ORIGINAL RESEARCH

Relation Between Blood Pressure and Clinical Outcome in Hypertensive Subjects With Previous Stroke

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***Background*—**This study investigated whether a mean blood pressure (BP) of <130/80 mm Hg is associated with further reduction in cardiovascular outcomes in treated hypertensive subjects with previous stroke.

***Methods and Results*—**Subjects from the Korea National Health Insurance Service health examinee cohort diagnosed as having stroke and hypertension from January 1st, 2003 and December 31st, 2006 (N=2320) were grouped according to mean systolic (<130, 130–<140, and ≥140 mm Hg) and diastolic (<80, 80–<90, and ≥90 mm Hg) BP recorded during follow-up health examinations. All-cause and cardiovascular mortality over 11 years were compared. Compared with subjects with a systolic BP of ≥140 mm Hg (N=736), subjects with a systolic BP of 130 to <140 mm Hg (N=793) had a significantly lower risk of all-cause death (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.47–0.79; *P*<0.001), cardiovascular mortality (HR, 0.39; 95% CI, 0.25–0.61; *P*<0.001), and fatal ischemic stroke (HR, 0.25; 95% CI, 0.10–0.63; *P*=0.003). Systolic BP of <130 mm Hg (N=791) was associated with lower risk of nonfatal hemorrhagic stroke. Subjects with a diastolic BP of 80 to <90 mm Hg (N=1100) had significantly lower risk of all-cause death (HR, 0.60, 95% CI, 0.45–0.80; *P*<0.001) and cardiovascular mortality (HR, 0.45; 95% CI, 0.30–0.70; *P*<0.001) than those with a diastolic BP of ≥90 mm Hg (N=342). Diastolic BP of <80 mm Hg (N=878) was associated with reduced risk of nonfatal hemorrhagic stroke and further lowering of all-cause mortality and cardiovascular mortality.

***Conclusions*—**BP of <130/80 mm Hg was associated with improved outcomes in hypertensive subjects with previous stroke. **(*J Am Heart Assoc*. 2017;6:e007102. DOI: 10.1161/JAHA.117.007102.)**

Key Words: hypertension • mortality • myocardial infarction • stroke

Recently, the SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated that the treatment goal of systolic blood pressure (SBP) of <120 mm Hg was superior to the SBP goal of <140 mm Hg in reducing cardiovascular risk.[1] Although the SPRINT study included subjects with high cardiovascular risk, it excluded hypertensive subjects with previous stroke based on the SPS3 (Secondary Prevention of Small Subcortical Strokes) trial, an open-label randomized study that demonstrated the benefit of strict SBP lowering in subjects with previous lacunar infarction.[2] Compared with subjects randomized to a target SBP of 130 to 149 mm Hg, subjects randomized to a lower SBP target of <130 mm Hg demonstrated a nonsignificant reduction in the primary outcome of all strokes and a significantly lower rate of intracerebral hemorrhage.[2] Consequently, the American Stroke Association proposes the IIb recommendation for a target SBP of 130 mm Hg in subjects with previous lacunar infarction.[3] However, the SPS3 study was limited by its inclusion of only subjects with previous lacunar infarction, relative lack of statistical power, 2-by-2 multifactorial design, and enrollment of both normotensive and hypertensive subjects. Therefore, whether strict SBP lowering is beneficial for all hypertensive subjects with previous stroke is unclear. However, it is difficult to verify this through large-scale clinical studies, so using observational cohort data may be helpful.[4]

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Accompanying Data S1 and Tables S1 through S12 are available at http://jaha.ahajournals.org/content/6/12/e007102/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In a cohort of hypertensive subjects with previous stroke, a mean blood pressure (BP) of <130/80 mm Hg had optimal benefit in terms of mortality, cardiovascular mortality, and nonfatal hemorrhagic stroke.
- However, diastolic BP of <80 mm Hg was associated with significantly higher rate of nonfatal myocardial infarction compared with a diastolic BP of 80 to <90 mm Hg.

What Are the Clinical Implications?

- The results from this study may provide insight into the possible benefit of strict diastolic BP lowering in hypertensive subjects with previous stroke in terms of mortality reduction.
- However, the increased risk of myocardial infarction with strict diastolic BP lowering should be considered as well.

The present study aimed to evaluate whether lower mean BP in hypertensive subjects with previous stroke has a beneficial effect on reducing cardiovascular events, using the National Health Insurance Service (NHIS) cohort.

Methods

Study Population

This study used the NHIS health examinee cohort, comprising 514 866 individuals randomly selected from the NHIS health examination database in 2002.[5] The NHIS cohort profile was previously reported.[6] The NHIS provides free health examinations to eligible NHIS members aged ≥40 years. Detailed information about the health examination is described in Data S1. The intellectual property right of this database belongs to the National Health Insurance corporation. As such, we are not authorized to open the database to the public. However, any investigator can apply for use of the database because it has been open to the public for research purpose (https://nhiss.nhis.or.kr/). This cohort was followed up for 11 years until 2013. The cohort data consisted of qualifications; medical service claims; pharmacy claims; and health examination findings, including anthropometric data, blood chemistry, urine analysis, chest radiography, and information about lifestyle and personal and familial history of hypertension. The disposition of the study cohort is shown in Figure 1. We selected subjects who had been diagnosed as having stroke (Korean Classification of Disease [KCD] codes I60–I64), requiring hospitalization, and hypertension (KCD codes I10–I13) between January 1, 2003 and December 31, 2006 for inclusion in the study population. The KCD system is based on and similar to the *International Classification of Diseases, Tenth Revision* (*ICD-10*).[7] Stroke was classified into hemorrhagic stroke (KCD codes I60–I62), ischemic stroke (KCD code I63), and unspecified stroke (KCD code I64). Subjects diagnosed as having stroke and hypertension either simultaneously or separately during the index period were included; 1337 of the subjects received a diagnosis of hypertension before the diagnosis of stroke. Individuals diagnosed as having a previous or active malignancy (KCD codes C00–C97) after stroke diagnosis were excluded. In addition, individuals with prescription records for antihypertensive medications for <1 year during the follow-up or who had undergone health examination only once between January 1, 2003 and December 31, 2013 were excluded. Ultimately, 2320 individuals were included in the analysis. The Institutional Review Board of Yonsei University Health System approved the study (Institutional Review Board number 4-2016-1043), with waiver of informed consent because this was a retrospective observational study of an anonymized data set.

Definition of Medication History

Information about medications during the follow-up was obtained using a prescription database after the index date. We categorized the 5 first-line antihypertensive agents into 4 classes: renin-angiotensin system blocker; β-blocker; calcium channel blocker; and diuretics, including hydrochlorothiazide, chlortalidone, and metolazone. Subjects who had prescription data for antihypertensive agents for at least 1 year were assumed to be taking the medication. The first prescription date and total prescription duration of each medication were obtained from the prescription database. Only individuals who had taken antihypertensive agents for at least 1 year during follow-up were included. In addition, subjects who had taken aspirin or a statin for at least 1 year were assumed to be taking these medications for secondary stroke prevention. Diabetes mellitus was defined as a diagnosis of diabetes mellitus (KCD codes E11–E14) with prescription data for antidiabetic medications before the diagnosis of stroke.[8] Atrial fibrillation was determined by the presence of the corresponding diagnostic code (KCD code I48).

BP Measurement and Classification

BP was measured in hospitals and clinics certified as medical health examination centers by the Korean National Health Insurance Corporation. The measurement protocol was for brachial BP after 5 minutes of rest in the sitting position. BP measurement was repeated if the first measurement was

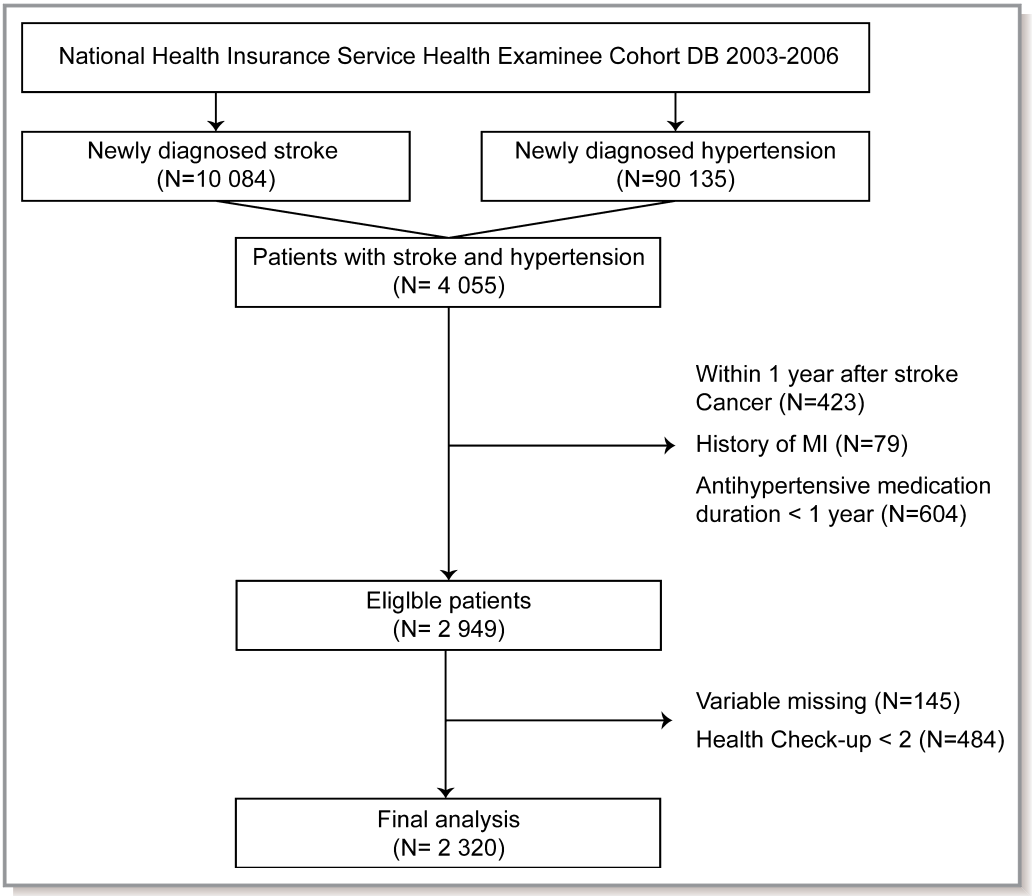

Figure 1. The disposition of the study cohort. DB indicates database; and MI, myocardial infarction.

>120/80 mm Hg. BP was measured by qualified medical personnel at each health examination center. Both automatic oscillometric devices and mercury sphygmomanometers were used for BP measurements. The choice of device was left to the discretion of individual examination centers, with the preferred recommendation for a mercury sphygmomanometer until 2015, when the sale of mercury sphygmomanometers was banned.

We defined strict SBP control as mean SBP of <130 mm Hg, consistent with the SPS3 study. Although diastolic BP (DBP) of <90 mm Hg is recommended in the current guidelines, studies using J curves have indicated that cardiovascular risk increases at <60 to 70 mm Hg.[9,10] Therefore, we also aimed to determine whether DBP lowering at <80 mm Hg was beneficial in poststroke hypertensive subjects.

The mean value of BP at all health examinations during the follow-up was used to determine the BP target that subjects had achieved. The study population was divided into 3 groups according to observed mean SBP and DBP: (1) mean SBP of <130 mm Hg (N=791), 130 to <140 mm Hg (N=793), and ≥140 mm Hg (N=736); and (2) mean DBP of <80 mm Hg (N=878), 80 to <90 mm Hg (N=1100), and ≥90 mm Hg (N=342).

Follow-Up and Outcome Measurement

The mean and median follow-up duration were 2987±757 and 3092 days (interquartile range, 2151- 3468 days), respectively. The primary outcomes were all-cause mortality and cardiovascular mortality. The dates and causes of death were obtained from the qualification data in the cohort database, which was prepared by Statistics Korea. Clinical outcomes were assessed after the diagnosis of stroke. Cardiovascular mortality was defined as death from a circulatory system disease (KCD codes I00–I99). Causes of cardiovascular mortality were further categorized as myocardial infarction (MI; KCD codes I21–I23), hemorrhagic stroke (KCD codes I60–I62), and ischemic stroke (KCD code I63).[11] We also analyzed rates of nonfatal MI and nonfatal stroke requiring hospitalization. We defined nonfatal stroke as rehospitalization with either nonfatal hemorrhagic or ischemic stroke as the major diagnosis, according to KCD code.

Statistical Analysis

Household income was categorized as upper 20%, middle 40%, and lower 40% based on income levels provided by the NHIS. Residential areas were classified as metropolitan cities or

Table 1. Clinical Characteristics of the Total Study Population According to Observed Mean SBP (N=2320)

Characteristics	Observed Mean SBP, mm Hg			*P* Value
	<130 (N=791)	130–<140 (N=793)	≥140 (N=736)	
Types of stroke				0.377
Hemorrhagic	158 (20.0)	139 (17.5)	144 (19.6)	
Ischemic	606 (76.6)	619 (78.1)	571 (77.6)	
Unspecified	27 (3.4)	35 (4.4)	21 (2.9)	
SBP, mm Hg	122.7±5.8	134.3±2.8	149.2±9.0	<0.001
No. of BP measurements	4.6±1.9	4.7±1.9	3.9±1.8	<0.001
Age, y	59.1±9.0	60.6±9.1	62.4±9.1	<0.001
Sex				0.136
Male	430 (54.4)	437 (55.1)	435 (59.1)	
Female	361 (45.6)	356 (44.9)	301 (40.9)	
Residential area				0.118
Metropolitan	281 (35.5)	243 (30.6)	246 (33.4)	
Province	510 (64.5)	550 (69.4)	490 (66.6)	
Household income				0.005
Upper 20%	249 (31.5)	208 (26.2)	178 (24.2)	
Middle 40%	309 (39.1)	300 (37.8)	294 (39.9)	
Lower 40%	233 (29.5)	285 (35.9)	264 (35.9)	
Smoking status				0.572
Never smoker	517 (65.4)	546 (68.9)	504 (68.5)	
Ex-smoker	62 (7.8)	57 (7.2)	57 (7.7)	
Current smoker	212 (26.8)	190 (24.0)	175 (23.8)	
Alcohol frequency				0.133
Never	492 (62.2)	500 (63.1)	447 (60.7)	
2–3 Drinks/mo	96 (12.1)	79 (10.0)	68 (9.2)	
1–2 Drinks/wk	93 (11.8)	86 (10.8)	94 (12.8)	
3–4 Drinks/wk	64 (8.1)	59 (7.4)	57 (7.7)	
Daily	46 (5.8)	69 (8.7)	70 (9.5)	
Body mass index, kg/m^2	24.3±2.9	24.4±3.0	24.4±3.1	0.781
Total cholesterol, mg/dL	206.6±44.4	206.5±43.2	204.3±42.1	0.530
Fasting glucose, mg/dL	106.4±53.0	104.1±35.6	114.2±62.8	<0.001
Baseline SBP, mm Hg	127.8±14.3	139.0±15.2	155.5±19.0	<0.001
Baseline DBP, mm Hg	80.0±10.3	85.1±11.2	92.1±12.8	<0.001
History of DM	46 (5.8)	47 (5.9)	51 (6.9)	0.614
History of atrial fibrillation	31 (3.9)	19 (2.4)	8 (1.1)	0.002
Medications during follow-up				
RASBs	536 (67.8)	566 (71.4)	519 (70.5)	0.263
RASB duration, d	1580.5±1201.7	1618.9±1193.0	1605.4±1218.3	0.836
β-Blockers	202 (25.5)	221 (27.9)	234 (31.8)	0.024
β-Blocker duration, d	1023.2±1189.8	901.6±1024.2	931.2±1052.8	0.278
CCBs	540 (68.3)	591 (74.5)	576 (78.3)	<0.001

Continued

Table 1. Continued

Characteristics	Observed Mean SBP, mm Hg			*P* Value
	<130 (N=791)	130–<140 (N=793)	≥140 (N=736)	
CCB duration, d	1668.7±1266.7	1749.2±1224.0	1782.9±1288.5	0.227
Diuretics	171 (21.6)	240 (30.3)	212 (28.8)	<0.001
Diuretic duration, d	782.6±896.9	863.1±909.3	779.0±869.7	0.325
Statins	362 (45.8)	340 (42.9)	297 (40.4)	0.102
Statin duration, d	1357.1±1069.6	1351.4±1086.1	1210.4±1028.0	0.068
Aspirin	368 (46.5)	340 (42.9)	322 (43.8)	0.314
Aspirin duration, d	1068.4±952.2	1012.4±958.0	953.7±911.1	0.151
Warfarin	55 (7.0)	36 (4.5)	27 (3.7)	0.010
Warfarin duration, d	1454.3±1455.9	1100.1±1213.7	910.3±1175.6	0.045
P2Y12	284 (35.9)	272 (34.3)	265 (36.0)	0.732
P2Y12 duration, d	1344.1±1144.5	1377.1±1144.9	1267.9±1090.3	0.385
Follow-up duration, d	3087.6±669.4	3030.2±663.4	2832.6±904.0	<0.001

Data are presented as mean±SD or number (percentage). Each type of stroke was defined with diagnostic codes, as follows: hemorrhagic stroke, I60 to I62; ischemic stroke, I63; and unspecified stroke, I64. BP indicates blood pressure; CCB, calcium channel blocker; DBP, diastolic BP; DM, diabetes mellitus; RASB, renin-angiotensin system blocker; and SBP, systolic BP.

provinces. Group differences in continuous variables were analyzed by using 1-way analysis of variance. Categorical variables were summarized as numbers and percentages of the total group and compared by χ^2 test. The effects of BP on all-cause mortality and cardiovascular mortality were analyzed by using Kaplan-Meier curves. The association between BP and clinical events, including both fatal and nonfatal outcomes, was evaluated by using Cox proportional hazard models with the covariate adjustment method using the propensity scores, because some end points had a rare event problem when we used the multivariate Cox proportional hazard model with all confounders. The effect of each level of BP on mortality and clinical events was determined by comparison to the uncontrolled hypertension group (SBP ≥140 mm Hg or DBP ≥90 mm Hg). We also compared the effect of each BP level on mortality and clinical events by comparison to the SBP of 130 to <140 mm Hg and DBP of 80 to <90 mm Hg groups. Propensity scores were assigned using multinomial logistic regression for groups stratified by mean SBP and DBP based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline SBP, baseline DBP, diabetes mellitus history, and atrial fibrillation history. Medication exposure was not included to estimate propensity score because it is information of medication after the index date. Instead, a subgroup analysis was conducted for aspirin or statin users (Tables S1 and S2) and subjects without baseline atrial fibrillation (Tables S3 and S4). In addition, we analyzed the subject regardless of duration of antihypertensive medication (Tables S5 and S6).

All statistical analyses were performed using R statistical software, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2 sided, and statistical significance was defined as $P<0.05$.

Results

Demographic Data

Clinical characteristics of the study population, according to mean SBP and DBP grouping, are shown in Tables 1 and 2. The proportions of ischemic stroke and hemorrhagic stroke were 77.4% and 19.8%, respectively. Previous stroke type did not differ according to mean SBP group. The SBP of <130 mm Hg group included a higher percentage of subjects with atrial fibrillation and a significantly lower proportion of subjects taking β-blockers, calcium channel blockers, and diuretics. Although the percentage of subjects taking aspirin and statins during the follow-up did not significantly differ, there was a higher percentage of warfarin users among subjects with an SBP of <130 mm Hg.

Unlike mean SBP, subjects with a higher mean DBP had a higher percentage with hemorrhagic stroke. The group with a mean DBP of <80 mm Hg had a significantly lower percentage of subjects taking calcium channel blockers and diuretics and a significantly higher percentage of subjects taking aspirin, statins, and warfarin.

Clinical Outcomes According to Mean SBP and DBP

Kaplan-Meier analyses for all-cause death and cardiovascular death, according to mean SBP and DBP, revealed significantly

Table 2. Clinical Characteristics of the Total Study Population According to Observed Mean DBP (N=2320)

Characteristics	Observed Mean DBP, mm Hg			*P* Value
	<80 (N=878)	80–<90 (N=1100)	≥90 (N=342)	
Types of stroke				0.008
Hemorrhagic	148 (16.9)	209 (19.0)	84 (24.6)	
Ischemic	693 (78.9)	850 (77.3)	253 (74.0)	
Unspecified	37 (4.2)	41 (3.7)	5 (1.5)	
DBP, mm Hg	74.9±3.9	83.9±2.6	94.5±5.4	<0.001
No. of BP measurements	4.5±1.7	4.6±2.0	3.7±2.0	<0.001
Age, y	61.2±8.6	60.6±9.3	59.4±9.9	0.008
Sex				0.001
Male	450 (51.3)	645 (58.6)	207 (60.5)	
Female	428 (48.7)	455 (41.4)	135 (39.5)	
Residential area				0.498
Metropolitan	299 (34.1)	352 (32.0)	119 (34.8)	
Province	579 (65.9)	748 (68.0)	223 (65.2)	
Household income				0.095
Upper 20%	264 (30.1)	287 (26.1)	84 (24.6)	
Middle 40%	335 (38.2)	441 (40.1)	127 (37.1)	
Lower 40%	279 (31.8)	372 (33.8)	131 (38.3)	
Smoking status				0.561
Never smoker	608 (69.2)	739 (67.2)	220 (64.3)	
Ex-smoker	61 (6.9)	86 (7.8)	29 (8.5)	
Current smoker	209 (23.8)	275 (25.0)	93 (27.2)	
Alcohol frequency				<0.001
Never	589 (67.1)	671 (61.0)	179 (52.3)	
2–3 Drinks/mo	94 (10.7)	113 (10.3)	36 (10.5)	
1–2 Drinks/wk	86 (9.8)	132 (12.0)	55 (16.1)	
3–4 Drinks/wk	52 (5.9)	89 (8.1)	39 (11.4)	
Daily	57 (6.5)	95 (8.6)	33 (9.6)	
Body mass index, kg/m^2	24.2±2.9	24.4±3.0	24.8±3.1	0.009
Total cholesterol, mg/dL	206.9±46.2	205.2±41.5	204.9±41.1	0.638
Fasting glucose, mg/dL	109.2±54.0	107.0±46.4	108.9±60.4	0.609
Baseline SBP, mm Hg	131.6±16.7	142.1±17.6	157.9±20.6	<0.001
Baseline DBP, mm Hg	78.0±9.3	87.4±10.0	98.9±13.0	<0.001
History of DM	60 (6.8)	63 (5.7)	21 (6.1)	0.598
History of atrial fibrillation	30 (3.4)	20 (1.8)	8 (2.3)	0.076
Medications during follow-up				
RASBs	607 (69.1)	768 (69.8)	246 (71.9)	0.632
RASB duration, d	1585.7±1195.8	1621.1±1217.2	1580.7±1182.2	0.785
β-Blockers	244 (27.8)	293 (26.6)	120 (35.1)	0.009
β-Blocker duration, d	1006.3±1115.8	901.4±1077.0	957.9±1051.3	0.322
CCBs	603 (68.7)	848 (77.1)	256 (74.9)	<0.001

Continued

Table 2. Continued

Characteristics	Observed Mean DBP, mm Hg			*P* Value
	<80 (N=878)	80–<90 (N=1100)	≥90 (N=342)	
CCB duration, d	1634.9±1263.6	1820.0±1246.5	1702.4±1276.6	0.008
Diuretics	209 (23.8)	312 (28.4)	102 (29.8)	0.031
Diuretic duration, d	839.7±920.5	796.9±883.0	790.3±863.3	0.727
Statins	424 (48.3)	452 (41.1)	123 (36.0)	<0.001
Statin duration, d	1420.5±1080.6	1227.1±1034.5	1263.5±1091.8	0.006
Aspirin	432 (49.2)	466 (42.4)	132 (38.6)	0.001
Aspirin duration, d	1115.4±990.5	966.3±910.7	874.4±873.9	0.001
Warfarin	58 (6.6)	43 (3.9)	17 (5.0)	0.025
Warfarin duration, d	1376.6±1428.5	1099.4±1215.2	939.8±1252.0	0.184
P2Y12	322 (36.7)	385 (35.0)	114 (33.3)	0.512
P2Y12 duration, d	1334.0±1150.2	1359.4±1119.2	1223.8±1090.3	0.391
Follow-up duration, d	3084.3±681.6	2966.0±737.0	2805.0±947.2	<0.001

Data are presented as mean±SD or number (percentage). Each type of stroke was defined with diagnostic codes, as follows: hemorrhagic stroke, I60 to I62; ischemic stroke, I63; and unspecified stroke, I64. BP indicates blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; RASB, renin-angiotensin system blocker; and SBP, systolic blood pressure.

lower cumulative all-cause (SBP, log-rank $P<0.001$ [Figure 2A]; DBP, $P<0.001$ [Figure 2B]) and cardiovascular (SBP, log-rank $P<0.001$ [Figure 2C]; DBP, $P<0.001$ [Figure 2D]) deaths in lower BP groups compared with the higher BP groups (SBP ≥140 mm Hg and DBP ≥90 mm Hg).

Table 3 shows the results of Cox proportional hazard models for all-cause death, cardiovascular death, detailed cause of death, and nonfatal events, including MI and stroke, according to mean SBP. The propensity-adjusted model revealed that subjects with a mean SBP of 130 to <140 mm Hg had a significantly lower risk of all-cause death (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.47–0.79; $P<0.001$), cardiovascular mortality (HR, 0.39; 95% CI, 0.25–0.61; $P<0.001$), and fatal ischemic stroke (HR, 0.25; 95% CI, 0.10–0.63; $P=0.003$) compared with subjects with a mean SBP of ≥140 mm Hg. There was no additional benefit for mean SBP of <130 mm Hg with regard to all-cause or cardiovascular death. In terms of nonfatal events, the risks of nonfatal MI and nonfatal ischemic stroke did not differ according to mean SBP groups. However, the risk of nonfatal hemorrhagic stroke was significantly lower in the mean SBP of <130 mm Hg group (HR, 0.57; 95% CI, 0.33–0.97; $P=0.038$) compared with subjects with a mean SBP of ≥140 mm Hg.

Subjects with a mean DBP of 80 to <90 mm Hg had a significantly lower risk of all-cause death (HR, 0.60; 95% CI, 0.45–0.80; $P<0.001$) and cardiovascular mortality (HR, 0.45; 95% CI, 0.30–0.70; $P<0.001$) compared with subjects with a mean DBP of ≥90 mm Hg (Table 4). Mean DBP of <80 mm Hg was associated with a significantly lower risk of all-cause death (HR, 0.45; 95% CI, 0.32–0.63; $P<0.001$), cardiovascular mortality (HR, 0.29; 95% CI, 0.17–0.49; $P<0.001$), fatal MI (HR, 0.04; 95% CI, 0.01–0.28; $P=0.001$), and fatal hemorrhagic stroke (HR, 0.21; 95% CI, 0.05–0.92; $P=0.039$). Mean DBP of <80 mm Hg was associated with further reduction in all-cause mortality, cardiovascular mortality, and fatal MI compared with subjects with a mean DBP of 80 to <90 mm Hg (Table 4). However, the risk of nonfatal MI was significantly higher in subjects with a mean DBP of <90 mm Hg compared with subjects with a mean DBP of 80 to <90 mm Hg. Subjects with a mean DBP of 80 to <90 mm Hg had a trend for lower risk of nonfatal hemorrhagic stroke (HR, 0.65; 95% CI, 0.40–1.07; $P=0.091$), whereas subjects with a mean DBP of <80 mm Hg were associated with a significantly lower risk of nonfatal hemorrhagic stroke (HR, 0.47; 95% CI, 0.26–0.85; $P=0.012$). To exclude the possibility of events being caused by the initial stroke itself, we performed an additional analysis to exclude subjects who died within 1 year from the index stroke event (Tables S7 and S8) and observed a similar trend in clinical outcomes compared with the original analyses. In addition, we analyzed the subject regardless of duration of antihypertensive medication. This also showed similar results (Tables S5 and S6). Further analysis of the effect of mean SBP of <120 mm Hg showed a tendency for lower risk of cardiovascular death and fatal ischemic stroke. The risks of both fatal and nonfatal events were not significantly lower in subjects with a mean SBP of <120 mm Hg compared with subjects with a mean SBP of ≥140 mm Hg (Table S9). Mean DBP of <70 mm Hg showed a tendency for reduced risk of cardiovascular death, but there was no reduction in risk of other outcomes (Table S10). When DBP of 80 to <90 mm Hg was

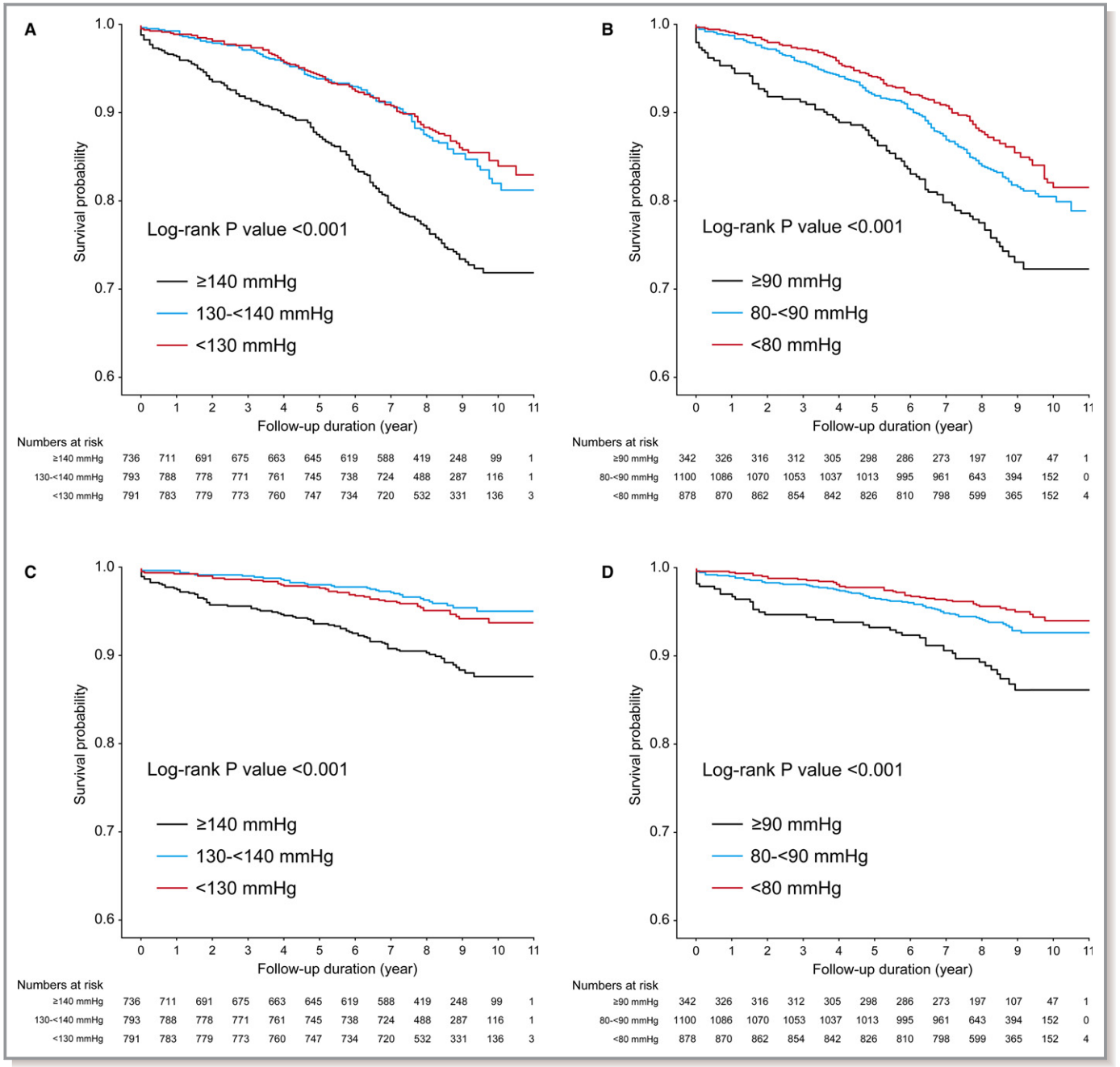

Figure 2. Kaplan-Meier curves for all-cause death according to mean systolic (A) and diastolic (B) blood pressure levels and for cardiovascular death according to mean systolic (C) and diastolic (D) blood pressure levels.

used as a reference, DBP of 70 to <80 mm Hg had a significantly higher risk of nonfatal MI (Table S10).

Clinical Outcomes According to Mean SBP and DBP in Subjects Taking Aspirin and/or Statins During Follow-Up

The clinical characteristics of study subjects who were taking aspirin or statins are shown in Tables S1 and S2, respectively. Subjects with a mean SBP of 130 to <140 mm Hg had a significantly lower risk of cardiovascular mortality (HR, 0.39; 95% CI, 0.19–0.81; *P*=0.012; Table 5) than subjects with a mean SBP of >140 mm Hg. In terms of DBP, subjects with a mean DBP of 80 to <90 mm Hg had a significantly lower risk of all-cause death (HR, 0.54; 95% CI, 0.34–0.87; *P*=0.012), cardiovascular mortality (HR, 0.28; 95% CI, 0.14–0.60; *P*=0.001), and fatal MI (HR, 0.12; 95% CI, 0.02–0.61; *P*=0.011) than subjects with a mean DBP of ≥90 mm Hg (Table 6). Mean DBP of <80 mm Hg was associated with a significantly lower risk of all-cause death, cardiovascular

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Table 3. Cox Proportional Hazard Models for Mortality According to Observed Mean SBP Groups in the Total Study Population

Outcome	Category, mm Hg	No. (%) of Events	Unadjusted		Age and Sex Adjusted		Propensity Adjusted (Reference group: ≥140)		Propensity Adjusted (Reference group: 130–<140)	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death	<130	106 (13.40)	0.48 (0.38–0.61)	<0.001	0.65 (0.51–0.82)	<0.001	0.65 (0.48–0.87)	0.005	1.07 (0.80–1.41)	0.654
	130–<140	113 (14.25)	0.52 (0.41–0.66)	<0.001	0.60 (0.48–0.76)	<0.001	0.61 (0.47–0.79)	<0.001	Reference	Reference
	≥140	186 (25.27)	Reference	Reference	Reference	Reference	Reference	Reference	1.65 (1.27–2.13)	<.001
Cardiovascular death	<130	42 (5.31)	0.46 (0.32–0.66)	<0.001	0.61 (0.42–0.89)	0.010	0.56 (0.35–0.90)	0.017	1.43 (0.88–2.31)	0.148
	130–<140	33 (4.16)	0.36 (0.24–0.54)	<0.001	0.42 (0.28–0.63)	<0.001	0.39 (0.25–0.61)	<0.001	Reference	Reference
	≥140	81 (11.01)	Reference	Reference	Reference	Reference	Reference	Reference	2.54 (1.63–3.94)	<0.001
Fatal MI	<130	4 (0.51)	0.33 (0.10–1.03)	0.056	0.46 (0.14–1.45)	0.182	0.54 (0.13–2.25)	0.396	1.27 (0.29–5.49)	0.750
	130–<140	4 (0.50)	0.34 (0.11–1.06)	0.062	0.40 (0.13–1.26)	0.117	0.42 (0.12–1.47)	0.176	Reference	Reference
	≥140	11 (1.49)	Reference	Reference	Reference	Reference	Reference	Reference	2.35 (0.68–8.13)	0.176
Fatal hemorrhagic stroke	<130	3 (0.38)	0.20 (0.06–0.68)	0.011	0.22 (0.06–0.78)	0.019	0.47 (0.11–2.02)	0.312	1.24 (0.26–5.85)	0.787
	130–<140	4 (0.50)	0.26 (0.09–0.80)	0.018	0.28 (0.09–0.85)	0.025	0.38 (0.12–1.25)	0.111	Reference	Reference
	≥140	14 (1.90)	Reference	Reference	Reference	Reference	Reference	Reference	2.62 (0.80–8.57)	0.111
Fatal ischemic stroke	<130	7 (0.88)	0.30 (0.13–0.71)	0.006	0.41 (0.17–0.97)	0.044	0.23 (0.08–0.66)	0.006	0.92 (0.31–2.77)	0.886
	130–<140	7 (0.88)	0.30 (0.13–0.72)	0.006	0.36 (0.15–0.84)	0.019	0.25 (0.10–0.63)	0.003	Reference	Reference
	≥140	21 (2.85)	Reference	Reference	Reference	Reference	Reference	Reference	3.99 (1.59–10.00)	0.003
Nonfatal MI	<130	22 (2.78)	1.20 (0.64–2.25)	0.579	1.35 (0.71–2.57)	0.354	1.98 (0.87–4.52)	0.103	1.67 (0.84–3.34)	0.143
	130–<140	16 (2.02)	0.87 (0.44–1.73)	0.696	0.94 (0.47–1.87)	0.864	1.19 (0.55–2.55)	0.662	Reference	Reference
	≥140	17 (2.31)	Reference	Reference	Reference	Reference	Reference	Reference	0.84 (0.39–1.81)	0.662
Nonfatal hemorrhagic stroke	<130	35 (4.42)	0.59 (0.39–0.90)	0.015	0.56 (0.36–0.86)	0.008	0.57 (0.33–0.97)	0.038	0.75 (0.47–1.20)	0.232
	130–<140	45 (5.67)	0.76 (0.51–1.13)	0.182	0.74 (0.50–1.10)	0.134	0.76 (0.49–1.18)	0.222	Reference	Reference
	≥140	54 (7.34)	Reference	Reference	Reference	Reference	Reference	Reference	1.32 (0.85–2.05)	0.222
Nonfatal ischemic stroke	<130	170 (21.5)	0.85 (0.69–1.05)	0.134	0.93 (0.76–1.16)	0.532	0.91 (0.70–1.19)	0.494	0.99 (0.79–1.24)	0.941
	130–<140	174 (21.9)	0.88 (0.71–1.08)	0.232	0.93 (0.75–1.15)	0.496	0.92 (0.73–1.16)	0.479	Reference	Reference
	≥140	179 (24.3)	Reference	Reference	Reference	Reference	Reference	Reference	1.09 (0.86–1.37)	0.479

Propensity-adjusted models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline SBP, baseline diastolic blood pressure, history of diabetes mellitus, and history of atrial fibrillation. CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; and SBP, systolic blood pressure.

Table 4. Cox Proportional Hazard Models for Mortality According to Observed Mean DBP Groups in the Total Study Population

Outcome	Category, mm Hg	No. (%) of Events	Unadjusted		Age and Sex Adjusted		Propensity Adjusted (Reference group: ≥90)		Propensity Adjusted (Reference group: 80–<90)	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death	<80	128 (14.58)	0.52 (0.40–0.68)	<0.001	0.45 (0.34–0.29)	<0.001	0.45 (0.32–0.63)	<0.001	0.75 (0.58–0.96)	0.023
	80–<90	191 (17.36)	0.65 (0.51–0.84)	0.001	0.57 (0.44–0.73)	<0.001	0.60 (0.45–0.80)	<0.001	Reference	Reference
	≥90	86 (25.15)	Reference	Reference	Reference	Reference	Reference	Reference	1.67 (1.25–2.21)	<0.001
Cardiovascular death	<80	43 (4.90)	0.37 (0.24–0.57)	<0.001	0.33 (0.22–0.51)	<0.001	0.29 (0.17–0.49)	<0.001	0.63 (0.42–0.96)	0.031
	80–<90	71 (6.45)	0.51 (0.35–0.75)	0.001	0.46 (0.31–0.67)	<0.001	0.45 (0.30–0.70)	<0.001	Reference	Reference
	≥90	42 (12.28)	Reference	Reference	Reference	Reference	Reference	Reference	2.20 (1.44–3.38)	<0.001
Fatal MI	<80	2 (0.23)	0.11 (0.02–0.51)	0.005	0.10 (0.02–0.46)	0.004	0.04 (0.01–0.28)	0.001	0.14 (0.02–0.69)	0.016
	80–<90	10 (0.91)	0.44 (0.17–1.16)	0.095	0.39 (0.15–1.02)	0.055	0.32 (0.10–0.97)	0.044	Reference	Reference
	≥90	7 (2.05)	Reference	Reference	Reference	Reference	Reference	Reference	3.16 (1.03–9.66)	0.044
Fatal hemorrhagic stroke	<80	4 (0.46)	0.19 (0.06–0.64)	0.007	0.18 (0.05–0.60)	0.005	0.21 (0.05–0.92)	0.039	0.55 (0.15–2.01)	0.368
	80–<90	9 (0.82)	0.35 (0.13–0.91)	0.031	0.33 (0.13–0.87)	0.024	0.37 (0.13–1.09)	0.071	Reference	Reference
	≥90	8 (2.34)	Reference	Reference	Reference	Reference	Reference	Reference	2.70 (0.92–7.91)	0.071
Fatal ischemic stroke	<80	9 (1.03)	0.34 (0.14–0.83)	0.018	0.30 (0.12–0.75)	0.009	0.20 (0.06–0.60)	0.004	0.54 (0.22–1.32)	0.175
	80–<90	16 (1.45)	0.49 (0.22–1.08)	0.077	0.44 (0.20–0.98)	0.045	0.37 (0.15–0.88)	0.025	Reference	Reference
	≥90	10 (2.92)	Reference	Reference	Reference	Reference	Reference	Reference	2.73 (1.13–6.57)	0.025
Nonfatal MI	<80	27 (3.08)	1.04 (0.50–2.14)	0.923	1.05 (0.51–2.17)	0.896	1.38 (0.56–3.41)	0.479	2.36 (1.23–4.54)	0.010
	80–<90	18 (1.64)	0.55 (0.26–1.20)	0.133	0.54 (0.25–1.17)	0.119	0.59 (0.25–1.36)	0.214	Reference	Reference
	≥90	10 (2.92)	Reference	Reference	Reference	Reference	Reference	Reference	1.71 (0.73–3.97)	0.214
Nonfatal hemorrhagic stroke	<80	40 (4.56)	0.50 (0.31–0.81)	0.004	0.50 (0.31–0.80)	0.004	0.47 (0.26–0.85)	0.012	0.71 (0.46–1.10)	0.128
	80–<90	64 (5.82)	0.65 (0.42–1.01)	0.054	0.66 (0.42–1.01)	0.057	0.65 (0.40–1.07)	0.091	Reference	Reference
	≥90	30 (8.77)	Reference	Reference	Reference	Reference	Reference	Reference	1.53 (0.94–2.49)	0.091
Nonfatal ischemic stroke	<80	193 (21.98)	0.82 (0.64–1.05)	0.122	0.78 (0.61–1.01)	0.056	0.76 (0.56–1.04)	0.084	0.97 (0.79–1.19)	0.757
	80–<90	243 (22.09)	0.84 (0.66–1.07)	0.157	0.81 (0.64–1.04)	0.095	0.79 (0.60–1.03)	0.082	Reference	Reference
	≥90	87 (25.44)	Reference	Reference	Reference	Reference	Reference	Reference	1.27 (0.97–1.66)	0.082

Propensity-adjusted models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline DBP, history of diabetes mellitus, and history atrial fibrillation. CI indicates confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; and MI, myocardial infarction.

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Table 5. Propensity-Adjusted Cox Proportional Hazard Models for Mortality According to Observed Mean SBP Groups in Aspirin and/or Statin Users

		Reference group (≥140)		Reference group (130–<140)	
Mortality	No. (%) of Events	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death, mm Hg					
<130	52 (10.00)	0.97 (0.61–1.53)	0.883	1.41 (0.92–2.17)	0.118
130–<140	43 (8.60)	0.69 (0.45–1.04)	0.077	Reference	Reference
≥140	70 (15.35)	Reference	Reference	1.46 (0.96–2.22)	0.077
Cardiovascular death, mm Hg					
<130	19 (3.65)	0.60 (0.28–1.27)	0.180	1.53 (0.71–3.29)	0.274
130–<140	12 (2.40)	0.39 (0.19–0.81)	0.012	Reference	Reference
≥140	27 (5.92)	Reference	Reference	2.57 (1.23–5.38)	0.012
Fatal MI, mm Hg					
<130	3 (0.58)	1.15 (0.18–7.53)	0.881	1.99 (0.30–13.10)	0.473
130–<140	2 (0.40)	0.58 (0.09–3.60)	0.558	Reference	Reference
≥140	4 (0.88)	Reference	Reference	1.73 (0.28–10.74)	0.558
Fatal hemorrhagic stroke, mm Hg					
<130	1 (0.19)	0.49 (0.03–8.45)	0.627	1.22 (0.07–22.76)	0.892
130–<140	1 (0.20)	0.40 (0.03–4.76)	0.472	Reference	Reference
≥140	3 (0.66)	Reference	Reference	2.47 (0.21–29.16)	0.472
Fatal ischemic stroke, mm Hg					
<130	4 (0.77)	0.71 (0.14–3.78)	0.692	2.03 (0.35–11.82)	0.431
130–<140	2 (0.40)	0.35 (0.06–2.10)	0.251	Reference	Reference
≥140	4 (0.88)	Reference	Reference	2.84 (0.48–16.96)	0.251
Nonfatal MI, mm Hg					
<130	20 (3.85)	1.69 (0.70–4.04)	0.243	1.87 (0.88–4.00)	0.105
130–<140	12 (2.40)	0.90 (0.38–2.11)	0.809	Reference	Reference
≥140	14 (3.07)	Reference	Reference	1.11 (0.47–2.61)	0.809
Nonfatal hemorrhagic stroke, mm Hg					
<130	18 (3.46)	0.60 (0.28–1.29)	0.193	0.96 (0.48–1.93)	0.907
130–<140	18 (3.60)	0.63 (0.32–1.22)	0.171	Reference	Reference
≥140	26 (5.70)	Reference	Reference	1.59 (0.82–3.11)	0.171
Nonfatal ischemic stroke, mm Hg					
<130	113 (21.73)	0.82 (0.59–1.15)	0.253	0.92 (0.70–1.22)	0.558
130–<140	114 (22.80)	0.90 (0.67–1.20)	0.459	Reference	Reference
≥140	114 (25.00)	Reference	Reference	1.12 (0.83–1.49)	0.459

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline SBP, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation. CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; and SBP, systolic blood pressure.

mortality, and fatal MI (Table 6). Mean DBP of <80 mm Hg was associated with a tendency for further reduction in fatal MI compared with subjects with a mean DBP of 80 to <90 mm Hg. However, the risk of nonfatal MI was increased in subjects with a mean DBP of <80 mm Hg compared with subjects with a mean DBP of 80 to <90 mm Hg.

Discussion

The key findings from this study are as follows. First, in hypertensive subjects with previous stroke, an SBP of <140 mm Hg was associated with a significant reduction in all-cause mortality, cardiovascular mortality, and fatal

ischemic stroke. Second, an SBP of <130 mm Hg was associated with a significantly lower risk of nonfatal hemorrhagic stroke compared with subjects with a mean SBP of ≥140 mm Hg. Third, a DBP of <80 mm Hg was associated with a further reduction in all-cause mortality, cardiovascular mortality, and fatal MI compared with subjects with a DBP of 80 to <90 mm Hg. However, there was a significant increase in risk of nonfatal MI. Because the association between BP and stroke incidence is stronger in Asian populations than Western populations, the target BP in Asian subjects may differ from that in other ethnicities.[12]

The present results differ from the SPS3 study, which demonstrated an insignificant benefit of strict SBP control in reducing the composite outcome of fatal MI or vascular death. This discrepancy may be related to the 3.7-year mean follow-up of the SPS3 study, which may have been insufficient to discern a difference in cardiovascular mortality, and limited enrollment to subjects with previous lacunar infarction. However, the SPS3 study detected a significant 63% reduction in intracerebral hemorrhage, which is consistent with this study, in which mean SBP of <130 mm Hg, compared with subjects with a mean SBP of ≥140 mm Hg, was associated with a significant reduction in nonfatal hemorrhagic stroke. In addition, mean DBP of <80 mm Hg showed notable risk reduction for both fatal and nonfatal hemorrhagic stroke. A previous post-hoc analysis and meta-analysis have supported the benefit of strict BP control in hypertensive subjects with stroke. In a subgroup analysis of the ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial), intensive BP treatment was associated with significant reduction in both total stroke and nonfatal stroke.[13] In a metaregression analysis of 618 815 participants in 123 studies, every 10–mm Hg reduction in SBP was associated with a 27% reduction in stroke risk, regardless of baseline disease history, suggesting a significant benefit of strict BP lowering.[14] In the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) study post-hoc analysis, reduction of on-treatment SBP to <130 mm Hg was only beneficial for further reduction of stroke risk, without any benefit for cardiovascular mortality, MI, or congestive heart failure.[15]

However, some studies have demonstrated a potential for harm with lower BP. In a community-based study of participants from the National Health and Nutrition Examination Survey (1998–2004) with a self-reported history of stroke, a baseline SBP <120 mm Hg was associated with higher all-cause mortality and a trend toward higher vascular mortality compared with normal SBP (120–140 mm Hg) and high SBP (>140 mm Hg).[16] Our study differs from this previous study in that we analyzed the difference in cardiovascular mortality risk according to mean SBP during follow-up rather than baseline SBP. In addition, our study excluded subjects with concomitant malignancies or subjects who died within 1 year of the diagnosis of stroke. These factors may have reduced the inclusion of subjects in poorer general condition in the present study, in whom lower baseline BP may be associated with higher mortality.[17,18] The significant reductions in both fatal ischemic and nonfatal hemorrhagic stroke in our study are supported by the post-hoc analysis of the INVEST (International Verapamil-Trandolapril Study), which demonstrated a J-shaped phenomenon for MI but not for fatal or nonfatal stroke.[10,19] Also, in the post-hoc analysis of the ONTARGET (Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial), a J curve was demonstrated at a mean SBP of <130 mm Hg for total and cardiovascular mortality and coronary events, but not for fatal and nonfatal stroke.[20] Further analysis of this study did not reveal an increased risk of clinical outcomes in subjects with a mean SBP of <120 mm Hg or a mean DBP of <70 mm Hg compared with subjects with a mean BP of ≥140/90 mm Hg. However, because the number of subjects with a mean SBP of <120 mm Hg (N=199) or a mean DBP of <70 mm Hg (N=92) was small, these results should be interpreted with caution. In a post-hoc analysis of the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) study, subjects with a mean SBP between 120 and 140 mm Hg had the lowest risk of recurrent stroke, and subjects with a mean SBP of <120 mm Hg had an increased risk of recurrent stroke.[21] Also, when we analyzed for the presence of the J curve with SBP of 130 to <140 mm Hg or DBP of 80 to <90 mm Hg as reference, we found that DBP of <80 mm Hg was associated with increased risk of nonfatal MI. It is uncertain why there was a reduction in fatal MI but an increase in nonfatal MI for subjects with a mean DBP of <80 mm Hg. It may be that subjects who have a lower mean DBP have a lower severity of MI or that the low number of fatal MIs in this analysis was a chance phenomenon. Another explanation may be the limitation of *ICD-10*–based diagnosis of nonfatal events. In a study to determine the accuracy of acute MI based on *ICD* codes using the Korean National Medical Health Insurance claims data, the accuracy of acute MI was 73.1%, according to the European Society of Cardiology/American College of Cardiology criteria.[22]

Several limitations of this study should be discussed. First, because this study was based on a retrospective cohort analysis, the results can only be interpreted as hypothesis generating. However, this study demonstrated that lower mean BP is associated with a reduction in mortality, cardiovascular mortality, and nonfatal strokes in hypertensive subjects with previous stroke and provides important insight into the potential benefit of strict BP lowering in this population. The ongoing SHOT (Systolic Hypertension Optimal Treatment Trial), a trial enrolling 7500 subjects >65 years with previous stroke or transient ischemic attack to investigate the relationship between SBP treatment targets and recurrent stroke, will help to validate this important issue in hypertension management.[23] Second, because this study was based on claims data using *ICD-10* diagnosis codes, it was limited in

Table 6. Propensity-Adjusted Cox Proportional Hazard Models for Mortality According to Observed Mean DBP Groups in Aspirin and/or Statin Users

		Reference group (≥90)		Reference group (80–<90)	
Mortality	No. (%) of Events	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death, mm Hg					
<80	64 (10.61)	0.49 (0.29–0.85)	0.011	0.91 (0.62–1.32)	0.618
80–<90	70 (10.29)	0.54 (0.34–0.87)	0.012	Reference	Reference
≥90	31 (16.06)	Reference	Reference	1.84 (1.15–2.96)	0.012
Cardiovascular death, mm Hg					
<80	20 (3.32)	0.18 (0.07–0.42)	<0.001	0.62 (0.32–1.19)	0.151
80–<90	24 (3.53)	0.28 (0.14–0.60)	0.001	Reference	Reference
≥90	14 (7.25)	Reference	Reference	3.52 (1.68–7.37)	0.001
Fatal MI, mm Hg					
<80	1 (0.17)	0.01 (0.00–0.19)	0.001	0.12 (0.01–1.14)	0.065
80–<90	4 (0.59)	0.12 (0.02–0.61)	0.011	Reference	Reference
≥90	4 (2.07)	Reference	Reference	8.61 (1.64–45.13)	0.011
Fatal hemorrhagic stroke, mm Hg					
<80	1 (0.17)	0.34 (0.01–10.57)	0.536	0.34 (0.03–4.10)	0.398
80–<90	3 (0.44)	0.98 (0.07–13.60)	0.989	Reference	Reference
≥90	1 (0.52)	Reference	Reference	1.02 (0.07–14.11)	0.989
Fatal ischemic stroke, mm Hg					
<80	6 (1.00)	0.43 (0.04–4.93)	0.498	1.31 (0.29–5.82)	0.726
80–<90	3 (0.44)	0.33 (0.03–3.58)	0.362	Reference	Reference
≥90	1 (0.52)	Reference	Reference	3.04 (0.28–33.10)	0.362
Nonfatal MI, mm Hg					
<80	24 (3.98)	0.93 (0.34–2.52)	0.886	2.14 (1.04–4.38)	0.038
80–<90	14 (2.06)	0.43 (0.17–1.12)	0.085	Reference	Reference
≥90	8 (4.15)	Reference	Reference	2.30 (0.89–5.92)	0.085
Nonfatal hemorrhagic stroke, mm Hg					
<80	22 (3.65)	0.50 (0.21–1.18)	0.114	1.00 (0.53–1.89)	0.991
80–<90	25 (3.68)	0.50 (0.24–1.04)	0.063	Reference	Reference
≥90	15 (7.77)	Reference	Reference	2.00 (0.96–4.13)	0.063
Nonfatal ischemic stroke, mm Hg					
<80	141 (23.38)	0.76 (0.51–1.14)	0.190	0.97 (0.75–1.25)	0.800
80–<90	152 (22.35)	0.79 (0.55–1.13)	0.198	Reference	Reference
≥90	48 (24.87)	Reference	Reference	1.27 (0.88–1.81)	0.198

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline DBP, history of diabetes mellitus, and history atrial fibrillation. CI indicates confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; and MI, myocardial infarction.

terms of determining stroke severity. Therefore, we cannot rule out the confounding effect of stroke severity on the outcomes of these subjects. Third, we cannot conclude whether subjects with a relatively well-controlled mean BP were more compliant with their BP, statin, and aspirin prescriptions. However, a similar trend was demonstrated in the Cox regression analysis for subjects taking aspirin and statins. Fourth, because health examinations supported by the National Health Insurance Corporation were performed in various hospitals and clinics, there was a lack of uniformity of BP measuring devices. Fifth, the study subjects were relatively young and able to receive the nationwide health examination. As such, subjects with stroke with more severe disabilities would more than likely have been omitted from participation.

Therefore, the results from this study cannot be generalized to the entire stroke population. Sixth, because the inclusion criteria allowed for subjects who received diagnoses of stroke and hypertension either simultaneously or separately during the index period, 1337 were diagnosed as having hypertension before being diagnosed as having stroke. As such, the mean BP reflects the mean BP of the study population from the start of the index period rather than after the stroke event. Because health examinations are performed every 2 years for office workers and annually for manual laborers, a cardiovascular event within 1 year after stroke will most likely reflect the average BP measured during the index period before the development of stroke. We cannot rule out the possibility that BP measured before stroke does not accurately reflect BP after stroke because of more active intervention to lower BP after the stroke event. In addition, the frequency of health examination received varied among the study subjects. However, analyses using the last BP measurement before mortality, clinical events, or the last health examination showed a trend to the original results (Tables S11 and S12). Seventh, ≈40% of all the subjects with stroke during the index period had a diagnosis of hypertension. Because the diagnosis of hypertension was based on the *ICD-10* code of claims data and not on the BP level or prescription of antihypertensive medications, we cannot rule out the possibility that subjects with stroke who had hypertension were missed because of omission of the diagnostic code for hypertension. Because we had aimed to analyze subjects with stroke who had hypertension, we believed that the strict inclusion criteria to analyze only subjects with a diagnosis of hypertension were appropriate. Last, the large difference in the HR for some of the clinical events, such as fatal MI, may be attributable to the relatively few events. Also, because this was a retrospective analysis of an observational cohort, there is a possibility that subjects with a lower BP may have been more compliant with medication and lifestyle modifications, important factors that may have an additive effect on the HR.

In conclusion, in hypertensive subjects with previous stroke, a mean DBP of <80 mm Hg was associated with significant benefit in total mortality, cardiovascular mortality, and some of the nonfatal cardiovascular events. However, there was an increase in nonfatal MI in subjects with a mean DBP of <80 mm Hg compared with subjects with a mean DBP of 80 to <90 mm Hg. Mean SBP of <130 mm Hg was associated with a significantly lower risk of nonfatal hemorrhagic strokes. The results from this study require validation by future randomized clinical trials.

Perspectives

Previously, only the SPS3 study sought to demonstrate the potential benefit of strict BP control in patients after stroke. However, because the SPS3 study was performed in patients after lacunar infarction, the benefit of strict BP lowering in all hypertensive patients after stroke is not clear. The results from the present study demonstrate the potential benefit of a BP of <130/80 mm Hg in hypertensive subjects with prior stroke. However, the potential risk for increased risk of nonfatal MI in subjects with a mean DBP of <80 mm Hg was observed. Also, because this study is based on an observational cohort, the results from this study are only hypothesis generating. Nevertheless, the results support the necessity for future studies to demonstrate the benefit of strict BP control in all patients with stroke.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Health examination program provided by the Korean National Health Insurance Corporation

The Korean National Health Insurance Service provides nationwide health examination program to improve the health of citizens and reduce their health care costs through the prevention of cardio-cerebrovascular diseases affected by lifestyle. Nationwide health examination consists of a general and a life-transition health examination.[1] Employee subscriber, its dependents, regional insurance subscriber who is a regional householder, and its family members can receive the general health examination biennially. For non-office workers among employee subscribers, this examination is conducted annually. The life-transition health examination is given to people reaching ages of 40 and 66, who is eligible to receive the general health examination.[1,2] The National Health Insurance Service health examinee cohort (NHIS-HealS) was made with data of nationwide health examinations conducted by the NHIS in 2002–13.[3]

Table S1. Clinical characteristics of aspirin and/or statin users according to observed mean systolic blood pressure.

	<130 mmHg (N=520)	130 to <140 mmHg (N=500)	≥140 mmHg (N=456)	P value
Average SBP, mmHg	122.7±5.9	134.4±2.8	148.9±8.8	<0.001
Number of BP measurement	4.7±1.8	4.8±1.9	4.1±1.8	<0.001
Age (year)	58.6±8.5	60.5±9.1	61.7±8.7	<0.001
Sex, N (%)				0.564
Male	285 (54.8)	271 (54.2)	262 (57.5)	
Female	235 (45.2)	229 (45.8)	194 (42.5)	
Residential area, N (%)				
Metropolitan	174 (33.5)	162 (32.4)	164 (36.0)	0.493
Province	346 (66.5)	338 (67.6)	292 (64.0)	
Household income, N (%)				
Upper 20%	161 (31.0)	143 (28.6)	112 (24.6)	0.194
Middle 40%	200 (38.5)	185 (37.0)	183 (40.1)	
Lower 40%	159 (30.6)	172 (34.4)	161 (35.3)	
Smoking status, N (%)				0.862
Never smoker	347 (66.7)	346 (69.2)	317 (69.5)	
Ex-smoker	41 (7.9)	36 (7.2)	30 (6.6)	
Current smoker	132 (25.4)	118 (23.6)	109 (23.9)	
Alcohol frequency, N (%)				0.091
Never	321 (61.7)	317 (63.4)	275 (60.3)	
2~3/month	64 (12.3)	51 (10.2)	39 (8.6)	
1~2/week	67 (12.9)	56 (11.2)	72 (15.8)	
3~4/week	44 (8.5)	36 (7.2)	34 (7.5)	
Daily	24 (4.6)	40 (8.0)	36 (7.9)	
Body mass index, kg/m^2	24.4±2.9	24.7±2.8	24.8±3.0	0.141
Total cholesterol, mg/dL	211.2±40.8	211.8±45.4	211.1±44.0	0.960
Fasting glucose, mg/dL	107.3±44.0	106.5±37.7	113.6±63.9	0.055
Baseline SBP, mmHg	128.0±14.1	138.8±15.0	155.6±18.7	<0.001
Baseline DBP, mmHg	80.0±10.0	84.6±11.4	91.8±12.2	<0.001
History of DM, N (%)	30 (5.8)	31 (6.2)	31 (6.8)	0.802
History of atrial fibrillation, N (%)	19 (3.7)	12 (2.4)	5 (1.1)	0.035
Antihypertensive medication				
RASB, N (%)	379 (72.9)	398 (79.6)	358 (78.5)	0.024
RASB duration, day	1712.3±1220.3	1828.6±1190.9	1894.0±1204.1	0.073
BB, N (%)	151 (29.0)	153 (30.6%)	156 (34.2)	0.208
BB duration, day	1116.4±1167.5	978.2±1037.8	1022.1±1110.4	0.353
CCB, N (%)	358 (68.8)	384 (76.8)	375 (82.2)	<0.001
CCB duration, day	1747.7±1283.4	1856.8±1241.7	2014.0±1274.8	0.008
Diuretics, N (%)	118 (22.7)	174 (34.8)	158 (34.6)	<0.001
Diuretics duration, day	807.0±864.0	935.5±938.7	930.7±934.4	0.227
Statin, N (%)	362 (69.6)	340 (68.0)	297 (65.1)	0.322
Statin duration, day	1582.6±1015.4	1599.3±1030.4	1436.9±992.7	0.059

Aspirin, N (%)	368 (70.8)	340 (68.0)	322 (70.6)	0.565
Aspirin duration, day	1262.1±931.6	1256.2±939.5	1224.3±889.7	0.825
Follow-up duration, day	3161.2±576.5	3104.5±532.4	3023.8±668.3	0.001

Data are presented as mean ± SD or N (%).

BB, beta blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; RASB, renin angiotensin system blocker; SBP, systolic blood pressure.

Table S2. Clinical characteristics of aspirin and/or statin users according to observed mean diastolic blood pressure.

	<80 mmHg (N=603)	80 to <90 mmHg (N=680)	≥90 mmHg (N=193)	P value
Average DBP, mmHg	126.5±8.9	137.3±8.3	151.8±12.3	<0.001
Number of BP measurement	4.6±1.7	4.7±2.0	3.9±2.0	<0.001
Age (year)	60.9±8.4	60.1±9.0	58.6±9.6	0.005
Sex, N (%)				0.008
Male	310 (51.4)	385 (56.6)	123 (63.7)	
Female	293 (48.6)	295 (43.4)	70 (36.3)	
Residential area, N (%)				
Metropolitan	199 (33.0)	225 (33.1)	76 (39.4)	0.223
Province	404 (67.0)	455 (66.9)	117 (60.6)	
Household income, N (%)				0.469
Upper 20%	184 (30.5)	184 (27.1)	48 (24.9)	
Middle 40%	227 (37.6)	267 (39.3)	74 (38.3)	
Lower 40%	192 (31.8)	229 (33.7)	71 (36.8)	
Smoking status, N (%)				0.223
Never smoker	430 (71.3)	454 (66.8)	126 (65.3)	
Ex-smoker	44 (7.3)	51 (7.5)	12 (6.2)	
Current smoker	129 (21.4)	175 (25.7)	55 (28.5)	
Alcohol frequency, N (%)				
Never	404 (67.0)	413 (60.7)	96 (49.7)	0.001
2~3/month	63 (10.4)	70 (10.3)	21 (10.9)	
1~2/week	67 (11.1)	88 (12.9)	40 (20.7)	
3~4/week	33 (5.5)	61 (9.0)	20 (10.4)	
Daily	36 (6.0)	48 (7.1)	16 (8.3)	
Body mass index, kg/m^2	24.3±2.9	24.7±2.9	25.2±2.8	<0.001
Total cholesterol, mg/dL	211.1±43.5	212.0±43.7	210.4±41.8	0.884
Fasting glucose, mg/dL	109.2±43.8	108.3±47.7	110.4±67.9	0.864
Baseline SBP, mmHg	131.9±16.5	142.4±17.3	158.6±21.0	<0.001
Baseline DBP, mmHg	78.2±9.1	87.5±10.1	99.2±12.4	<0.001
History of DM, N (%)	36 (6.0)	43 (6.3)	13 (6.7)	0.921
History of atrial fibrillation, N (%)	21 (3.5)	11 (1.6)	4 (2.1)	0.091
Antihypertensive medication				
RASB, N (%)	441 (73.1)	538 (79.1)	156 (80.8)	0.015
RASB duration, day	1707.7±1218.9	1873.5±1204.8	1889.5±1159.9	0.040
BB, N (%)	185 (30.7)	201 (29.6)	74 (38.3)	0.063
BB duration, day	1073.3±1143.7	988.5±1078.0	1088.3±1089.8	0.525
CCB, N (%)	423 (70.1)	539 (79.3)	155 (80.3)	<0.001
CCB duration, day	1727.7±1286.6	1953.2±1246.5	2002.5±1271.4	0.004
Diuretics, N (%)	158 (26.2)	232 (34.1)	60 (31.1)	0.009
Diuretics duration, day	905.3±929.8	880.1±895.3	936.4±967.8	0.839
Statin, N (%)	424 (70.3)	452 (66.5)	123 (63.7)	0.154
Statin duration, day	1627.7±1024.7	1467.5±994.0	1544.0±1045.8	0.043
Aspirin, N (%)	432 (71.6)	466 (68.5)	132 (68.4)	0.434

Aspirin duration, day	1305.9±970.3	1215.8±889.3	1176.1±859.0	0.160
Follow-up duration, day	3160.1±554.4	3076.4±586.2	2991.6±716.4	0.001

Data are presented as mean ± SD or N (%).

BB, beta blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; DM, diabetes mellitus; RASB, renin angiotensin system blocker; SBP, systolic blood pressure.

Table S3. Propensity-adjusted Cox proportional hazard models for mortality according to observed mean SBP groups in study population without baseline atrial fibrillation (<120 [N=760], 120 to <130 [N=774], ≥120 mmHg [N=728]).

		No. of events (%)	HR (95% CI)	P value
All-cause death	<130 mmHg	100 (13.16)	0.63 (0.47-0.86)	0.003
	130 to <140 mmHg	108 (13.95)	0.59 (0.46-0.77)	<0.001
	≥140 mmHg	183 (25.14)	reference	reference
Cardiovascular death	<130 mmHg	37 (4.87)	0.52 (0.32-0.85)	0.009
	130 to <140 mmHg	30 (3.88)	0.37 (0.23-0.58)	<0.001
	≥140 mmHg	80 (10.99)	reference	reference
Fatal MI	<130 mmHg	4 (0.53)	0.54 (0.13-2.24)	0.398
	130 to <140 mmHg	4 (0.52)	0.42 (0.12-1.46)	0.172
	≥140 mmHg	11 (1.51)	reference	reference
Fatal hemorrhagic stroke	<130 mmHg	3 (0.39)	0.47 (0.11-2.02)	0.310
	130 to <140 mmHg	4 (0.52)	0.38 (0.12-1.26)	0.115
	≥140 mmHg	14 (1.92)	reference	reference
Fatal ischemic stroke	<130 mmHg	5 (0.66)	0.19 (0.06-0.62)	0.006
	130 to <140 mmHg	5 (0.65)	0.20 (0.07-0.56)	0.002
	≥140 mmHg	20 (2.75)	reference	reference
Non-fatal MI	<130 mmHg	22 (2.89)	1.97 (0.86-4.50)	0.109
	130 to <140 mmHg	15 (1.94)	1.11 (0.51-2.41)	0.796
	≥140 mmHg	17 (2.34)	reference	reference
Non-fatal hemorrhagic stroke	<130 mmHg	35 (4.61)	0.57 (0.34-0.97)	0.040
	130 to <140 mmHg	44 (5.68)	0.74 (0.47-1.16)	0.188
	≥140 mmHg	54 (7.42)	reference	reference
Non-fatal ischemic stroke	<130 mmHg	163 (21.45)	0.93 (0.71-1.22)	0.601
	130 to <140 mmHg	168 (21.71)	0.93 (0.74-1.18)	0.558
	≥140 mmHg	174 (23.90)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
SBP, systolic blood pressure; MI, myocardial infarction.

Table S4. Propensity-adjusted Cox proportional hazard models for mortality according to observed mean DBP groups in study population without baseline atrial fibrillation (<80 [N=848], 80 to <90 [N=1080], ≥90 mmHg [N=334]).

		No. of events (%)	HR (95% CI)	P value
All-cause death	<80 mmHg	122 (14.39)	0.43 (0.31-0.61)	<0.001
	80 to <90 mmHg	186 (17.22)	0.59 (0.44-0.78)	<0.001
	≥90 mmHg	83 (24.85)	reference	reference
Cardiovascular death	<80 mmHg	39 (4.60)	0.26 (0.15-0.45)	<0.001
	80 to <90 mmHg	68 (6.30)	0.44 (0.28-0.68)	<0.001
	≥90 mmHg	40 (11.98)	reference	reference
Fatal MI	<80 mmHg	2 (0.24)	0.04 (0.01-0.28)	0.001
	80 to <90 mmHg	10 (0.93)	0.31 (0.10-0.95)	0.041
	≥90 mmHg	7 (2.10)	reference	reference
Fatal hemorrhagic stroke	<80 mmHg	4 (0.47)	0.20 (0.04-0.92)	0.039
	80 to <90 mmHg	9 (0.83)	0.37 (0.13-1.09)	0.072
	≥90 mmHg	8 (2.40)	reference	reference
Fatal ischemic stroke	<80 mmHg	8 (0.94)	0.20 (0.06-0.66)	0.008
	80 to <90 mmHg	14 (1.30)	0.36 (0.14-0.94)	0.036
	≥90 mmHg	8 (2.40)	reference	reference
Nonfatal MI	<80 mmHg	26 (3.07)	1.33 (0.54-3.30)	0.532
	80 to <90 mmHg	18 (1.67)	0.58 (0.25-1.36)	0.211
	≥90 mmHg	10 (2.99)	reference	reference
Non-fatal hemorrhagic stroke	<80 mmHg	40 (4.72)	0.48 (0.26-0.87)	0.016
	80 to <90 mmHg	63 (5.83)	0.65 (0.40-1.06)	0.085
	≥90 mmHg	30 (8.98)	reference	reference
Non-fatal ischemic stroke	<80 mmHg	186 (21.93)	0.78 (0.57-1.06)	0.116
	80 to <90 mmHg	237 (21.94)	0.80 (0.61-1.05)	0.106
	≥90 mmHg	82 (24.55)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
DBP, diastolic blood pressure; MI, myocardial infarction.

Table S5. Propensity-adjusted Cox proportional hazard models for clinical events according to observed mean SBP groups in study population including subjects with antihypertensive medication duration <1 year (<120 [N=927], 120 to <130 [N=880], ≥120 mmHg [N=835]).

		No. of events (%)	Adjusted HR (95% CI)	P value
All-cause death	<130 mmHg	150 (16.18)	0.58 (0.45-0.75)	<0.001
	130 to <140 mmHg	150 (17.05)	0.57 (0.45-0.71)	<0.001
	≥140 mmHg	248 (29.70)	reference	reference
Cardiovascular death	<130 mmHg	60 (6.47)	0.52 (0.34-0.78)	0.002
	130 to <140 mmHg	50 (5.68)	0.43 (0.30-0.63)	0.000
	≥140 mmHg	110 (13.17)	reference	reference
Fatal MI	<130 mmHg	6 (0.65)	0.29 (0.09-1.00)	0.050
	130 to <140 mmHg	5 (0.57)	0.29 (0.10-0.87)	0.027
	≥140 mmHg	16(1.92)	reference	reference
Fatal hemorrhagic stroke	<130 mmHg	9 (0.97)	0.89 (0.32-2.50)	0.823
	130 to <140 mmHg	5 (0.57)	0.36 (0.13-1.04)	0.059
	≥140 mmHg	20 (2.40)	reference	reference
Fatal ischemic stroke	<130 mmHg	9 (0.97)	0.20 (0.08-0.49)	<0.001
	130 to <140 mmHg	12 (1.36)	0.31 (0.15-0.65)	0.002
	≥140 mmHg	29 (3.47)	reference	reference
Non-fatal MI	<130 mmHg	25 (2.70)	2.01 (0.90-4.50)	0.090
	130 to <140 mmHg	17 (1.93)	1.23 (0.58-2.60)	0.587
	≥140 mmHg	18 (2.16)	reference	reference
Non-fatal hemorrhagic stroke	<130 mmHg	43 (4.64)	0.63 (0.39-1.03)	0.066
	130 to <140 mmHg	48 (5.45)	0.72 (0.48-1.09)	0.124
	≥140 mmHg	66 (7.90)	reference	reference
Non-fatal ischemic stroke	<130 mmHg	198 (21.36)	0.95 (0.74-1.22)	0.695
	130 to <140 mmHg	189 (21.48)	0.94 (0.75-1.18)	0.604
	≥140 mmHg	196 (23.47)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
SBP, systolic blood pressure; MI, myocardial infarction.

Table S6. Propensity-adjusted Cox proportional hazard models for clinical events according to observed mean DBP groups in study population including subjects with antihypertensive medication duration <1 year (<80 [N=1020], 80 to <90 [N=1230], ≥90 mmHg [N=392]).

		No. of events (%)	Adjusted HR (95% CI)	P value
All-cause death	<80 mmHg	184 (18.04)	0.42 (0.31-0.56)	<0.001
	80 to <90 mmHg	245 (19.92)	0.53 (0.42-0.68)	<0.001
	≥90 mmHg	119 (30.36)	reference	reference
Cardiovascular death	<80 mmHg	67 (6.57)	0.32 (0.20-0.50)	<0.001
	80 to <90 mmHg	96 (7.80)	0.45 (0.31-0.65)	<0.001
	≥90 mmHg	57 (14.54)	reference	reference
Fatal MI	<80 mmHg	4 (0.39)	0.08 (0.02-0.35)	0.001
	80 to <90 mmHg	14 (1.14)	0.38 (0.15-1.00)	0.050
	≥90 mmHg	9 (2.30)	reference	reference
Fatal hemorrhagic stroke	<80 mmHg	7 (0.69)	0.25 (0.07-0.81)	0.021
	80 to <90 mmHg	15 (1.22)	0.44 (0.19-1.04)	0.062
	≥90 mmHg	12 (3.06)	0reference	reference
Fatal ischemic stroke	<80 mmHg	13 (1.27)	0.22 (0.09-0.57)	0.002
	80 to <90 mmHg	23 (1.87)	0.40 (0.19-0.84)	0.015
	≥90 mmHg	14 (3.57)	reference	reference
Non-fatal MI	<80 mmHg	30 (2.94)	1.41 (0.59-3.38)	0.439
	80 to <90 mmHg	19 (1.54)	0.59 (0.26-1.34)	0.211
	≥90 mmHg	11 (2.81)	reference	reference
Non-fatal hemorrhagic stroke	<80 mmHg	47 (4.61)	0.48 (0.28-0.83)	0.009
	80 to <90 mmHg	72 (5.85)	0.64(0.41-1.00)	0.050
	≥90 mmHg	38 (9.69)	reference	reference
Non-fatal ischemic stroke	<80 mmHg	223 (21.86)	0.80 (0.60-1.07)	0.135
	80 to <90 mmHg	264 (21.46)	0.80 (0.62-1.03)	0.083
	≥90 mmHg	96 (24.49)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
DBP, diastolic blood pressure; MI, myocardial infarction.

Table S7. Propensity-adjusted Cox proportional hazard models for mortality according to observed mean SBP groups in survivors after 1 year from the index stroke (<120 [N=783], 120 to <130 [N=788], ≥120 mmHg [N=711]).

		No. of events (%)	Adjusted HR (95% CI)	P value
All-cause death	<130 mmHg	98 (12.52)	0.71 (0.52-0.97)	0.032
	130 to <140 mmHg	108 (13.71)	0.68 (0.52-0.89)	0.005
	≥140 mmHg	160 (22.54)	reference	reference
Cardiovascular death	<130 mmHg	37 (4.73)	0.65 (0.39-1.08)	0.093
	130 to <140 mmHg	31 (3.93)	0.47 (0.29-0.75)	0.001
	≥140 mmHg	63 (8.87)	reference	reference
Fatal MI	<130 mmHg	4 (0.51)	0.67 (0.15-3.05)	0.606
	130 to <140 mmHg	3 (0.38)	0.41 (0.10-1.69)	0.216
	≥140 mmHg	8 (1.13)	reference	reference
Fatal hemorrhagic stroke	<130 mmHg	3 (0.38)	0.66 (0.14-3.13)	0.598
	130 to <140 mmHg	4 (0.51)	0.57 (0.16-2.03)	0.383
	≥140 mmHg	9 (1.27)	reference	reference
Fatal ischemic stroke	<130 mmHg	3 (0.38)	0.16 (0.04-0.67)	0.012
	130 to <140 mmHg	6 (0.76)	0.31 (0.11-0.85)	0.023
	≥140 mmHg	14 (1.97)	reference	reference
Non-fatal MI	<130 mmHg	22 (2.8)	1.95 (0.86-4.45)	0.111
	130 to <140 mmHg	16 (2.0)	1.16 (0.54-2.50)	0.699
	≥140 mmHg	17 (2.4)	reference	reference
Non-fatal hemorrhagic stroke	<130 mmHg	35 (4.5)	0.57 (0.37-0.87)	0.010
	130 to <140 mmHg	45 (5.7)	0.74 (0.50-1.11)	0.150
	≥140 mmHg	52 (7.3)	reference	reference
Non-fatal ischemic stroke	<130 mmHg	170 (21.7)	0.91 (0.70-1.19)	0.508
	130 to <140 mmHg	173 (22.0)	0.91 (0.72-1.15)	0.437
	≥140 mmHg	175 (24.7)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
SBP, systolic blood pressure; MI, myocardial infarction.

Table S8. Propensity-adjusted Cox proportional hazard models for mortality according to observed mean DBP groups in survivors after 1 year from the index stroke event (<80 [N=870], 80 to <90 [N=1086], ≥90 mmHg [N=325]).

		No. of events (%)	Adjusted HR (95% CI)	P value
All-cause death	<80 mmHg	120 (13.79)	0.53 (0.37-0.77)	<0.001
	80 to <90 mmHg	177 (16.30)	0.69 (0.51-0.94)	0.020
	≥90 mmHg	69 (21.23)	reference	reference
Cardiovascular death	<80 mmHg	39 (4.48)	0.35 (0.19-0.62)	<0.001
	80 to <90 mmHg	61 (5.62)	0.50 (0.31-0.81)	0.005
	≥90 mmHg	31 (9.54)	reference	reference
Fatal MI	<80 mmHg	2 (0.23)	0.05 (0.01-0.36)	0.003
	80 to <90 mmHg	8 (0.74)	0.31 (0.09-1.18)	0.073
	≥90 mmHg	5 (1.54)	reference	reference
Fatal hemorrhagic stroke	<80 mmHg	3 (0.34)	0.16 (0.03-0.90)	0.038
	80 to <90 mmHg	7 (0.64)	0.33 (0.10-1.10)	0.071
	≥90 mmHg	6 (1.85)	0reference	reference
Fatal ischemic stroke	<80 mmHg	7 (0.80)	0.44 (0.10-1.99)	0.289
	80 to <90 mmHg	13 (1.20)	0.73 (0.20-2.70)	0.641
	≥90 mmHg	3 (0.92)	reference	reference
Non-fatal MI	<80 mmHg	27 (3.1)	1.33 (0.54-3.29)	0.533
	80 to <90 mmHg	18 (1.7)	0.57 (0.24-1.32)	0.187
	≥90 mmHg	10 (3.1)	reference	reference
Non-fatal hemorrhagic stroke	<80 mmHg	40 (4.6)	0.50 (0.31-0.80)	0.004
	80 to <90 mmHg	63 (5.8)	0.64 (0.41-1.00)	0.050
	≥90 mmHg	29 (8.9)	reference	reference
Non-fatal ischemic stroke	<80 mmHg	193 (22.2)	0.76 (0.56-1.04)	0.088
	80 to <90 mmHg	242 (22.3)	0.79 (0.60-1.04)	0.089
	≥90 mmHg	83 (25.5)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
DBP, diastolic blood pressure; MI, myocardial infarction.

Table S9. Propensity-adjusted Cox proportional hazard models for clinical events in 4 groups by mean SBP (<120 [N=199], 120 to <130 [N=592], 130 to <140 [N=793], ≥140 mmHg [N=736]).

		No. of events (%)	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	<120 mmHg	29 (14.57)	0.76 (0.46-1.23)	0.260	1.23 (0.77-1.98)	0.381
	120 to <130 mmHg	77 (13.01)	0.63 (0.46-0.86)	0.004	1.03 (0.76-1.39)	0.845
	130 to <140 mmHg	113 (14.25)	0.61 (0.47-0.79)	<0.001	reference	reference
	≥140 mmHg	186 (25.27)	reference	reference	1.63 (1.26-2.11)	<0.001
Cardiovascular death	<120 mmHg	8 (4.02)	0.46 (0.20-1.09)	0.077	1.18 (0.50-2.76)	0.709
	120 to <130 mmHg	34 (5.74)	0.59 (0.36-0.95)	0.031	1.50 (0.91-2.45)	0.109
	130 to <140 mmHg	33 (4.16)	0.39 (0.25-0.61)	<0.001	reference	reference
	≥140 mmHg	81 (11.01)	reference	reference	2.54 (1.64-3.95)	<0.001
Fatal MI	<120 mmHg	0 (0.00)	x	x	x	x
	120 to <130 mmHg	4 (0.68)	x	x	x	x
	130 to <140 mmHg	4 (0.50)	x	x	reference	reference
	≥140 mmHg	11 (1.49)	reference	reference	x	x
Fatal hemorrhagic stroke	<120 mmHg	1 (0.50)	0.96 (0.07-12.49)	0.978	2.46 (0.18-33.10)	0.496
	120 to <130 mmHg	2 (0.34)	0.41 (0.08-2.07)	0.279	1.04 (0.18-5.89)	0.963
	130 to <140 mmHg	4 (0.50)	0.39 (0.12-1.27)	0.118	reference	reference
	≥140 mmHg	14 (1.90)	reference	reference	2.56 (0.79-8.28)	0.118
Fatal ischemic stroke	<120 mmHg	1 (0.50)	0.14 (0.02-1.31)	0.085	0.59 (0.06-5.36)	0.637
	120 to <130 mmHg	6 (1.01)	0.26 (0.09-0.75)	0.012	1.06 (0.35-3.23)	0.921
	130 to <140 mmHg	7 (0.88)	0.25 (0.10-0.62)	0.003	reference	reference
	≥140 mmHg	21 (2.85)	reference	reference	4.07 (1.62-10.23)	0.003
Non-fatal MI	<120 mmHg	5 (2.51)	2.03 (0.59-7.01)	0.262	1.72 (0.55-5.37)	0.352

	120 to <130 mmHg	17 (2.87)	1.98 (0.86-4.57)	0.108	1.68 (0.83-3.41)	0.153
	130 to <140 mmHg	16 (2.02)	1.18 (0.55-2.53)	0.668	reference	reference
	≥140 mmHg	17 (2.31)	reference	reference	0.85 (0.39-1.82)	0.668
Non-fatal hemorrhagic stroke	<120 mmHg	9 (4.52)	0.56 (0.24-1.31)	0.185	0.74 (0.34-1.65)	0.468
	120 to <130 mmHg	26 (4.39)	0.57 (0.33-0.99)	0.046	0.75 (0.46-1.24)	0.259
	130 to <140 mmHg	45 (5.67)	0.76 (0.49-1.18)	0.222	reference	reference
	≥140 mmHg	54 (7.34)	reference	reference	1.32 (0.85-2.05)	0.222
Non-fatal ischemic stroke	<120 mmHg	5 (2.51)	1.10 (0.74-1.64)	0.626	1.20 (0.83-1.72)	0.336
	120 to <130 mmHg	17 (2.87)	0.88 (0.67-1.16)	0.360	0.95 (0.75-1.21)	0.697
	130 to <140 mmHg	16 (2.02)	0.92 (0.73-1.16)	0.497	reference	reference
	≥140 mmHg	17 (2.31)	reference	reference	1.08 (0.86-1.37)	0.497

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
SBP, systolic blood pressure; MI, myocardial infarction.

Table S10. Propensity-adjusted Cox proportional hazard models for clinical events in 4 groups by mean DBP (<70 [N=92], 70 to <80 [N=786], 80 to <90 [N=1100], ≥90 mmHg [N=342]).

		No. of events (%)	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
All-cause death	<70 mmHg	14 (15.22)	0.76 (0.41-1.41)	0.383	0.98 (0.54-1.75)	0.934
	70 to <80 mmHg	114 (14.50)	0.70 (0.51-0.94)	0.020	0.89 (0.70-1.13)	0.356
	80 to <90 mmHg	191 (17.36)	0.78 (0.60-1.02)	0.065	reference	reference
	≥90 mmHg	86 (25.15)	reference	reference	1.28 (0.98-1.68)	0.065
Cardiovascular death	<70 mmHg	3 (3.26)	0.34 (0.10-1.16)	0.086	0.59 (0.18-1.96)	0.389
	70 to <80 mmHg	40 (5.09)	0.48 (0.30-0.78)	0.003	0.84 (0.56-1.25)	0.392
	80 to <90 mmHg	71 (6.45)	0.57 (0.38-0.86)	0.007	reference	reference
	≥90 mmHg	42 (12.28)	reference	reference	1.74 (1.17-2.60)	0.007
Fatal MI	<70 mmHg	0 (0.00)	x	x	x	x
	70 to <80 mmHg	2 (0.25)	x	x	X	x
	80 to <90 mmHg	10 (0.91)	x	x	reference	reference
	≥90 mmHg	7 (2.05)	reference	reference	x	x
Fatal hemorrhagic stroke	<70 mmHg	0 (0.00)	x	x	\x	x
	70 to <80 mmHg	4 (0.51)	x	x	x	x
	80 to <90 mmHg	9 (0.82)	x	x	reference	reference
	≥90 mmHg	8 (2.34)	reference	reference	x	x
Fatal ischemic stroke	<70 mmHg	1 (1.09)	0.48 (0.05-4.22)	0.507	0.97 (0.12-7.87)	0.976
	70 to <80 mmHg	8 (1.02)	0.36 (0.13-1.00)	0.051	0.73 (0.31-1.75)	0.484
	80 to <90 mmHg	16 (1.45)	0.49 (0.22-1.14)	0.098	reference	reference
	≥90 mmHg	10 (2.92)	reference	reference	2.02 (0.88-4.65)	0.098
Non-fatal MI	<70 mmHg	2 (2.17)	1.09 (0.21-5.56)	0.922	1.67 (0.36-7.75)	0.513

	70 to <80 mmHg	25 (3.18)	1.40 (0.62-3.16)	0.414	2.16 (1.16-4.02)	0.016
	80 to <90 mmHg	18 (1.64)	0.65 (0.29-1.45)	0.294	reference	reference
	≥90 mmHg	10 (2.92)	reference	reference	1.54 (0.69-3.44)	0.294
Non-fatal hemorrhagic stroke	<70 mmHg	4 (4.35)	0.48 (0.16-1.48)	0.202	0.72 (0.25-2.10)	0.551
	70 to <80 mmHg	36 (4.58)	0.52 (0.30-0.88)	0.015	0.77 (0.51-1.18)	0.233
	80 to <90 mmHg	64 (5.82)	0.67 (0.42-1.05)	0.081	reference	reference
	≥90 mmHg	30 (8.77)	reference	reference	1.50 (0.95-2.37)	0.081
Non-fatal ischemic stroke	<70 mmHg	17 (18.48)	0.75 (0.43-1.30)	0.301	0.86 (0.51-1.43)	0.555
	70 to <80 mmHg	176 (22.39)	0.89 (0.67-1.18)	0.412	1.02 (0.84-1.25)	0.840
	80 to <90 mmHg	243 (22.09)	0.87 (0.67-1.13)	0.291	reference	reference
	≥90 mmHg	87 (25.44)	reference	reference	1.15 (0.89-1.48)	0.291

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
SBP, systolic blood pressure; MI, myocardial infarction.

Table S11. Propensity-adjusted Cox proportional hazard models for mortality according to SBP groups using last BP (<120 [N=718], 120 to <130 [N=633], ≥120 mmHg [N=969]).

		No. of events (%)	HR (95% CI)	P value
All-cause death	<130 mmHg	143 (14.8)	0.80(0.64-1.01)	0.066
	130 to <140 mmHg	101 (16.0)	0.76(0.59-0.98)	0.033
	≥140 mmHg	161 (22.4)	reference	reference
Cardiovascular death	<130 mmHg	52 (5.4)	0.69(0.48-1.00)	0.052
	130 to <140 mmHg	35 (5.5)	0.64(0.42-0.96)	0.030
	≥140 mmHg	69 (9.6)	reference	reference
Fatal MI	<130 mmHg	6 (0.6)	0.58(0.21-1.65)	0.309
	130 to <140 mmHg	3 (0.5)	0.38(0.10-1.39)	0.145
	≥140 mmHg	10 (1.4)	reference	reference
Fatal hemorrhagic stroke	<130 mmHg	3 (0.3)	0.27(0.07-1.00)	0.050
	130 to <140 mmHg	7 (1.1)	0.82(0.31-2.13)	0.681
	≥140 mmHg	11 (1.5)	reference	reference
Fatal ischemic stroke	<130 mmHg	6 (0.6)	0.23(0.09-0.58)	0.002
	130 to <140 mmHg	7 (1.1)	0.42(0.18-0.98)	0.046
	≥140 mmHg	22 (3.1)	reference	reference
Non-fatal MI	<130 mmHg	30 (3.1)	1.37(0.75-2.50)	0.304
	130 to <140 mmHg	7 (1.1)	0.44(0.18-1.05)	0.065
	≥140 mmHg	18 (2.5)	reference	reference
Non-fatal hemorrhagic stroke	<130 mmHg	51 (5.3)	0.87(0.58-1.32)	0.526
	130 to <140 mmHg	40 (6.3)	1.04(0.67-1.60)	0.865
	≥140 mmHg	43 (6.0)	reference	reference
Non-fatal ischemic stroke	<130 mmHg	218 (22.5)	1.12(0.91-1.38)	0.285
	130 to <140 mmHg	147 (23.2)	1.10(0.88-1.38)	0.419
	≥140 mmHg	158 (22.0)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
SBP, systolic blood pressure; MI, myocardial infarction.

Table S12. Propensity-adjusted Cox proportional hazard models for mortality according to DBP groups using last BP (<80 [N=978], 80 to <90 [N=871], ≥90 mmHg [N=471]).

		No. of events (%)	HR (95% CI)	P value
All-cause death	<80 mmHg	158 (18.1)	0.79(0.61-1.03)	0.080
	80 to <90 mmHg	98 (20.8)	0.94(0.73-1.22)	0.657
	≥90 mmHg	49 (5.01)	reference	reference
Cardiovascular death	<80 mmHg	61 (7.0)	0.59(0.39-0.89)	0.011
	80 to <90 mmHg	46 (9.8)	0.82(0.55-1.20)	0.301
	≥90 mmHg	1 (0.1)	reference	reference
Fatal MI	<80 mmHg	10 (1.2)	0.06(0.01-0.50)	0.009
	80 to <90 mmHg	8 (1.7)	0.76(0.29-1.94)	0.560
	≥90 mmHg	4 (0.4)	reference	reference
Fatal hemorrhagic stroke	<80 mmHg	10 (1.2)	0.36(0.10-1.26)	0.111
	80 to <90 mmHg	7 (1.5)	0.92(0.35-2.44)	0.866
	≥90 mmHg	12 (1.2)	reference	reference
Fatal ischemic stroke	<80 mmHg	10 (1.6)	0.46(0.21-1.03)	0.060
	80 to <90 mmHg	13 (2.8)	0.47(0.20-1.07)	0.073
	≥90 mmHg	26 (2.7)	reference	reference
Non-fatal MI	<80 mmHg	16 (1.8)	1.31(0.72-2.37)	0.380
	80 to <90 mmHg	13 (2.8)	0.44(0.18-1.06)	0.067
	≥90 mmHg	40 (4.1)	reference	reference
Non-fatal hemorrhagic stroke	<80 mmHg	64 (7.3)	0.91(0.60-1.37)	0.643
	80 to <90 mmHg	30 (6.4)	1.05(0.68-1.62)	0.823
	≥90 mmHg	221 (22.6)	reference	reference
Non-fatal ischemic stroke	<80 mmHg	190 (21.8)	1.08(0.88-1.33)	0.442
	80 to <90 mmHg	112 (23.8)	1.08(0.86-1.35)	0.500
	≥90 mmHg	158 (18.1)	reference	reference

All models were adjusted by propensity scores based on age, sex, residential area, household income, smoking status, alcohol frequency, body mass index, total cholesterol, fasting glucose, baseline systolic blood pressure, baseline diastolic blood pressure, history of diabetes mellitus, and history atrial fibrillation.
DBP, diastolic blood pressure; MI, myocardial infarction.

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