




ORIGINAL RESEARCH

Elevated Pulse Pressure and Recurrent Hemorrhagic Stroke Risk in Stroke With Cerebral Microbleeds or Intracerebral Hemorrhage

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BACKGROUND: Which type of recurrent stroke is associated with pulse pressure (PP) remains uncertain in ischemic stroke with cerebral microbleeds or intracerebral hemorrhage.

METHODS AND RESULTS: The PICASSO (Prevention of Cardiovascular Events in Ischemic Stroke Patients With High Risk of Cerebral Hemorrhage) database involving 1454 subjects was analyzed. Subjects were stratified into quartiles according to the distribution of mean PP (mm Hg) during follow-up (mean, 1.9 years): <47 (first quartile), 48 to 53 (second quartile), 54 to 59 (third quartile), and ≥ 60 mm Hg (fourth quartile). The primary end point was hemorrhagic stroke, and the secondary end points were ischemic stroke, stroke of any type, and major adverse cardiovascular events. Adjusted time-dependent area under the receiver operating characteristic curve analysis was performed to assess the prediction accuracy of mean PP. The mean frequency of visit for blood pressure checkup was 9.4 ± 5.5 times. The stroke incidence rate per 100 person-years was 3.14, 2.24, 5.52, and 6.22, respectively in increasing quartile of mean PP, and the rate of major adverse cardiovascular events was 3.82, 2.84, 6.37, and 7.14, respectively. In the presence of mean arterial pressure, hemorrhagic stroke risk was higher in the highest quartile (adjusted hazard ratio, 6.03; 95% CI, 1.04–34.99) versus the lowest quartile, which was evident at higher mean systolic blood pressure. Higher mean PP as a continuous variable was also a predictor of hemorrhagic stroke (1.09, 1.03–1.15). The time-dependent area under the receiver operating characteristic curve for hemorrhagic stroke was 0.79.

CONCLUSIONS: Long-term elevated PP with higher systolic blood pressure confers a greater risk of subsequent hemorrhagic stroke among stroke patients with cerebral microbleeds or intracerebral hemorrhage.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier, NCT01013532.

Key Words: blood pressure ■ intracranial hemorrhage ■ risk ■ stroke ■ vascular stiffness

Hypertension is one of the major risk factors for stroke,¹ which could be sufficiently reduced if blood pressure (BP) values were optimally controlled.² The current definitions and therapeutic guidelines of hypertension are heavily focused on systolic and diastolic blood pressure (SBP and DBP) but not on pulse pressure (PP).³

PP is defined as the difference between SBP and DBP and reflects large-artery stiffness.⁴ PP begins to increase with age and may be a key measure of BP in older individuals.⁵ According to the strain vessel hypothesis,⁶ small and short perforating arteries arising from large arteries in the brain are exposed to high pressure to maintain high vascular tone to

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CLINICAL PERSPECTIVE

What Is New?

- Pulse pressure (PP) reflects large-artery stiffness and physiologically influences cerebral small-vessel disease according to the strain vessel hypothesis.
- Elevated PP is associated with stroke risk, but it remains unknown whether an elevated PP may increase the risk of stroke among populations with an inherent high risk of hemorrhagic stroke.
- This study investigates whether elevated PP in patients with preexisting multiple cerebral microbleeds or intracerebral hemorrhage after noncardioembolic ischemic stroke increases the risk of recurrent stroke; we found that long-term elevated PP of ≥ 60 mm Hg was independently associated with an increased risk of hemorrhagic stroke, which was evident at higher mean systolic blood pressure.

What Are the Clinical Implications?

- An elevated PP, particularly if ≥ 60 mm Hg, in patients with noncardioembolic stroke with multiple cerebral microbleeds or in patients with prior intracerebral hemorrhage helps identify those at high-risk of hemorrhagic stroke.
- Aiming at controlling systolic blood pressure as means of reducing the PP in these subpopulations of patients with stroke may be helpful at reducing the risk of hemorrhagic stroke, but confirmatory studies or specific therapeutic trails for these subgroups are lacking.

Nonstandard Abbreviations and Acronyms

CMBs	cerebral microbleeds
DBP	diastolic blood pressure
ICH	intracerebral hemorrhage
MACE	major adverse cardiovascular event
PICASSO	Prevention of Cardiovascular Events in Ischemic Stroke Patients With High Risk of Cerebral Hemorrhage
PP	pulse pressure
SBP	systolic blood pressure
TAIST	Tinzaparin in Acute Ischaemic Stroke Trial

provide large pressure gradients from large arteries to perforating arteries.⁶ As arterial stiffness progresses, the pulse wave velocity increases; thus, PP increases resulting in more injury to perforating arteries. Indeed, increased arterial stiffness is physiologically correlated with developing cerebral small-vessel

disease, including white matter lesions and cerebral microbleeds (CMBs).^{7,8} Thus, identifying a relationship between PP and stroke outcomes in patients with cerebral small-vessel disease could be a useful prognostic indicator.

Notably, a recent systematic review and meta-analysis with 11 studies showed that elevated PP was linked to an increased risk of stroke⁹; however, the data on PP among the stroke population are relatively limited,¹⁰⁻¹³ and very few studies have evaluated the PP on the risk of recurrent stroke.¹³ Moreover, it is also important to confirm whether these associations between PP and stroke differ according to stroke type— ischemic versus hemorrhagic.

The recently completed PICASSO (Prevention of Cardiovascular Events in Ischemic Stroke Patients With High Risk of Cerebral Hemorrhage) trial¹⁴ provided a chance to assess the associations of PP with stroke outcomes. We hypothesized that higher PP would be more associated with increased risk of hemorrhagic stroke than that of ischemic stroke among patients following noncardioembolic stroke at high hemorrhagic risk.

METHODS

Data Availability

The anonymized data used in this study will be made available upon formal request to the corresponding author.

Study Subjects

PICASSO (ClinicalTrials.gov; identifier, NCT01013532) was a multinational, double-blind, randomized controlled clinical trial that comprised 1534 patients who had experienced ischemic stroke or transient ischemic attack within 6 months and who had symptomatic or asymptomatic intracerebral hemorrhage (ICH) (≥ 10 mm of old hemorrhage on gradient echo imaging) or multiple (≥ 2) CMBs, with a mean follow-up duration of 1.9 years.¹⁴ The main objective was to evaluate the efficacy and safety of the antiplatelet agent, cilostazol, and the additional benefit of probucol (a lipid-lowering cholesteryl ester transport protein activator) in the prevention of cardiovascular events among patients with noncardioembolic stroke with a high risk of cerebral hemorrhage.¹⁴ The demographic, clinical, laboratory, and brain magnetic resonance imaging (MRI) data were collected at randomization, with subsequent clinical data being obtained during follow-up visits at 1, 4, 7, 10, and 13 months and annually thereafter. Laboratory data were obtained at 1 and 13 months and at the final follow-up visit. Additionally, follow-up MRI was conducted after the 13-month visit.¹⁴ Approval for this study was obtained by institutional review board in each participating site, where the approved number of the affiliated center of the first author (J.-H.P.) was

MJH-2009-033. All the study participants provided written informed consent.

Imaging Markers

Imaging data were obtained after the PICASSO trial by the Imaging Review Committee. Information on white matter hyperintensities and presence of lacune before the qualifying stroke lesion was retrieved using 1.5 or 3.0 Tesla T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) imaging. The severity of white matter hyperintensities was rated in a decentralized manner by 2 stroke neurologists (M.H.L. and H.S.K.), who were blinded to the clinical information, with the help of the visual rating scale proposed by Fazekas scores ranging from 0 to 3.¹⁵ Also, the presence of lacune was determined by the same neurologists. Further markers including imaging evidence of ICH (symptomatic or asymptomatic) and CMB (<10 mm in diameter) were identified using 1.5 or 3.0 Tesla T2*-weighted gradient-echo imaging. Subjects who had no baseline MRI data were excluded from the current analysis.

BP Measurements

BP recordings were collected at randomization; 1 month later; and then at every 3 months (4, 7, 10, 13, 16, 19, 22 months, or further) until termination of the study. At every scheduled and unscheduled visit, the BP of participants was measured twice by using an automatic sphygmomanometer after they had rested in a sitting position for at least 5 minutes. The mean follow-up BP from the baseline to final visit was calculated for each subject. Mean PP was then calculated as the difference in mean SBP and mean DBP. Mean arterial pressure (MAP), defined as the average pressure in a patient's arteries during 1 cardiac cycle, was calculated as the mean DBP plus one-third of the mean PP. The predictive value of PP was compared with other generally used BP parameters such as SBP and MAP.

Vascular End Point

The primary end point was hemorrhagic stroke, defined as ICH. The secondary end points were ischemic stroke; stroke of any type; and major adverse cardiovascular events (MACEs), defined as a composite of stroke, coronary heart disease, or vascular death. The tertiary end point was all-cause death. Stroke event was confirmed by brain MRI or computed tomography, and each outcome event was verified by the Central Independent Adjudication Committee, which was blinded to the treatment assignments.

Statistical Analysis

Study participants were stratified into quartiles according to the distribution of mean PP during the follow-up. The lowest PP quartile was set as the reference group for the purpose of comparison. They were also

categorized into 4 groups according to the cutoff ranges for their mean PP values: normal (<50 mm Hg), high-normal (50 to <60 mm Hg), high (60–69 mm Hg), and very high (≥ 70 mm Hg). The group with the lowest PP was set as the reference group, because 50 mm Hg is considered the normal clinical PP value in both men and women.¹⁶ PP was also assessed as a continuous variable.

The baseline demographic and clinical covariates were preselected on the basis of previous studies of factors that influence vascular events after an ischemic stroke. The data are presented as mean \pm SD, number of subjects (%), or median (interquartile range [IQR]) as appropriate. Comparisons across the groups were examined using the Pearson's chi-square test for categorical variables and the 1-way ANOVA for continuous variables. Also, Bonferroni's and Dunnett's multiple comparisons with the lowest quartile as the reference group were made for categorical and continuous variables, respectively.

Using time-dependent Cox analysis with the Fine-Gray competing risks model,¹⁷ a cause-specific incidence was modeled to estimate hazards of vascular events at 2 years, after adjusting for baseline covariates such as age, sex, diabetes, smoking, family history of stroke, qualifying stroke severity, ICH (versus CMBs), SBP, glycosylated hemoglobin, serum levels of low-density lipoprotein cholesterol and creatinine, antihypertensive drug use (all $P < 0.10$), and cilostazol use (model 1) and after adjusting for aforementioned covariates plus MAP (model 2). In these models, all-cause death was considered as a competing event for ischemic stroke, hemorrhagic stroke, and stroke of any type, while nonvascular death was considered as a competing event for MACEs. For all-cause death, Cox proportional hazard regression analysis was performed. Subjects not having outcome events were censored at the last follow-up examination or the last visit until the subject died. Subjects lost to follow-up during the study were included in the Fine-Gray subdistribution hazard model until the last contact. Results were expressed by hazard ratio (HR) and 95% CI. A linear trend of adjusted HRs across the mean PP quartiles was examined using a likelihood ratio test.

The effects of mean PP on key vascular outcomes according to 10 mm Hg strata of mean SBP were examined using multivariable logistic regression by model 2. Kaplan-Meier curves were compared using the log-rank tests with Dunnett-Hsu multiple comparisons to assess the predictive value of risk classes for the risk of vascular recurrence. The predictive ability of the mean PP was assessed by calculating c-statistics (adjusted time-dependent area under the receiver operating characteristic curve analysis).¹⁸

Subgroup comparisons of mean PP as a continuous variable for the hazards of vascular events were

performed with respect to subject's demographics including age (<65 versus ≥65 years), sex, and their clinical characteristics, including diabetes, smoking, family history of stroke, ICH (versus CMBs), SBP (<120, 120 to <140, ≥140 mm Hg), qualifying stroke on the National Institutes of Health Stroke Scale (0, 1–4, ≥5), antihypertensive use, cilostazol use, and MAP (70–100 mm Hg versus >100 mm Hg). The subgroup comparisons were made by including appropriate interaction effects between the subgroups and mean PP in the multivariable model.

All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Cary, NC), MedCalc software (version 19.1, Mariakerke, Belgium), and MATLAB-based Toolbox R2020a (version 9.8, The MathWorks, Inc., Natick, MA). A 2-sided $P < 0.05$ was considered as the minimum level of statistical significance.

RESULTS

Subject Characteristics by Mean PP Categories

Of the 1534 participants, after excluding 80 subjects (5.2%) who had no MRI at baseline, a total of 1454 participants were included in this study (62.2% men; mean age, 65.9±10.8 years; mean follow-up period, 1.9±1.3 years [median, 1.8; IQR, 1.0–3.0]). The weighted kappa statistics for the concordance rate for white matter hyperintensities and for the presence of lacune(s) was 0.78 (95% CI; 0.75–0.80) and 0.77 (95% CI; 0.74–0.79), respectively. The study subjects had cerebral small-vessel disease (mean Fazekas score of white matter hyperintensities, 1.96±0.75 [median, 2; IQR, 1–3] in total; CMB in 74.5% of subjects with a median of 3 [IQR, 1–7] CMB; ICH in 38.8% of subjects; and lacune in 83.4% of subjects). Mean SBP and DBP, mean PP, and MAP of study subjects during the follow-up period was 131.3±11.3 mm Hg, 77.8±8.1 mm Hg, 53.5±8.7 mm Hg, and 95.6±8.2 mm Hg, respectively.

The mean frequency of visit for BP checkup was 9.4±5.5 times (median, 9; IQR, 5–14). Distributions of subjects by increasing number of visits for BP checkup are shown in Figure S1. The profile plot for individual PP values by number of BP checkups showed that intraindividual variability was not remarkably higher and the dispersion of intraindividual variability in mean PP was 17% (Figure S2A and B).

The resulting ranges of quartiles according to the distribution of mean PP were ≤47 mm Hg (first quartile), 48–53 mm Hg (second quartile), 54–59 mm Hg (third quartile), and ≥60 mm Hg (fourth quartile). Table 1 shows the baseline demographic and clinical characteristics by mean PP quartiles. Subjects in the higher quartile were older; more likely to have higher levels

of mean PP, baseline and mean SBP, MAP, glucose, glycosylated hemoglobin, low-density lipoprotein cholesterol, and creatinine; and greater frequencies of diabetes, imaging evidence of ICH, and antihypertensive medication. However, the proportion of male patients, frequencies of smoking, family history of stroke, qualifying stroke severity, and baseline and mean diastolic BP were more likely to be lower in subjects in the higher quartile.

Associations of Mean PP and Vascular Outcomes

During the follow-up period (mean, 1.9 years), a total of 117 (8.0%) stroke of any type, 25 (1.7%) hemorrhagic stroke, 93 (6.4%) ischemic stroke, 136 (9.4%) with MACEs, and 52 (3.6%) all-cause deaths were observed. Table 2 shows the incidence rate and unadjusted results of the association of mean PP with vascular outcomes in a stepwise manner and as a continuous variable. Compared with the lowest quartile group, the higher quartile group was associated with greater risk of hemorrhagic stroke (HR, 7.88; 95% CI, 1.76–35.24) for fourth; stroke of any type (HR, 1.75; 95% CI, 1.04–2.95) for fourth; MACEs (HR, 1.64; 95% CI, 1.02–2.62 for third; and HR, 1.80; 95% CI, 1.11–2.94 for fourth); and all-cause death (HR, 2.19; 95% CI, 1.04–4.64 for fourth). The risk of ischemic stroke trended to be higher in the third and fourth PP group. Higher mean PP as a continuous variable was significantly associated with occurrence of hemorrhagic stroke (HR, 1.09; 95% CI, 1.06–1.13), ischemic stroke (HR, 1.03; 95% CI, 1.00–1.06), stroke of any type (HR, 1.04; 95% CI, 1.02–1.07), and MACE (HR, 1.04; 95% CI, 1.02–1.07), whereas occurrence of all-cause of death tended to be higher.

Tables 3 and 4 (model 1 and model 2, respectively) present the adjusted results of stepwise and continuous associations between mean PP and vascular events. Compared with the lowest quartile, the highest quartile was significantly associated with increased risk of hemorrhagic stroke (HR, 7.97; 1.40–45.38), but not of stroke any type or MACE. Higher mean PP as a continuous variable was linked to increased risks of hemorrhagic stroke (HR, 1.11; 95% CI, 1.05–1.17), stroke of any type (HR, 1.04; 95% CI, 1.00–1.07) and MACE (HR, 1.03; 95% CI, 1.00–1.07) but not of ischemic stroke (Table 3). In model 2, mean PP remained significant after further adjustment for MAP for hemorrhagic stroke (HR, 6.03; 95% CI, 1.04–34.99) for the highest quartile ($P = 0.0194$ by linear trend test), whereas MAP persisted as an independent predictor of ICH (HR, 1.09; 95% CI, 1.01–1.17); stroke of any type (HR, 1.09; 95% CI, 1.06–1.12); and MACE (HR, 1.08; 95% CI, 1.05–1.11) in the presence of mean PP (Table 4). As such, higher mean PP as a continuous variable remained significant for the risk of hemorrhagic stroke (HR, 1.09; 95% CI, 1.03–1.15), while MAP remained an independent predictor

Table 1. Baseline Characteristics by Increasing Strata of Mean PP

	Quartile of mean PP				P value*
	1 (≤47 mm Hg)	2 (48–53 mm Hg)	3 (54–59 mm Hg)	4 (≥60 mm Hg)	
Number of subjects	371	403	357	323	
Demographics					
Age, y	61.4±11.1	64.7±10.2 [†]	67.7±10.2 [†]	70.5±9.4 [†]	<0.001
Male sex	247 (66.6)	267 (66.3)	212 (59.4)	178 (55.1) [†]	0.003
Medical history					
Hypertension	323 (87.1)	357 (88.6)	318 (89.1)	296 (91.6)	0.284
Diabetes	85 (22.9)	129 (32.0) [†]	114 (31.9) [†]	137 (42.4) [†]	<0.001
Coronary heart disease	21 (5.7)	19 (4.7)	15 (4.2)	12 (3.7)	0.645
Current smoking	195 (52.6)	185 (45.9)	146 (40.9) [†]	118 (36.5) [†]	<0.001
Family history of stroke	101 (27.2)	79 (19.6) [†]	76 (21.3)	58 (18.0) [†]	0.015
Qualifying ischemic event					0.649
Ischemic stroke	355 (95.7)	385 (95.5)	338 (94.7)	303 (93.8)	
Transient ischemic attack	16 (4.3)	18 (4.5)	19 (5.3)	20 (6.2)	
Time to randomization, days	17.0 (8.0, 36.0)	17.0 (7.0, 42.0)	18.0 (6.0, 40.0)	18.0 (9.0, 34.0)	0.869
Qualifying stroke NIHSS	2 (1, 4)	1 (0, 3)	2 (1, 3)	1 (0, 3) [†]	0.038
Index of high risk of ICH					0.011
Prior ICH	90 (24.3)	76 (18.9)	65 (18.2)	45 (13.9) [†]	
Imaging evidence of ICH	64 (17.3)	82 (20.3)	63 (17.6)	79 (24.5)	
CMBs (≥2)	217 (58.5)	245 (60.8)	229 (64.1)	199 (61.6)	
Presence of lacune	305 (90.0)	329 (88.7)	301 (90.7)	278 (93.0)	0.300
White matter hyperintensity					0.153
Score 0–1 [†]	114 (30.7)	136 (33.7)	94 (26.3)	84 (26.0)	
Score 2	170 (45.8)	163 (40.4)	170 (47.6)	147 (45.5)	
Score 3	87 (23.5)	104 (25.8)	93 (26.1)	92 (28.5)	
Vital signs					
Mean PP, mm Hg	43.3±3.7	50.6±1.7 [†]	56.3±1.6 [†]	65.5±5.9 [†]	<0.001
Systolic BP, mm Hg					
Baseline	127.6±16.5	132.5±16.5 [†]	137.9±17.4 [†]	145.2±17.4 [†]	<0.001
Mean	122.3±8.6	128.5±7.6 [†]	133.4±7.9 [†]	142.6±10.4 [†]	<0.001
Diastolic BP, mm Hg					
Baseline	81.6±12.2	80.3±11.3	80.2±12.2	79.1±11.3	0.053
Mean	79.0±8.0	77.8±7.5	77.1±7.7 [†]	77.1±8.4 [†]	0.003
MAP, mm Hg	93.4±8.0	94.7±7.5	95.9±7.8 [†]	99.0±8.7 [†]	<0.001
Heart rate, beats per min	80.5±13.9	81.1±13.9	81.7±15.0	80.3±14.7	0.571
Body mass index, kg/m ²	24.4±3.5	24.5±3.6	24.4±3.6	24.1±3.6	0.532
Laboratory findings					
Glucose, mg/dL	112.9±36.5	119.9±44.7	122.3±43.1 [†]	125.3±51.4 [†]	0.004
HbA _{1c} , %	6.0±1.0	6.2±1.0	6.3±1.2 [†]	6.4±1.4 [†]	0.001
Total cholesterol, mg/dL	168.2±40.3	167.4±41.0	169.2±40.9	171.8±42.8	0.569
LDL-C, mg/dL	100.5±33.8	101.7±37.2	103.8±35.8	107.4±35.9	0.088
Triglycerides, mg/dL	130.9±89.3	131.2±84.8	127.5±76.8	127.6±98.8	0.912
HDL-C, mg/dL	44.9±12.0	44.9±11.6	45.3±12.3	45.9±12.0	0.670
Creatinine, mg/dL	0.95±0.29	0.98±0.72	0.95±0.47	1.08±0.69 [†]	0.023
Concomitant medication					
Antihypertensive	263 (70.9)	299 (74.2)	253 (70.9)	254 (78.6)	0.070
RAS modifier	201 (54.2)	222 (55.1)	203 (56.9)	174 (53.9)	0.857

(Continued)

Table 1. Continued

	Quartile of mean PP				P value*
	1 (≤47 mm Hg)	2 (48–53 mm Hg)	3 (54–59 mm Hg)	4 (≥60 mm Hg)	
Beta blocker	38 (10.2)	45 (11.2)	41 (11.5)	42 (13.0)	0.721
Calcium channel blocker	178 (48.0)	181 (44.9)	176 (49.3)	158 (48.9)	0.610
Diuretics	51 (13.7)	55 (13.6)	46 (12.9)	48 (14.9)	0.905
Statin	291 (78.4)	327 (81.1)	290 (81.2)	252 (78.0)	0.579
Probucol	204 (55.0)	201 (49.9)	171 (47.9)	156 (48.3)	0.201
Antiplatelet drug					0.105
Cilostazol	193 (52.0)	200 (49.6)	185 (51.8)	141 (43.7)	
Aspirin	178 (48.0)	203 (50.4)	172 (48.2)	182 (56.3)	

Values provided are number (%), mean±SD, or median (interquartile range). BP indicates blood pressure; CMB, cerebral microbleed; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ICH, intracerebral hemorrhage; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; PP, pulse pressure; and RAS, renin angiotensin system.

*By Pearson's chi-square test for categorical variables and 1-way ANOVA test for continuous variables as appropriate.

†Indicates significant difference between them ($P<0.05$) by Dunnett test for continuous variables or by chi-square test with Bonferroni adjustment for categorical variables (lowest quartile of mean PP as a reference group).

‡Score 0 and 1 are merged because of small frequencies in the score of 0 ($n=2$).

of stroke of any type (HR, 1.09; 95% CI, 1.06–1.12) and MACE (1.07; 95% CI, 1.04–1.10). Figure 1 displays the multivariable effects of mean PP by mean SBP strata on the risk of key end points. The risk of hemorrhagic stroke was higher for patients with elevated mean PP

along with greater mean SBP levels. However, the effect of mean PP did not outweigh that of mean SBP for stroke of any type or MACE. Consistent with this, shown in Table S1, in the presence of MAP, the association of mean PP with hemorrhagic stroke was also

Table 2. Incidence Rate and Unadjusted HR of Mean PP for Outcome Events

	Quartile of mean PP				Mean PP, as a continuous variable
	1 (≤47 mm Hg)	2 (48–53 mm Hg)	3 (54–59 mm Hg)	4 (≥60 mm Hg)	
Hemorrhagic stroke, n*	2	4	7	12	
IR/100 PY (95% CI)	0.27 (0.07–1.09)	0.47 (0.18–1.26)	0.99 (0.47–2.08)	2.20 (1.25–3.87)	
Crude HR [†] (95% CI)	1 [Referent]	1.732 (0.317–9.466)	3.559 (0.737–17.188)	7.875 (1.760–35.241)	1.093 (1.058–1.130)
P value	...	0.5259	0.1141	0.0070	<0.001
Ischemic stroke, n*	23	16	32	22	
IR/100 PY (95% CI)	3.14 (2.09–4.73)	1.89 (1.16–3.08)	4.53 (3.20–6.41)	4.03 (2.65–6.11)	
Crude HR [†] (95% CI)	1 [Referent]	0.612 (0.324–1.156)	1.413 (0.829–2.409)	1.213 (0.674–2.182)	1.029 (1.001–1.057)
P value	...	0.1299	0.2041	0.5188	0.0409
Stroke of any type, n*	25	19 [‡]	39	34	
IR/100 PY (95% CI)	3.14 (2.31–5.05)	2.24 (1.43–3.52)	5.52 (4.04–7.56)	6.22 (4.45–8.71)	
Crude HR [†] (95% CI)	1 [Referent]	0.667 (0.368–1.211)	1.587 (0.962–2.619)	1.752 (1.042–2.945)	1.044 (1.020–1.068)
P value	...	0.1830	0.0706	0.0345	0.0002
MACE, n*	28	24	45	39	
IR/100 PY (95% CI)	3.82 (2.64–5.54)	2.84 (1.90–4.23)	6.37 (4.76–8.54)	7.14 (5.22–9.77)	
Crude HR [§] (95% CI)	1 [Referent]	0.752 (0.436–1.298)	1.638 (1.023–2.620)	1.801 (1.105–2.935)	1.042 (1.019–1.066)
P value	...	0.3062	0.0398	0.0183	0.0003
All-cause death, n*	11	14	9	18	
IR/100 PY (95% CI)	1.50 (0.83–2.71)	1.65 (0.98–2.79)	1.27 (0.66–2.44)	3.29 (2.07–5.23)	
Crude HR [¶] (95% CI)	1 [Referent]	1.109 (0.503–2.443)	0.840 (0.348–2.029)	2.192 (1.035–4.642)	1.031 (0.998–1.066)
P value	...	0.7971	0.6989	0.0404	0.0678

HR indicates hazard ratio; IR, incidence rate; MACE, major adverse cardiovascular event; PP, pulse pressure; and PY, person-year.

*Total number of events during the follow-up period.

†One patient had combined ischemic and hemorrhagic stroke.

‡Using Fine-Gray competing risk model for sub-distribution hazard. All-cause death is considered as a competing event.

§Using Fine-Gray competing risk model for subdistribution hazard. Nonvascular death is considered as a competing event.

¶Using Cox's proportional hazards regression model.

Table 3. Adjusted HR of Mean PP for Outcome Events (Model 1)

Model 1 (Single pressure)*	Hemorrhagic stroke		Stroke of any type		MACE	
	HR† (95% CI)	P value	HR† (95% CI)	P value	HR† (95% CI)	P value
Mean PP by quartile						
1 (≤47 mm Hg)	1 [Referent]		1 [Referent]		1 [Referent]	
2 (48–53 mm Hg)	1.599 (0.278–9.197)	0.5991	0.581 (0.303–1.113)	0.1014	0.566 (0.305–1.049)	0.0704
3 (54–59 mm Hg)	3.504 (0.664–18.488)	0.1395	1.323 (0.730–2.398)	0.3562	1.210 (0.694–2.109)	0.5020
4 (≥60 mm Hg)	7.973 (1.401–45.378)	0.0193	1.213 (0.619–2.374)	0.5737	0.955 (0.503–1.811)	0.8871
Mean PP, as a continuous variable	1.109 (1.048–1.174)	0.0003	1.038 (1.004–1.073)	0.0274	1.017 (0.987–1.048)	0.2719

HR indicates hazard ratio; MACE, major adverse cardiovascular events as stroke, coronary heart disease, or vascular death; and PP, pulse pressure.

*Adjusted for age, sex, diabetes, smoking, family history of stroke, qualifying stroke severity, intracerebral hemorrhage (versus cerebral microbleeds), systolic blood pressure, glycosylated hemoglobin, low-density lipoprotein cholesterol, creatinine, antihypertensive use, and cilostazol use.

†Using Fine-Gray competing risk model for sub-distribution hazard. All-cause death is considered as a competing event.

‡Using Fine-Gray competing risk model for subdistribution hazard. Nonvascular death is considered as a competing event.

evident among subjects with high PP (60–69 mm Hg; HR, 9.34; 95% CI, 1.74–50.30) and those with very high PP (≥70 mm Hg; HR, 11.03; 95% CI, 1.14–107.07) versus subjects with normal PP (<50 mm Hg). Higher mean PP as a continuous variable was also a predictor of hemorrhagic stroke (HR, 1.09; 95% CI, 1.04–1.15).

Figure 2 depicts the Kaplan-Meier curves for the end points of (A) hemorrhagic stroke, (B) ischemic stroke, (C) stroke of any type, and (D) MACE among subjects during the 2-year follow-up period, for PP stratified by quartiles. A higher risk was seen in the highest quartile group ($P=0.0016$, $P=0.0402$, $P=0.0013$, and $P=0.0009$, respectively, by log-rank test). Compared with the lowest quartile, the risk of hemorrhagic stroke and MACE was significantly greater in the highest quartile ($P=0.0016$ and $P=0.0396$, respectively) by Dunnett-Hsu multiple comparison tests. The adjusted time-dependent area under the receiver operating characteristic curve of mean PP for hemorrhagic stroke

was 0.79 (c-statistic, 0.79; 95% CI, 0.24–1.14), while the prognostic accuracy for stroke of any type and MACE was 0.72 and 0.69, respectively (Figure S3). As shown in Table 1, mean SBP was more likely higher by increasing burden of mean PP, but independent associations of mean SBP by 10 mm Hg strata with key end points were not significant (Table S2), the finding of which is in line with that from Figure 1. The adjusted HRs of covariates included in the time-dependent Cox model appears in Table S3. Among them, age was an independent predictor of stroke of any type and MACE. Serum creatinine was associated with an increased risk of hemorrhagic stroke, stroke of any type, and MACE. Cilostazol medication was linked to a lesser risk of hemorrhagic stroke.

Subgroup Analysis

The interaction effect between subgroups and mean PP as a continuous variable on the risk of vascular

Table 4. Adjusted HR of Mean PP for Outcome Events (Model 2)

Model 2 (Two pressure)*	Hemorrhagic stroke		Stroke of any type		MACE	
	HR† (95% CI)	P value	HR† (95% CI)	P value	HR† (95% CI)	P value
Mean PP by quartile [§]						
1 (≤47 mm Hg)	1 [Referent]		1 [Referent]		1 [Referent]	
2 (48–53 mm Hg)	1.490 (0.266–8.343)	0.6500	0.519 (0.269–1.000)	0.0501	0.566 (0.305–1.049)	0.0704
3 (54–59 mm Hg)	2.926 (0.540–15.865)	0.2132	1.108 (0.612–2.009)	0.7345	1.210 (0.694–2.109)	0.5020
4 (≥60 mm Hg)	6.028 (1.038–34.994)	0.0453	0.858 (0.431–1.708)	0.6634	0.955 (0.503–1.811)	0.8871
MAP, mm Hg	1.089 (1.010–1.173)	0.0267	1.092 (1.062–1.123)	<0.0001	1.077 (1.048–1.107)	<0.0001
Mean PP, as a continuous variable	1.086 (1.029–1.147)	0.0030	1.017 (0.985–1.051)	0.2993	1.017 (0.987–1.048)	0.2719
MAP, mm Hg	1.076 (0.995–1.164)	0.0654	1.088 (1.057–1.119)	<0.0001	1.073 (1.044–1.104)	<0.0001

HR indicates hazard ratio; MACE, major adverse cardiovascular event as stroke, coronary heart disease, or vascular death; MAP, mean arterial pressure; and PP, pulse pressure.

*Adjusted for age, sex, diabetes, smoking, family history of stroke, qualifying stroke severity, intracerebral hemorrhage (versus cerebral microbleeds), systolic blood pressure, glycosylated hemoglobin, low-density lipoprotein cholesterol, creatinine, antihypertensive use, cilostazol use, and MAP.

†Using Fine-Gray competing risk model for subdistribution hazard. All-cause death is considered as a competing event.

‡Using Fine-Gray competing risk model for sub-distribution hazard. Nonvascular death is considered as a competing event.

§P for trend=0.0194 for hemorrhagic stroke; P for trend=0.6767 for stroke of any type; and P for trend=0.4377 for MACE.

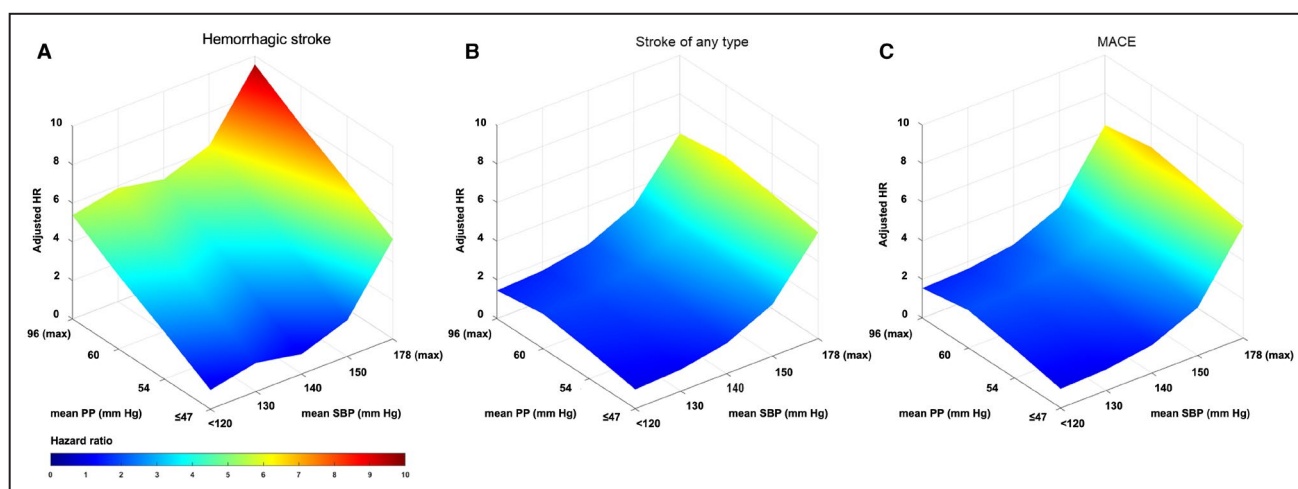


Figure 1. Multivariable effect of mean PP on (A) hemorrhagic stroke, (B) stroke of any type (B), and (C) MACE by 10 mm Hg strata of mean SBP.

HR indicates hazard ratio; MACE, major adverse cardiovascular event; PP, pulse pressure; and SBP, systolic blood pressure.

events is shown in Figure 3. Only significant interaction was observed between age <65 years and high mean PP for the risk of MACE ($P=0.026$).

DISCUSSION

We observed that in this analysis of prospectively collected data on >1400 participants after noncardioembolic stroke who had multiple CMBs or ICH, elevated long-term mean PP was independently associated with higher risk of recurrent hemorrhagic stroke among patients with higher mean SBP during the 2-year follow-up period. Interestingly, imaging evidence of ICH before the PICASSO-qualifying stroke was noted more likely frequent among the groups with higher PP quartile, maybe indirectly supporting the notion that stroke survivors with CMBs and higher PP are, in particular, prone to hemorrhagic strokes. Specifically, mean PP ≥ 60 mm Hg was related to significant relative risk increases in hemorrhagic stroke by 6-fold, when compared with the lowest quartile. These findings were found to be independent of older age, high levels of baseline and mean SBP, diabetes, and MAP, and remained significant despite a lower frequency of smoking and family history of stroke, and a higher rate of antihypertensive medication and cilostazol use, than the reference group. At the very least, our findings suggest that elevated long-term PP may be of prognostic value for identifying high-risk patients predisposed to recurrent hemorrhagic stroke among patients with stroke with CMBs or ICH while on secondary stroke prevention.

These results regarding why elevated mean PP is more related to risk of hemorrhagic than ischemic stroke may be attributable to the findings that patients with higher PP quartile were older, more likely to have higher long-term SBP, MAP, and impaired renal

function. Furthermore, they harbored a greater rate of imaging evidence of ICH, reflecting a more bleeding-prone condition than the reference group. Considering these factors, the long-term burden of elevated PP along with MAP in such frail patients might have placed the perforating arteries at a higher risk for hemorrhagic stroke. As such, discrimination of the mean PP for hemorrhagic stroke was about 0.79, suggesting a modest value.¹⁹

The null association of PP with risk of ischemic stroke in our study might be explained by the prespecified stroke cohort harboring CMBs or ICH, which is, however, contradicted with a recent pooled analysis that the absolute risk of ischemic stroke is consistently substantially higher than that of ICH over time, regardless of the number or anatomic distribution of CMBs.²⁰ Thus, a possibility of inadequate follow-up period (mean, 1.9 years) cannot be excluded. Also, a previous study showed that the impact of PP was weaker than that of MAP on the prediction of future ischemic stroke.²¹

The result of our analysis regarding association between mean PP and stroke of any type (HR, 1.02; 95% CI, 0.99–1.05) in model 2 is similar to that of a recent meta-analysis that showed a significant association between PP and stroke risk (pooled HR, 1.05; 95% CI, 1.03–1.07).⁹ However, that meta-analysis included only 11 studies and was mainly composed of heterogeneous individuals free of stroke. By contrast, studies assessing PP based on the stroke population were small, and all were evaluated in an acute stroke setting. Higher mean PP during the acute phase of stroke was linked to an increased risk of 1-year mortality¹⁰ or of poor stroke outcome¹¹ and mortality¹² at 3 months. In a post hoc analysis from the TAIST (Tinzaparin in Acute Ischaemic Stroke Trial), elevated PP at baseline among patients within 48 hours after ischemic stroke was independently

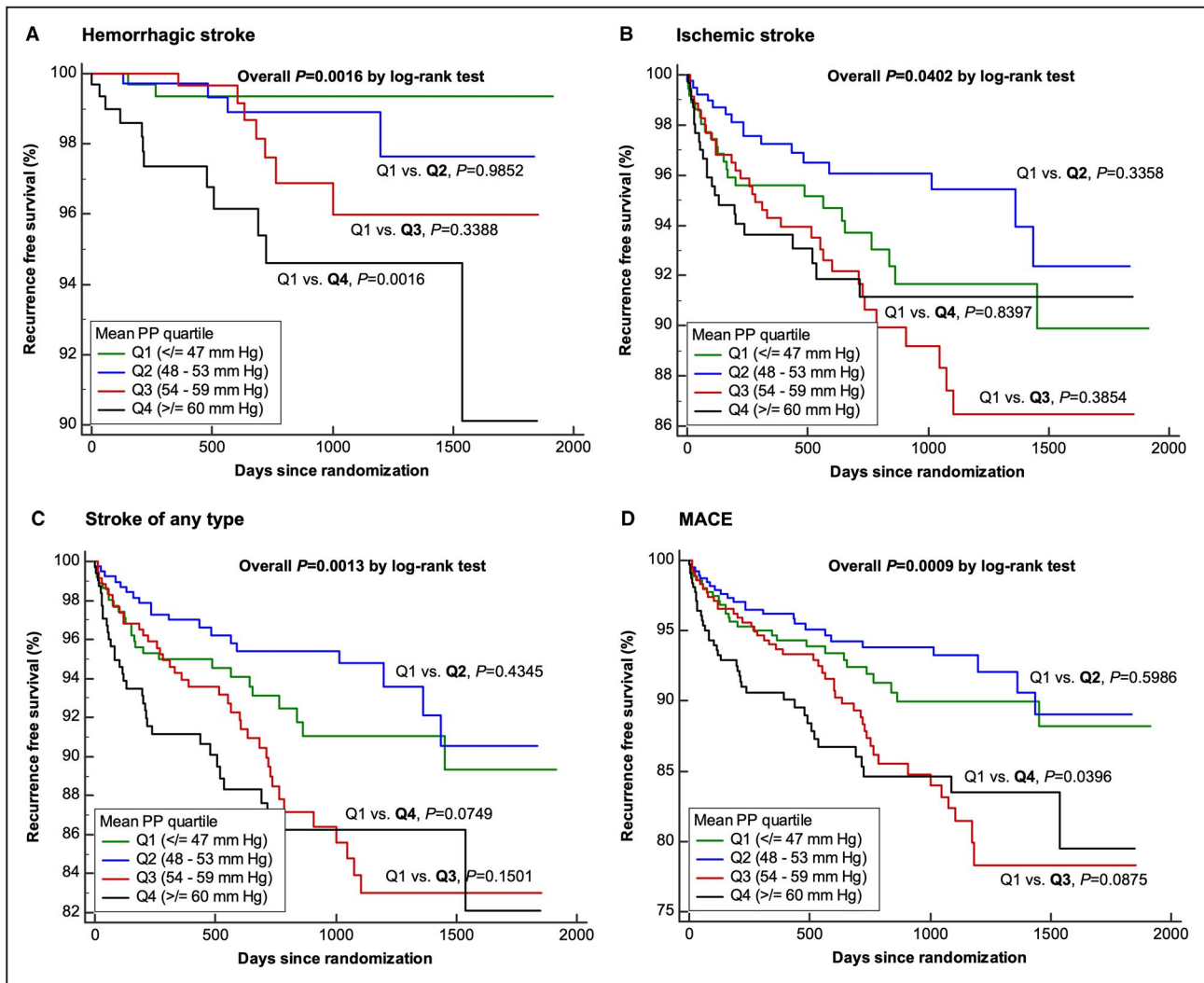


Figure 2. Kaplan-Meier curves for the end points of (A) hemorrhagic stroke, (B) ischemic stroke, (C) stroke of any type, and (D) MACE.

MACE indicates major adverse cardiovascular event; and PP, pulse pressure.

associated with death or neurologic deterioration (odds ratio, 1.02; 95% CI, 1.01–1.03) and recurrent stroke (odds ratio, 1.03; 95% CI, 1.01–1.04) at day 10¹³; the latter finding is relatively consistent with our findings.

With increasing age, a continual rise in SBP with a late fall in DBP after 60 years of age is related to increased PP, reflecting more developed large-artery stiffness.^{22,23} Higher SBP, unless treated, can aggravate large-artery stiffness, leading to deleterious outcomes.²² Given the higher prevalence of hemorrhagic stroke in Asian people than in Western people,²⁴ more research is needed to explore PP reduction as an additional potential therapeutic target among patients with stroke at high hemorrhagic risk. Since elevated PP independently influenced the risk of hemorrhagic stroke at higher SBP, for now the implementation of stable SBP control would be at least a reasonable proxy for reducing recurrent stroke.

Our study has some limitations. First, it is a retrospective post hoc analysis of a prospective study to evaluate the efficacy and safety of prespecified drugs. Therefore, our results should be viewed as hypothesis-generating findings and thus cannot prove a causal relationship of PP with hemorrhagic stroke risk. Second, the trajectory of PP varies for each individual, but PP analysis was not performed on the basis of intraindividual variability, which otherwise might have influenced our results. Third, a total of 126 (8.7%) patients had relatively few follow-up BP data <3 times of checkup. However, its influence on the result findings would be low, given that the median frequency of visit for BP check was 9 (IQR, 5–14). Fourth, the risk of hemorrhagic stroke associated with higher PP was greater: the small number of stroke events, especially hemorrhagic type, meant that CIs were wide, jeopardizing the precision of estimates for recurrent vascular outcomes. Fifth, the PICASSO cohort consisted of Asian

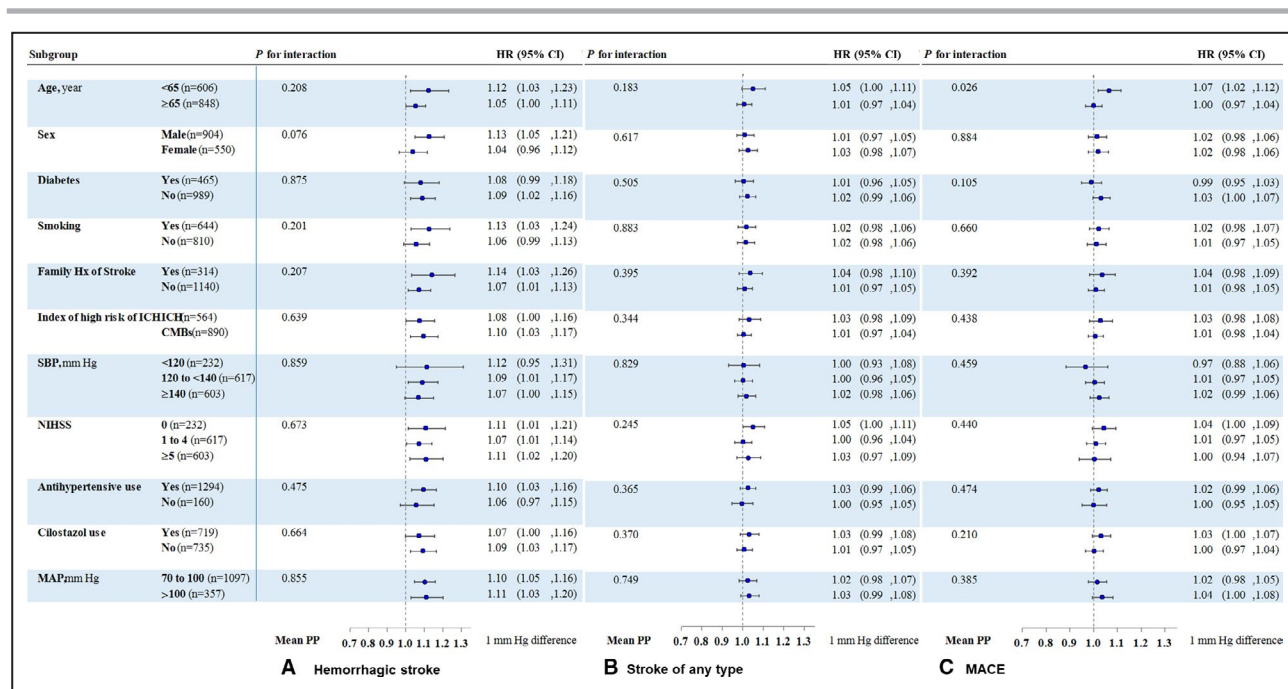


Figure 3. Subgroup analysis of key endpoints

CMBs indicates cerebral microbleeds; HR, hazard ratio; ICH, intracerebral hemorrhage; MACE, major adverse cardiovascular event; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; PP, pulse pressure; and SBP, systolic blood pressure.

(primarily Korean) patients with stroke, and specifically those at high risk of ICH recruited from academic centers, thus limiting the generalizability of our results to the general stroke population or other ethnic stroke populations, especially for White populations. Last, because of nonavailability of carotid-femoral pulse wave velocity, we could not correlate it with PP. Nevertheless, discrimination of mean PP for identifying high-risk subjects predisposed to having hemorrhagic stroke was modest; therefore, our findings need to be confirmed in future studies with a larger stroke population. The strengths of our study include the PP measurement not being based on the baseline value during acute stroke but rather on the mean value during a relatively long-term follow-up period for better prediction and variable vascular endpoint measures, particularly for stroke type (hemorrhagic versus ischemic) and the confirmation of stroke event based on computed tomography or MRI findings.

CONCLUSIONS

This study suggests that after adjusting for several important confounders including SBP and MAP, long-term elevated PP of ≥ 60 mm Hg along with higher SBP may confer an increased risk of recurrent stroke, especially for hemorrhagic type among individuals with preexisting multiple CMBs or ICH following noncardioembolic stroke. Our findings require confirmation in future large-scale prospective studies with wider ranges of PP distribution.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Adjusted HR of mean PP for Outcome Events.

	Hemorrhagic stroke	<i>P</i>	Stroke of any type	<i>P</i>	MACE	<i>P</i>
	HR† (95% CI)		HR† (95% CI)		HR‡ (95% CI)	
Mean PP categories by 4*						
Normal (<50 mm Hg)	1 [Referent]		1 [Referent]		1 [Referent]	
High-normal (50 to <60 mm Hg)	4.45 (0.98–20.23)	0.054	1.16 (0.70–1.93)	0.573	1.08 (0.67–1.74)	0.743
High (60 to 69 mm Hg)	9.34 (1.74–50.30)	0.009	1.14 (0.59–2.21)	0.692	1.08 (0.58–1.99)	0.816
Very-high (≥70 mm Hg)	11.03 (1.14–107.07)	0.038	1.38 (0.47–4.04)	0.560	1.45 (0.55–3.84)	0.456
MAP, mm Hg	1.08 (1.01–1.15)	0.025	1.08 (1.05–1.12)	<0.001	1.07 (1.04–1.10)	<0.001
Mean PP, as a continuous variable*	1.09 (1.04–1.15)	0.001	1.02 (0.99–1.06)	0.183	1.02 (0.99–1.05)	0.187
MAP, mm Hg	1.07 (0.99–1.15)	0.086	1.08 (1.05–1.11)	<0.001	1.07 (1.04–1.10)	<0.001

MACE indicates major adverse cardiovascular events; PP, pulse pressure; MAP, mean arterial pressure; HR, hazard ratio; CI, confidence interval. *Adjusted for age, sex, diabetes mellitus, smoking, family history of stroke, imaging evidence of intracerebral hemorrhage, systolic blood pressure, body mass index, serum creatinine, antihypertensive use, cilostazol use, and MAP. †Using Fine–Gray competing risk model for sub-distribution hazard. All-cause death is considered as a competing event. ‡Using Fine–Gray competing risk model for sub-distribution hazard. Nonvascular death is considered as a competing event.

Table S2. Adjusted HR of mean SBP with Key Vascular Endpoints.

	Hemorrhagic stroke	<i>P</i>	Stroke of any type	<i>P</i>	MACE	<i>P</i>
	HR† (95% CI)		HR† (95% CI)		HR‡ (95% CI)	
Mean SBP by 10 mm Hg strata*						
1 (<120 mm Hg)	1 [Referent]		1 [Referent]		1 [Referent]	
2 (120 to 139 mm Hg)	1.065 (0.091–12.448)	0.9602	0.730 (0.294–1.810)	0.4968	0.735 (0.325–1.664)	0.4602
3 (≥140 mm Hg)	1.799 (0.075–43.277)	0.7176	0.967 (0.265–3.530)	0.9591	1.033 (0.313–3.412)	0.9572
Mean PP	1.078 (1.008–1.153)	0.0292	1.009 (0.973–1.046)	0.6314	1.011 (0.976–1.047)	0.5399
MAP, mm Hg	1.046 (0.956–1.144)	0.3257	1.067 (1.025–1.111)	0.0017	1.055 (1.015–1.097)	0.0070
Mean SBP, as a continuous variable§	—		—		—	
Mean PP	—		—		—	
MAP, mm Hg	—		—		—	

SBP indicates systolic blood pressure; PP, pulse pressure; MACE, major adverse cardiovascular events; MAP, mean arterial pressure; HR, hazard ratio; CI, confidence interval. *Adjusted for age, sex, hypertension, diabetes mellitus, smoking, mean PP, MAP, body mass index, glycosylated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, antihypertensive use, probucol use, and cilostazol use. †Using Fine–Gray competing risk model for sub-distribution hazard. All-cause death is considered as a competing event. ‡Using Fine–Gray competing risk model for sub-distribution hazard. Nonvascular death is considered as a competing event. §Independent associations with key vascular endpoints were non-computable due to multicollinearity when adjusting for mean PP.

Table S3. Adjusted HRs of Covariates Included in the Time-Dependent Cox Models of Vascular Outcomes (Model 2) by Increasing Strata of Mean Pulse Pressure.

Covariates	Hemorrhagic stroke		Stroke of any type		MACE	
	HR (95%, CI)	<i>P</i>	HR (95%, CI)	<i>P</i>	HR (95%, CI)	<i>P</i>
Age (1-yr difference)	0.984 (0.939–1.032)	0.5172	1.032 (1.010–1.054)	0.0037	1.027 (1.008–1.047)	0.0061
Male sex	0.816 (0.286–2.331)	0.7046	1.271 (0.741–2.178)	0.3839	1.144 (0.698–1.874)	0.5935
Diabetes mellitus	0.856 (0.316–2.318)	0.7599	1.154 (0.698–1.907)	0.5763	1.357 (0.852–2.163)	0.1991
Smoking	0.711 (0.223–2.261)	0.5628	0.946 (0.554–1.617)	0.8399	0.947 (0.574–1.564)	0.8320
Family history of stroke	1.007 (0.342–2.968)	0.9898	1.464 (0.927–2.311)	0.1020	1.440 (0.938–2.212)	0.0958
Qualifying stroke severity	1.010 (0.891–1.146)	0.8714	1.032 (0.965–1.103)	0.3538	1.041 (0.977–1.109)	0.2113
ICH (vs. CMBs)*	1.047 (0.421–2.607)	0.9208	1.178 (0.778–1.783)	0.4402	1.194 (0.814–1.750)	0.3648
SBP†	0.986 (0.962–1.012)	0.2898	0.988 (0.978–0.999)	0.0376	0.993 (0.983–1.003)	0.1694
Glycosylated hemoglobin	1.108 (0.776–1.581)	0.5720	1.023 (0.854–1.224)	0.8074	0.993 (0.841–1.174)	0.9374
LDL-C	0.990 (0.981–1.000)	0.0415	1.000 (0.994–1.005)	0.8576	0.998 (0.993–1.004)	0.5598
Creatinine	1.484 (1.165–1.890)	0.0014	1.223 (1.020–1.467)	0.0298	1.255 (1.083–1.454)	0.0025
Antihypertensive use	0.917 (0.366–2.296)	0.8534	0.864 (0.563–1.324)	0.5017	0.929 (0.619–1.395)	0.7225
Cilostazol use	0.410 (0.170–0.989)	0.0473	0.667 (0.444–1.001)	0.0506	0.820 (0.564–1.193)	0.2987

MACE indicates major adverse cardiovascular events as stroke, coronary heart disease, or vascular death; ICH, intracerebral hemorrhage; CMB, cerebral microbleed; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval. * CMBs as a reference group. †Baseline variable used due to multicollinearity effect when adjusting for mean SBP.

Figure S1. Proportion of study subjects by increasing number of visits for blood pressure. Values provided are number of subjects.

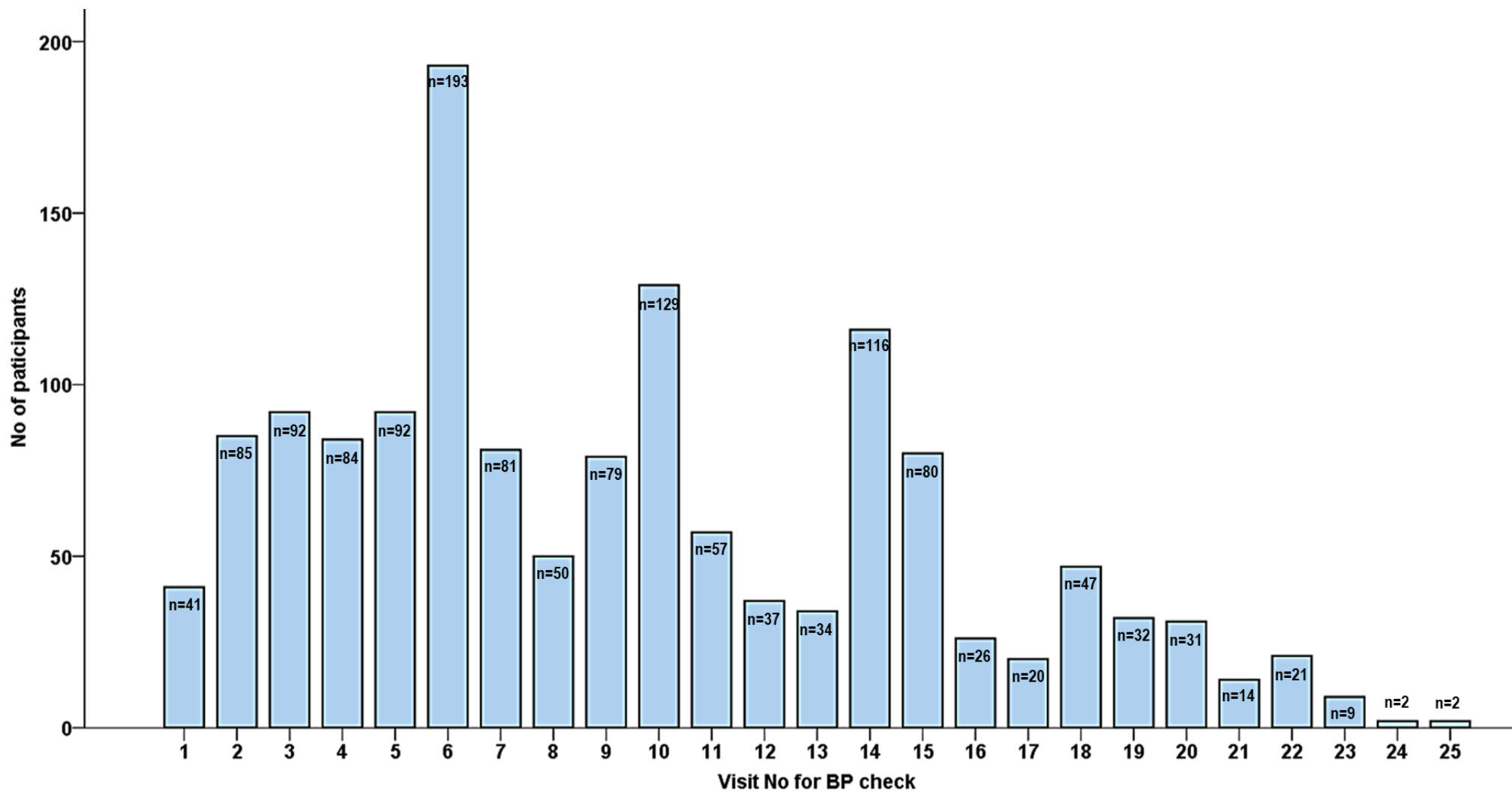
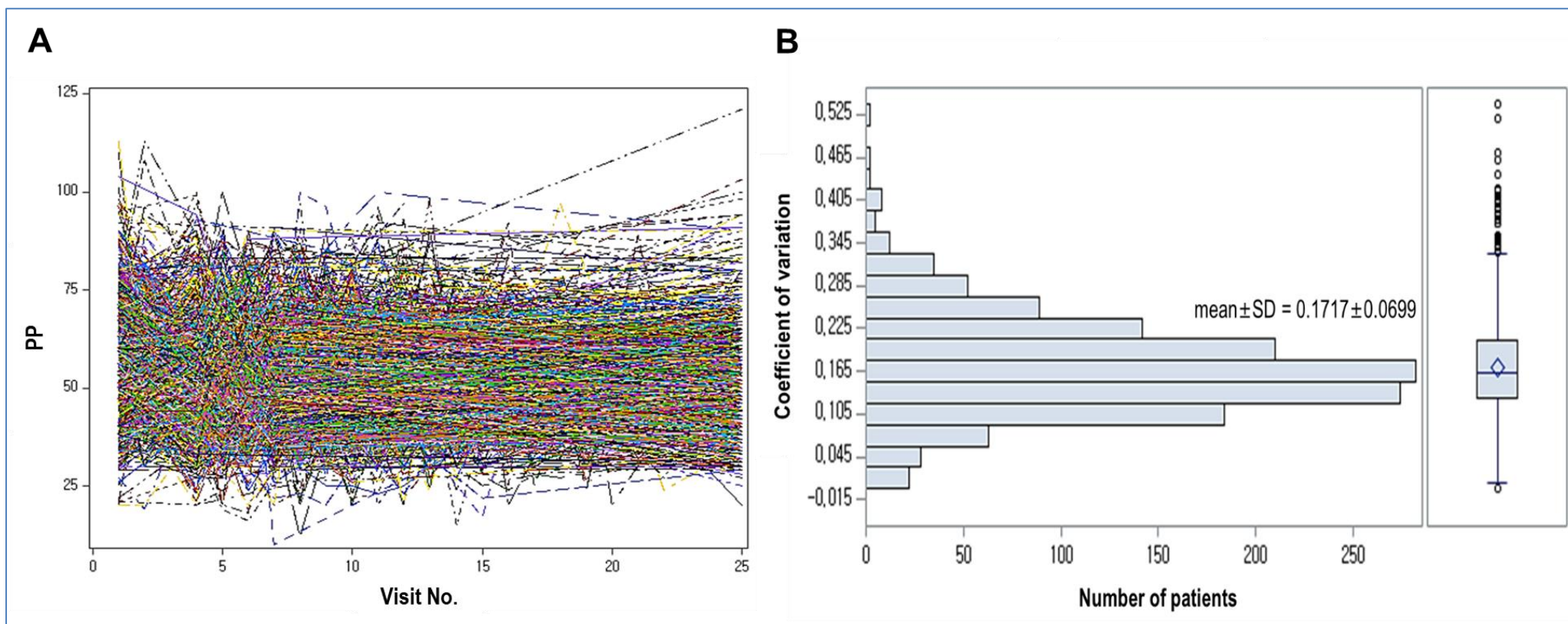
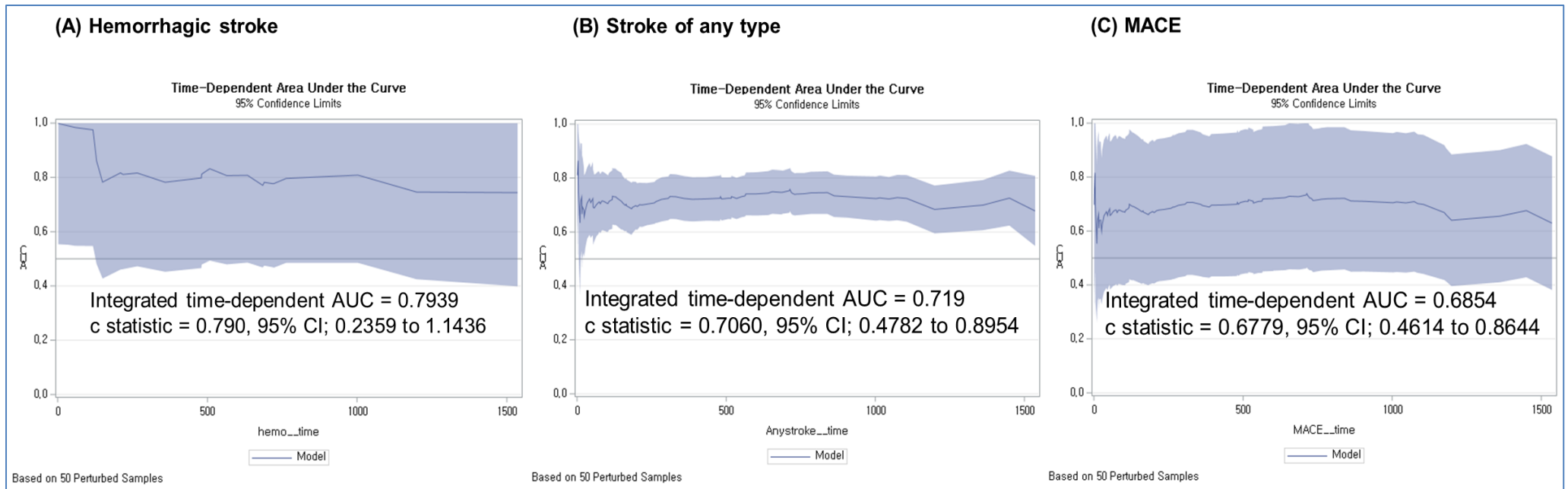


Figure S2. The profile plot for individual PP by number of BP check-up (A) and the normal distribution of CV (B), in which the mean value of CV is 0.17.



These findings demonstrate that intra-individual variability seems not remarkably higher and explain that the dispersion of intra-individual variability in mean PP is 17%. PP indicates pulse pressure; BP, blood pressure; CV, coefficient of variation.

Figure S3. Adjusted time-dependent area under the receiver operating characteristic curve with 95% confidence limits of the mean pulse pressure for (1) hemorrhagic stroke, (2) stroke of any type, and (3) MACE.



MACE indicates major adverse cardiovascular events.