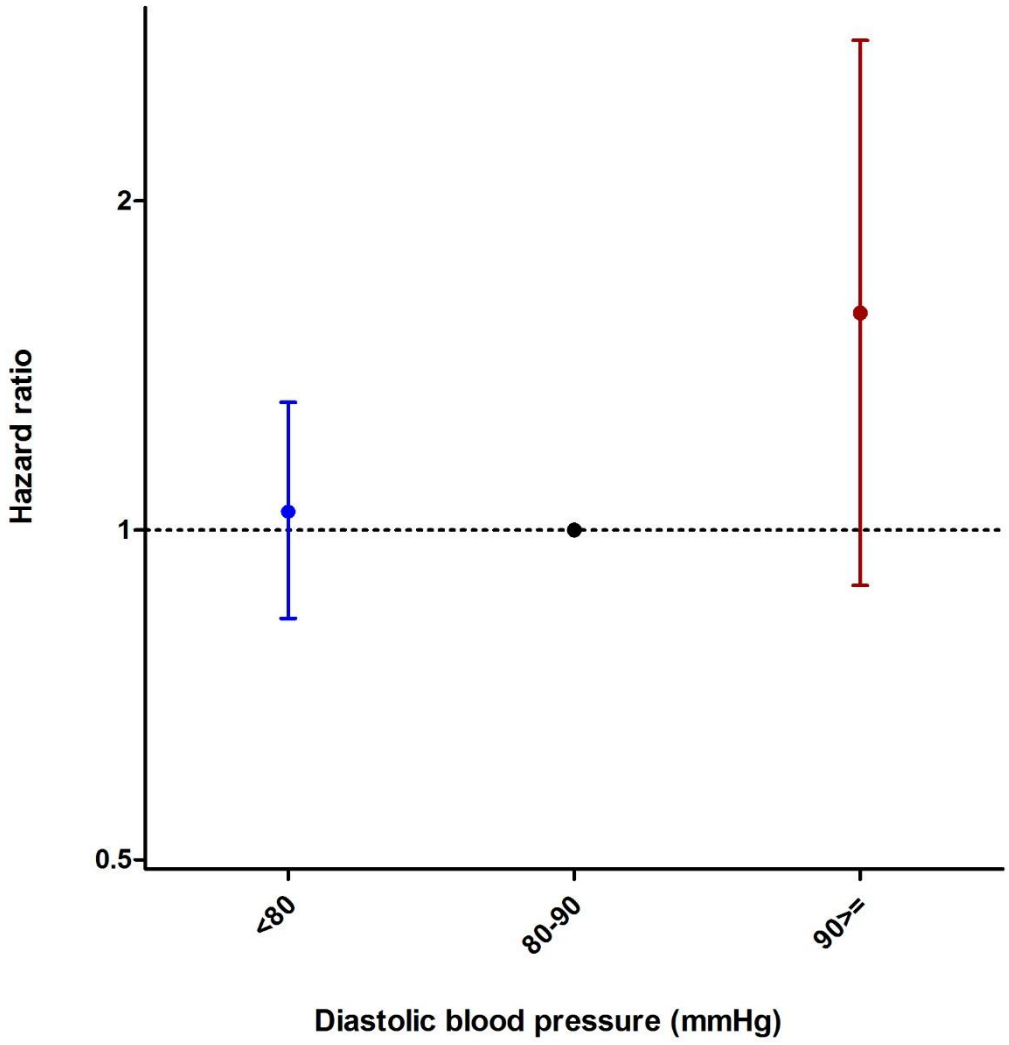
SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = hazard ratio; CI = confidential interval; Ref. = reference

Figure 7. Risk of ischemic stroke and systemic embolism according to controlled systolic blood pressure level



Adjusted for CHA_2DS_2-VASc score and oral anticoagulant

Figure 8. Risk of ischemic stroke and systemic embolism according to controlled diastolic blood pressure level



Adjusted for CHA_2DS_2-VASc score and oral anticoagulant

Figure 9. ROC curve for prediction of ischemic stroke and systemic embolism with controlled systolic blood pressure level

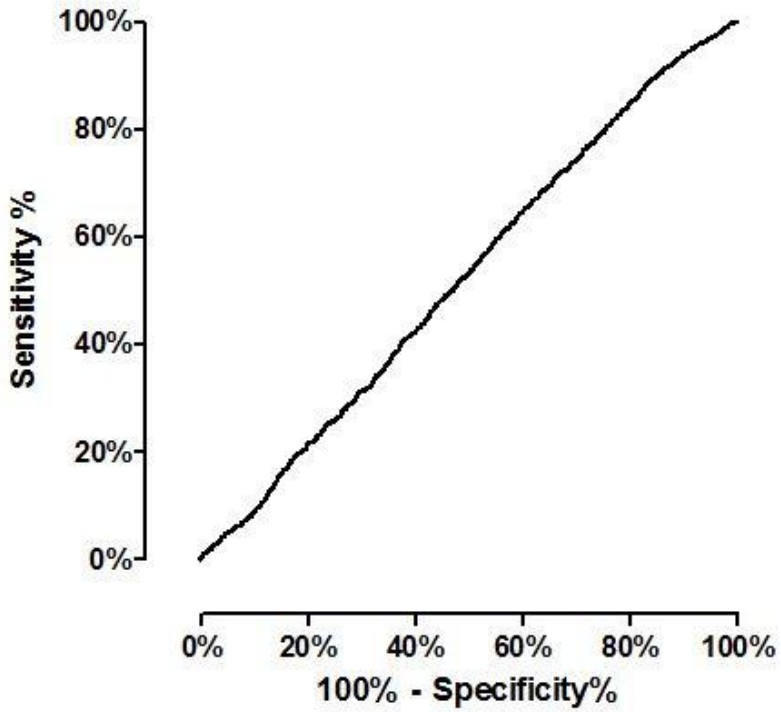
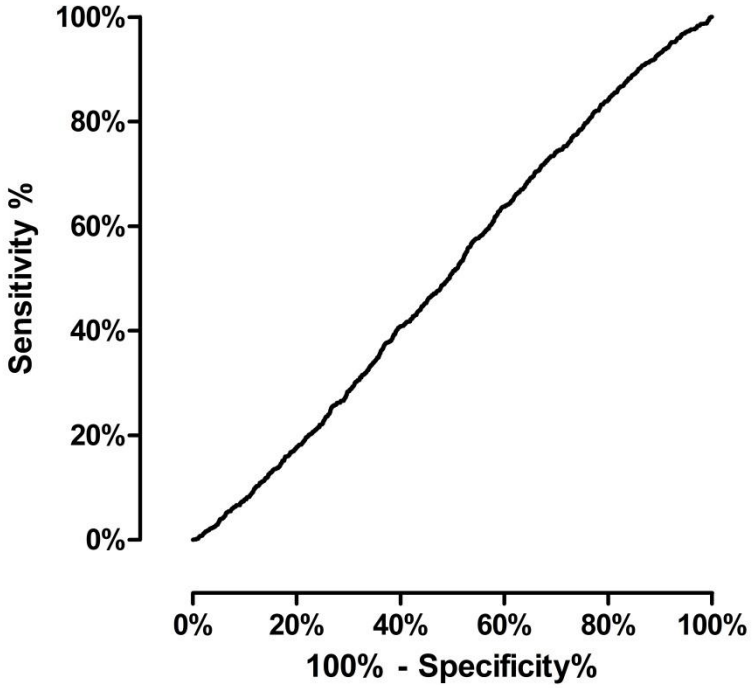


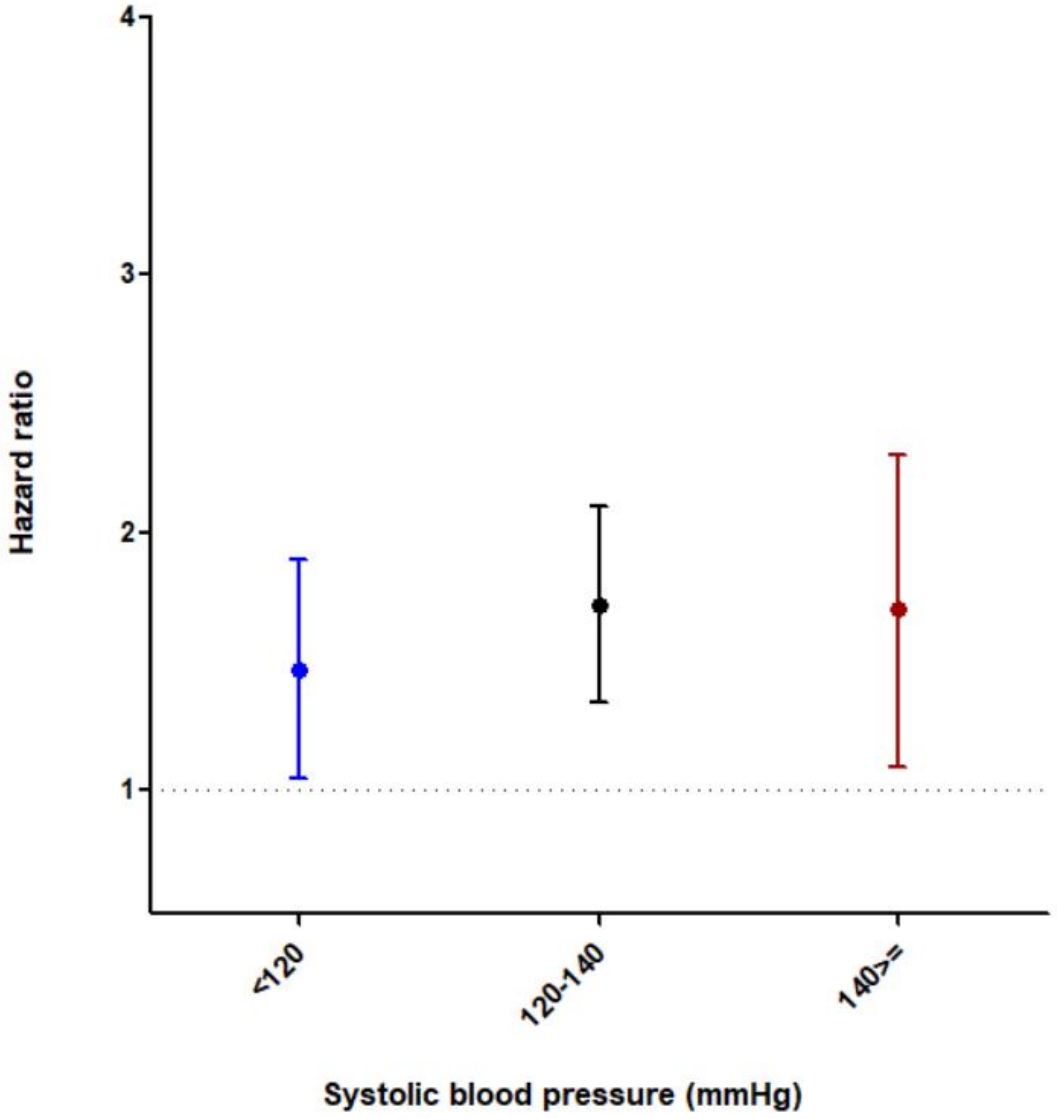
Figure 10. ROC curve for prediction of ischemic stroke and systemic embolism with controlled diastolic blood pressure level



Comparison to patients without history of hypertension

Compared with patients without history of hypertension and follow up BP lower than 140/90 mmHg, patients with treated hypertension consistently showed significantly increased risk of ischemic stroke and systemic embolism (Figure 11). Even in intensively controlled systolic BP group (lower than 120mmHg), risk of ischemic stroke and systemic embolism was increased compared with patients without history of hypertension.

Figure 11. Risk of ischemic stroke and systemic embolism for patients with treated hypertension regarding the controlled systolic blood pressure level compared with patients without history of hypertension

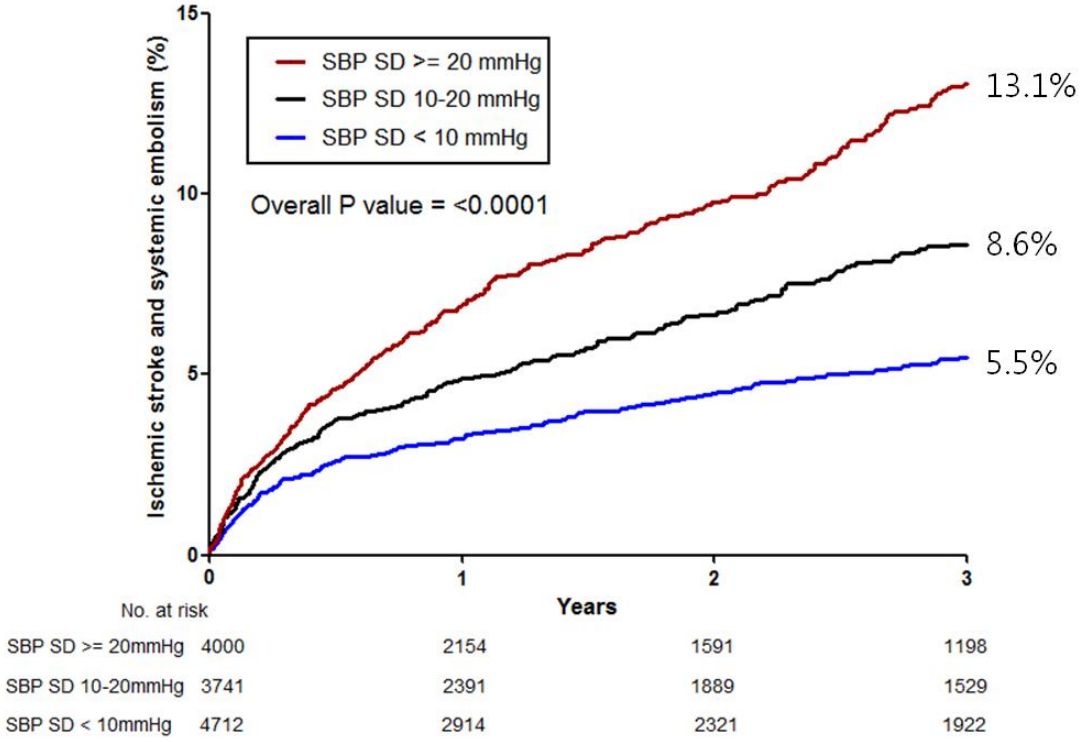


Adjusted for CHA_2DS_2-VASc components except hypertension and oral anticoagulant

Variation of blood pressures within each patient

The mean standard deviation (SD) of BP measurements within each patient was 15.3 ± 6.4 mmHg for systolic BP and 9.9 ± 4.0 mmHg for diastolic BP. The crude incidence of ischemic stroke or systemic embolism regarding the variation (standard deviation) of measured BP within each patient is shown in Figure 12 (systolic BP) and Figure 13 (diastolic BP). High variation of both systolic and diastolic BP within each patient significantly increase the risk of ischemic stroke and systemic embolism after adjustment with CHA_2DS_2-VASc score and oral anticoagulants (standard variation of systolic BP as continuous variable, HR 1.05, 95% CI 1.04-1.06, $p < 0.001$; standard deviation of diastolic BP as continuous variable, HR 1.06, 95% CI 1.05-1.08, $p < 0.001$).

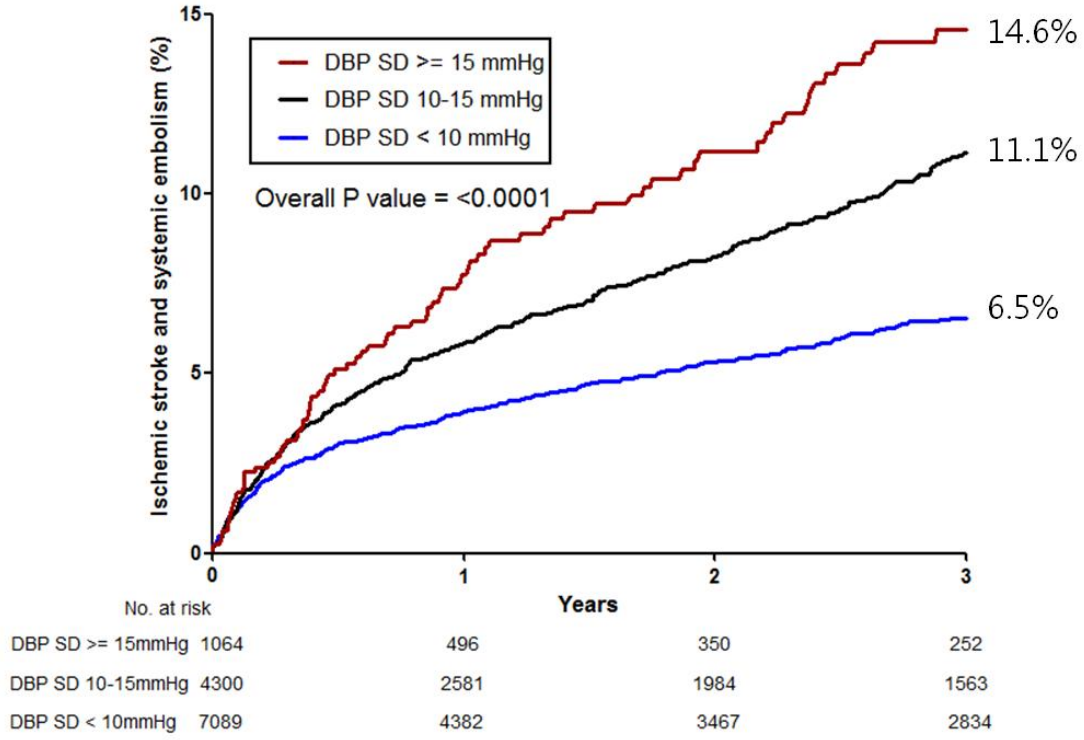
Figure 12. Incidience of ischemic stroke or systemic embolism according to standard deviation of controlled systolic blood pressure level within each patient



No. at risk				
SBP SD >= 20mmHg	4000	2154	1591	1198
SBP SD 10-20mmHg	3741	2391	1889	1529
SBP SD < 10mmHg	4712	2914	2321	1922

SBP=systolic blood pressure; SD=standard deviation

Figure 13. Incidience of ischemic stroke or systemic embolism according to standard deviation of controlled diastolic blood pressure level within each patient



DBP=diastolic blood pressure; SD=standard deviation

Discussion

The following is the major findings of the present study: In hypertensive nonvalvular AF patients, (1) controlled systolic BP lower than 120mmHg were in lower risk of ischemic stroke or systemic embolism, (2) higher standard deviation of measured BP in each patient during the follow up period is related with increased risk of ischemic stroke or systemic embolism. And (3) treated hypertension patients were in higher risk of ischemic stroke or systemic embolism than patients without history of hypertension regardless of controlled BP level.

There is no specific goal of blood pressure for AF patients in current guideline [7),8)]. Only a few studies have been commented about this issue. For example, Apurva et al. reported with post-hoc analysis of AFFIRM trial that blood pressure should not be controlled under 110/60mmHg because of increased all-cause mortality and composite outcomes [14)]. Rienstra et al showed that a BP goal <120/80 mmHg improves sinus rhythm maintenance in patients with persistent AF and heart failure [15)]. Parkash et al showed that, after catheter ablation for patients with AF, BP goal <120/80 mmHg did not reduce the atrial arrhythmia recurrence [16)]. Recently, DH Kim et al have suggested the optimal BP target in patients with AF as systolic BP between 120 to 129 mmHg and diastolic BP under 80 mmHg, which may lower the risk of cardiovascular event or death [9)].

For prevention of stroke in patients with AF, target of BP for hypertensive patients is not well known. In SPRINT trial which was studied in hypertensive patients not specific to AF, intensive treatment group with target BP lower than 120mmHg had statistically non-significant trend toward lower risk of stroke (HR 0.89, 95% CI 0.63-1.25, p =0.50) [11)]. In limited data for AF patients, intensive treatment of hypertension did not show a benefit for prevention of the stroke. DH Kim et al showed data from Korean National Health Insurance Service (NHIS) that suboptimal (130-139/80-89mmHg) and poor control (≥140/90mmHg) group was in higher risk of ischemic stroke than optimal (120-129/<80mmHg) group. However, intensive (<120/80mmHg) group did not show a difference compared with optimal group (HR 1.00, 95% CI 0.96-1.05, p =0.910) [9)]. Japanese J-RHYTHM registry

reported by Eitaro et al. showed that BP lower than 125mmHg for systolic BP and lower than 65mmHg for diastolic BP was related to the trend toward increased risk of thromboembolism [17]. In post-hoc analysis of ARISTOTLE study, Meena et al. reported that history of hypertension and elevated BP (more than 140/90mmHg) at baseline or at any time during study period increased the risk of stroke or systemic embolism[18].

Lower risk of ischemic stroke or systemic embolism in controlled systolic BP lower than 120mmHg was major finding of our study which might be conflict with previous studies. However, previous studies have limitation that they only counted the baseline or last BP measurement for the analysis [9, 17]. We counted approximately 19 BP measurements with interval of 49 days. Regarding that BP in AF patients have beat to beat variation [19], our result might be more accurate.

Stroke risk of AF patients with well controlled hypertension is not well known. Only a few studies have mentioned about this issue. Controlled BP level, not history of hypertension was important in risk of thromboembolism [17]. In another study, history of hypertension itself increased the risk of stroke and systemic embolism regardless of controlled BP level [18]. However, both of previous studies focused on whether the patients have history of hypertension or not. They did not compare the patients without history of hypertension and well controlled hypertensive patients. In this study, even intensively controlled hypertensive patients (systolic BP lower than 120mmHg) showed higher risk of ischemic stroke or systemic embolism compared with patients without history of hypertension. This suggest that even if hypertensive AF patients were well controlled for BP, they were still in high risk of stroke and needed for anticoagulation.

Beat-to-beat BP variability in patients with AF was substantially higher than in patients with sinus rhythm [19]. In stroke patients, beat-to-beat variation of BP showed significant increased risk of recurrent stroke, and day-to-day variation of BP showed trend toward increased risk of recurrent stroke [20]. Our result corresponds with previous study that AF patients with high visit-to-visit variation of BP have significantly increased risk of ischemic stroke or systemic embolism.

Our study is limited in that it was a retrospective review of a single-center registry, which carries the possibility of selection bias. There is limited evidence and significant heterogeneity in the studies that validated automated oscillometric blood pressure monitors in atrial fibrillation. These monitors appear to be accurate in measuring systolic BP but not diastolic BP [21]. So, analysis about the diastolic BP should be understand in caution. Study with BP measurement acquired from out-patient clinic might be helpful in real-world out-patient clinic practice, but it has limitation that measurement was not strictly controlled. Considering that research study BP is 10/7 mmHg lower than routine office BP [22], accuracy of BP measurement is further limited. Prescription of oral anticoagulant was relatively low might be because of long study period.

Conclusion

Controlled systolic BP lower than 120 mmHg showed lower risk of ischemic stroke and systemic embolism in patients with hypertension and nonvalvular AF. Degree of diastolic BP control did not show a significant difference. Treated hypertension patients were in higher risk of ischemic stroke or systemic embolism than patients without history of hypertension regardless of controlled BP level. High variation of visit-to-visit BP in hypertensive AF patients was related with increased risk of ischemic stroke or systemic embolism.

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국문 요약

목적: 고혈압은 심방세동 환자에 있어서 흔한 동반질환이며 뇌졸중의 위험인자이다. 하지만 고혈압을 지닌 심방세동환자에서 혈압관리의 목표에 대해서는 정확히 알려진 바가 없다.

방법: 서울아산병원에서 2006 년부터 2017 년동안 12,453 명의 고혈압을 지닌 비판막성 심방세동 환자가 연구에 포함되었다. 외래에서 시행된 혈압을 선형보간법을 사용하여 연구기간동안의 평균 혈압을 계산하였다. 혈압 조절에 따른 허혈성 뇌졸중과 전신색전증의 위험도를 보고자 하였다.

결과: 전체 12.453 명의 환자중, 평균 수축기혈압이 140mmHg 이상인 환자가 1,352 명, 120−140mmHg 사이인 환자가 6,641 명, 120mmHg 이하인 환자가 4,460 명이었다. 평균연령은 67.3±11.2 세였으며, 평균 추적관찰기간은 949.0±1001.4 일이었고, 평균 혈압측정 49.4±55.3 일이었다. 연간 허혈성 뇌졸중과 전신색전증의 발생건수는 평균 수축기혈압이 120mmHg 이하인 그룹에서 2.5%, 120−140mmHg 인 그룹에서 3.0%, 140mmHg 이상인 그룹에서 3.3%로 확인되었다. 평균 수축기혈압이 120−140mmHg 인 그룹과 비교하여 120mmHg 이하인 그룹에서 낮은 허혈성 뇌졸중과 전신색전증의 위험도를 보였으며 (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.72−0.96, p−value = 0.01), 140mmHg 이상인 그룹에서는 통계적으로 유의한 차이를 보이지는 않았다 (HR 1.09, 95% CI 0.88−1.35, p−value = 0.433). 이완기 혈압은 허혈성 뇌졸중과 전신색전증의 위험도에 있어서 유의한 영향을 미치지 않았다. 수축기 및 이완기 혈압의 일별 변동성이 큰 것은 허혈성 뇌졸중과 전신색전증의 위험도를 유의하게 높였다. 고혈압을 진단받은 환자는 혈압조절의 정도와 상관 없이 고혈압을 진단받은 적이 없는 환자에 비해서 허혈성 뇌졸중과 전신색전증의 위험도가 높았다.

결론: 고혈압을 지닌 비판막성 심방세동 환자에서 수축기혈압을 120mmHg 이하로 조절하는 것과 혈압측정값의 일별 변동값이 적은 것은 허혈성 뇌졸중과 전신색전증의 위험도를 감소시켰다. 고혈압의 과거력은 혈압조절의 정도와 관계 없이 허혈성 뇌졸중과 전신색전증의 위험도를 높였다.

중심단어: 비판막성 심방세동, 고혈압, 혈압 조절, 허혈성 뇌졸중, 전신성 색전증