ARTICLE

Relationship between blood pressure and outcome changes over time in acute ischemic stroke

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Abstract

Objective

To evaluate whether the relationship between systolic blood pressure (SBP) and stroke outcome varies during the acute stage of ischemic stroke as a function of the elapsed time after stroke onset.

Methods

Patients who were hospitalized due to ischemic stroke within 6 hours of onset were retrospectively analyzed. SBP data were collected at 8 time points (1, 2, 4, 8, 16, 24, 48, and 72 hours after onset). The primary functional outcome measure was a poor outcome, defined as a modified Rankin Scale score of >2 at 3 months after stroke. Linear and quadratic models were constructed at each time point to assess relationships between SBP and outcome.

Results

Of the 2,546 patients, 728 (28.6%) had a poor outcome. SBP, as either a linear or quadratic term, had a significant effect on functional outcome, except at 4 hours after onset. For the initial 2 hours after onset, SBP had nonlinear U-shaped relationships with functional outcome, and patients with SBP of approximately 165 mm Hg were the least likely to have a poor outcome. Quadratic models exhibited a significantly better model fit. For 8–24 hours postonset, SBP exhibited linear relationships with functional outcome. For 48–72 hours postonset, SBP exhibited a J-shaped relationship with functional outcome, and the predicted probability of poor outcome was the lowest in patients with SBP of approximately 125 mm Hg. These relationships were relatively consistent across various sensitivity analyses.

Conclusion

This study revealed that the relationship between SBP and functional outcome may depend on elapsed time from stroke onset.

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Glossary

AIC = Akaike Information Criterion; **BMI** = body mass index; **BP** = blood pressure; **CI** = confidence interval; **EVT** = endovascular treatment; **IQR** = interquartile range; **IRB** = institutional review board; **IVT** = IV thrombolysis; **LL** = log-likelihood; **LR** = likelihood ratio; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **SBP** = systolic blood pressure; **SRMI** = sequential regression multiple imputation; **SYSO** = symptomatic steno-occlusion of the cerebral artery; **TOAST** = Trial of ORG 10172 in Acute Stroke Treatment; **VISTA** = Virtual Stroke International Stroke Trial Archive.

Blood pressure (BP) during the acute phase of ischemic stroke is an important determinant of outcome, but clinical equipoise remains for BP management during this phase.[1] Randomized controlled trials in which BP was lowered at the acute stage of stroke showed a neutral effect on outcome.[2,3] Studies on drug-induced hypertension have yielded insufficient evidence.[4,5] In observational studies, both high and low acute systolic BP (SBP) were associated with poor clinical outcome in some studies and favorable outcome in others.[6–12]

Inconsistent results might be explained by the timing of BP measurement after stroke onset. SBP generally increases when stroke occurs, then decreases over hours to days.[13–15] Autoregulation of cerebral blood flow is impaired during the acute phase, rendering cerebral perfusion directly dependent on BP.[6,12,16] Considering that BP itself and the effect of BP on perfusion changes over time after onset, the relationship between SBP and outcome may also change.

The effect of high SBP on outcome has been reported to strengthen during the initial day after stroke, and subsequently weaken.[6] That study was limited, however, as the odds ratio (OR) was used as a summary measure based on an assumption of a linear relationship between SBP and clinical outcome. Because previous studies suggested a J- or U-shaped relationship, the possibility of nonlinearity should be considered.[9,11,12] Our study evaluated whether the magnitude and shape of the relationship between SBP and 3-month functional outcome changed with the time elapsed from onset during the acute stage of ischemic stroke.

Methods

Study population

From a prospective stroke registry database,[17,18] a consecutive series of patients with acute ischemic stroke admitted to Seoul National University Bundang Hospital within 6 hours after stroke onset between January 2004 and March 2018 were identified (n = 3,988). Among these 3,988 patients, we excluded 1,278 patients who had unclear-onset stroke, defined as the first time when abnormalities were noted being not the same as the last time when the patient felt well, for whom 3-month modified Rankin Scale (mRS) scores were unavailable in 77, and 87 whose BP was measured less than 4 times among the 8 time points. This left 2,546 patients in the study.

Standard protocol approvals, registrations, and patient consents

Collection of clinical information for improving the quality of stroke care was approved by the institutional review board (IRB) with a waiver of informed consent due to study subject anonymity and minimal risk to participants (IRB approval B-1007-105-122). Additional collection of clinical information, including BP data, and the use of these data for this study were also approved (IRB approval B-1901-514-116).

Data collection

Demographics (age, sex, and body mass index [BMI]), vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking status, and previous stroke or TIA), laboratory findings (creatinine and blood glucose levels), previous medications (antiplatelets, anticoagulants, and statins), acute management (IV thrombolysis [IVT] and endovascular treatment [EVT]), discharge medications (antiplatelets, anticoagulants, statins, and antihypertensive medication), and stroke characteristics were collected prospectively during hospitalization. Stroke characteristics included the initial stroke severity according to the NIH Stroke Scale (NIHSS) score, stroke subtype classified according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria with some modifications,[19] and symptomatic steno-occlusion of the cerebral artery (SYSO), defined as occlusion or stenosis of ≥50% of the lumen diameter of the intracranial or extracranial major cerebral artery relevant to the ischemic lesion detected by CT, MRI, or conventional angiography.

BP was measured by a standard mercury sphygmomanometer or a noninvasive BP monitoring device on the nonparalytic arm on a regular basis following the institutional protocols for acute stroke management. BP data obtained in routine clinical practice during hospitalization were recorded into the electronic health record system, and the study participants' BP data during hospitalization were downloaded from the clinical data warehouse of our institution. From the collected BP data, we extracted the SBP at 8 time points (1, 2, 4, 8, 16, 24, 48, and 72 hours after stroke onset). Time points were determined in reference to a previous study for comparability.[6] Meanwhile, 2 additional time points (4 and 8 hours after stroke onset) were included to allow us to more closely examine the relationships among SBP, time points after stroke onset, and outcome. To specify the range of each time point, all intervals between the time points were divided in half. The nearest SBP values in the prescribed range of each time point were used in the analysis

(supplemental data available from Dryad, figure e-1, doi.org/10.5061/dryad.zw3r22855).

To assess the functional outcome of patients with ischemic stroke, we used the 3-month mRS score,[20] which was prospectively collected at 3 months after stroke onset through a structured telephone interview by trained stroke coordinators. For the primary analysis, the 3-month mRS score was dichotomized into poor (mRS score of 3–6) vs good outcome (mRS score of 0–2). In the secondary analysis, ordinal logistic regression was applied with the full range of the 3-month mRS scores (0–6) as an outcome variable. Details of the clinical definitions and data management of the registry are described elsewhere.[17,18]

Statistical analysis

The baseline characteristics of patients are presented as mean (SD) or median (interquartile range [IQR]) for continuous variables or frequency (percentage) for categorical variables. Missing SBP data were excluded rather than imputed.

The relationship between SBP and outcome was assessed using adjusted models, and the following predetermined covariates were entered into the models: age, sex, initial NIHSS score, stroke subtype, and acute recanalization therapy (IVT or EVT). As primary analysis, for the 3-month mRS score dichotomized into poor vs good outcome, multivariable logistic regression models were constructed at each time point of SBP measured. Multivariable ordinal logistic regression models were also considered for the mRS score in itself under the assumption of proportionality of odds. For all analyses, participant's SBP was used as a continuous variable.

Because we considered the possibility of a nonlinear relationship, 2 models were examined: one with only a linear term of SBP and the other with both linear and quadratic terms of SBP. Two criteria were used to compare those models: an Akaike Information Criterion (AIC) value and a likelihood ratio (LR) statistic. Because an area under curve—a commonly used criterion in clinical research—changes very little if statistically valuable predictors were already incorporated into models, we decided on the AIC as a proper measure for evaluating the significance of quadratic term of SBP.[21] The AIC value is defined as: $2k - 2\ln(\hat{L})$, where k is the number of estimated parameters in the model and $\hat{L}$ is the maximum value of the likelihood function for the model.[21–23] It considers both the goodness of fit and the simplicity of a model with a lower AIC value being indicative of a better fit of the model. In contrast, a LR test is based on −2 log-likelihood (LL) differences between 2 models, one is nested in the other, and helps to choose a better model, which maximizes its likelihood function. Meanwhile, we used the Wald test to check significances of coefficients of SBP in each logistic regression model. The goodness of fit of models was examined using the Hosmer-Lemeshow c statistic.

As sensitivity analysis, robustness of our study results was examined by following 3 methods. First, analysis was restricted to patients who did not receive acute recanalization therapy in order to mitigate a potential influence of the change in vessel status and perfusion during the acute stage. Second, we reanalyzed the data adjusting all potential confounders that we thought could affect the outcome: age, sex, BMI, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking status, previous stroke or TIA, creatinine, blood glucose, previous use of antiplatelets, previous use of anticoagulants, previous use of statins, IVT, EVT, antiplatelet use at discharge, anticoagulant use at discharge, statin use at discharge, initial NIHSS score, TOAST classification, and SYSO.[6,24,25] In this sensitivity analysis, unlike the primary analysis with no missing covariate value, multiple imputation with a method of sequential regression multiple imputation (SRMI) was performed to recover missing values of BMI, creatinine, blood glucose, previous medications (antiplatelets, anticoagulants, and statins), and statin use at discharge. Ten imputed datasets were created and the results were combined to account for uncertainty in the imputed data. Third, a complete case analysis of excluding patients who had any missing covariate information with all the potential confounders was performed to compare its results with that of multiple imputation. As post hoc analysis, we also examined whether stroke severity and subtypes played a role of effect modifier on a relationship between SBP and functional outcome.

BP data were extracted using Python 3.5.2 (python.org). The SRMI method was used by IVEware software (University of Michigan, Ann Arbor; src.isr.umich.edu/software/). All other analyses were performed using R version 3.6.2 (The R foundation, r-project.org) and SAS software version 9.4 (SAS institute, Cary, NC). All p values reported are 2-tailed, and a value <0.05 was considered significant.

Data availability

The data used in this article will be available on a reasonable request to the authors by researchers who submit a legitimate academic research proposal for a public purpose.

Results

A total of 2,546 patients with 17,196 SBP measurements were analyzed (table 1). The mean age was 66.7 years, 62% were men, and 64% were diagnosed with hypertension. The baseline median NIHSS score was 3 (IQR 1–9), and 34% received hyperacute recanalization therapy.

The distributions with mean values and SDs of SBP at each time point are presented in figure 1. The mean SBP ranged from 153.5 mm Hg to 131.5 mm Hg and the SDs ranged from 26.6 mm Hg to 20.3 mm Hg.

At 3 months after stroke, 728 patients (28.6%) had a poor outcome. The relationship between SBP and poor outcome was checked before modeling; changes by elapsed time from

Table 1 Baseline characteristics of 2,546 patients included in analysis

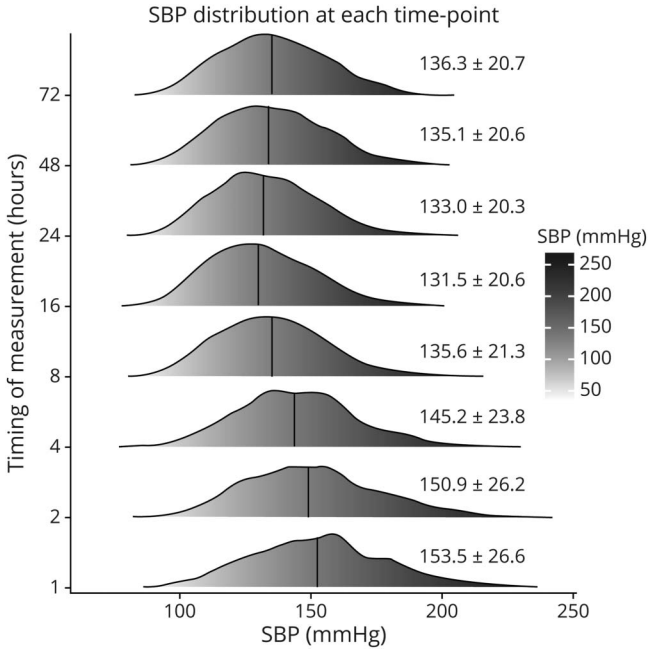
Characteristics	Values, n (%) or mean ± SD
Age, y	66.74 ± 12.86
Male	1,575 (62)
BMI, kg/m^2	23.79 ± 3.34
<18.50	140 (6)
18.50–24.99	1,582 (62)
25.00–29.99	732 (29)
≥30.00	92 (4)
Onset to admission, h	2.02 ± 6.05
≤3	1,830 (72)
3–6	716 (28)
Initial NIHSS, median (IQR)	3 (1–9)
<6	1,654 (65)
6–10	323 (13)
≥11	569 (22)
TOAST	
LAD	797 (31)
SVO	342 (13)
CE	764 (30)
OD or UD	643 (25)
SYSO	1,009 (40)
Recanalization therapy	857 (34)
IVT only	377 (44)
EVT only	182 (21)
Combined IVT–EVT	298 (35)
Hypertension	1,634 (64)
Diagnosed before stroke	1,510 (92)
Newly diagnosed	124 (8)
Diabetes mellitus	704 (28)
Hyperlipidemia	749 (29)
Atrial fibrillation	506 (20)
Previous TIA or stroke	1,911 (75)
Smoking	1,034 (41)
Creatinine, mg/dL	23.8 ± 0.99
Glucose, at admission mg/dL	138.3 ± 55.17
Previous medication	
Antiplatelet	738 (38)
Anticoagulation	157 (8)
Statin	514 (26)
Discharge medication	
Antiplatelet	1824 (72)
Anticoagulation	738 (29)
Statin	1,553 (78)
Antihypertension	866 (44)

Abbreviations: BMI = body mass index; CE = cardioembolism; EVT = endovascular treatment; IVT = IV thrombolysis; IQR = interquartile range; LAD = large artery disease; NIHSS = NIH Stroke Scale; OD = other determined; SVO = small vessel occlusion; SYSO = symptomatic steno-occlusion of major cerebral arteries; UD = undetermined.

stroke onset were observed (figure 2 and data available from Dryad, figure e-3, doi.org/10.5061/dryad.zw3r22855). AIC differences, the significance of the LR test, and the significance of SBP terms in the logistic regression models at individual time points are presented in table 2 after adjusting predetermined covariates of age, sex, initial NIHSS score, stroke subtype, and acute recanalization therapy. The relationship between SBP and outcome varied across different time points. At 1 and 2 hours after stroke onset, the quadratic models revealed significantly low AIC values, suggesting nonlinear relationship. At 8–24 hours, the AICs were low in linear models, and the −2 LL values demonstrated no superiority of the quadratic models over linear models. In terms of a 10-mm Hg change in SBP, the ORs (95% confidence intervals [CIs]) were 1.10 (1.04–1.16) at 8 hours, 1.16 (1.10–1.23) at 16 hours, and 1.17 (1.11–1.24) at 24 hours. At 48 and 72 hours after stroke onset, the quadratic models were significantly better than the linear models.

Similar patterns were observed with the ordinal regression analysis: the quadratic model exhibiting initial superiority, followed by the linear model and a return to the quadratic model (table 2). The results of the sensitivity analysis confined to patients who did not receive recanalization therapy were similar to those of the primary analysis (data available from Dryad, table e-1, doi.org/10.5061/dryad.zw3r22855). Another sensitivity analysis of adjusting all 22 covariates with multiple imputation also showed similar results (data available from Dryad, table e-2, doi.org/10.5061/dryad.zw3r22855). The significance of covariates in the model are presented in data available from Dryad (figure e-2, doi.org/10.5061/dryad.zw3r22855). Among the 22 covariates, age, history of stroke or TIA, initial NIHSS score, and discharge medications were significantly associated with poor outcome. The results of the complete case analysis demonstrated a close agreement with the results of the preceding analysis with multiple imputation (data available from Dryad, table e-3, doi.org/10.5061/dryad.zw3r22855). In post hoc analysis, stroke severity and subtype did not work as

Figure 1 Distributions of systolic blood pressure (SBP) at each time point



effect modifiers in a time-dependent relationship between SBP and functional outcome (data available from Dryad, table e-4, doi.org/10.5061/dryad.zw3r22855).

The time points were categorized into 3 groups by the sign of the AIC differences in the logistic regression models. The predicted probability of poor outcome according to the SBP values was calculated using the adjusted models and displayed by groups (figure 3). We excluded 4 hours in figure 3 because none of the coefficients were significant. Each group presented the same shape of the relationship, namely, a U-shape in a hyperacute period, then a linear shape in an acute period, and a J-shape in a subacute period. In the quadratic models, the SBP values showing the best outcome decreased gradually as time elapsed from stroke onset: 169 mm Hg at 1 hour, 164 mm Hg at 2 hours, 123 mm Hg at 48 hours and 72 hours. The equations of the best fitting models were as follows:

$$\begin{aligned} logit(p_1) &= -0.63 + 0.07age - 0.17male + 0.17NIHSS_{initial} \\ &\quad - 0.41tx_{ivia} - 0.37SVO - 0.71CE - 0.34ODorUD \\ &\quad - 0.72(SBP_{1h}/10) + 0.021(SBP_{1h}/10)^2 \end{aligned}$$

$$\begin{aligned} logit(p_2) &= -0.77 + 0.07age - 0.33male + 0.16NIHSS_{initial} \\ &\quad - 0.22tx_{ivia} - 0.79SVO - 0.68CE - 0.26ODorUD \\ &\quad - 0.71(SBP_{2h}/10) + 0.021(SBP_{2h}/10)^2 \end{aligned}$$

$$\begin{aligned} logit(p_8) &= -7.29 + 0.06age - 0.26male + 0.18NIHSS_{initial} \\ &\quad - 0.46tx_{ivia} - 0.56SVO - 0.42CE - 0.01ODorUD \\ &\quad + 0.09(SBP_{8h}/10) \end{aligned}$$

$$\begin{aligned} logit(p_{16}) &= -7.79 + 0.06age - 0.29male + 0.18NIHSS_{initial} \\ &\quad - 0.47tx_{ivia} - 0.56SVO - 0.37CE - 0.01ODorUD \\ &\quad + 0.15(SBP_{16h}/10) \end{aligned}$$

$$\begin{aligned} logit(p_{24}) &= -7.87 + 0.06age - 0.29male + 0.18NIHSS_{initial} \\ &\quad - 0.49tx_{ivia} - 0.57SVO - 0.34CE - 0.01ODorUD \\ &\quad + 0.16(SBP_{24h}/10) \end{aligned}$$

$$\begin{aligned} logit(p_{48}) &= -1.83 + 0.06age - 0.27male + 0.18NIHSS_{initial} \\ &\quad - 0.49tx_{ivia} - 0.57SVO - 0.41CE - 0.05ODorUD \\ &\quad - 0.69(SBP_{48h}/10) + 0.028(SBP_{48h}/10)^2 \end{aligned}$$

$$\begin{aligned} logit(p_{72}) &= -2.87 + 0.06age - 0.27male + 0.18NIHSS_{initial} \\ &\quad - 0.51tx_{ivia} - 0.59SVO - 0.42CE - 0.02ODorUD \\ &\quad - 0.51(SBP_{72h}/10) + 0.021(SBP_{72h}/10)^2 \end{aligned}$$

Standard errors of coefficients are presented in data available from Dryad (table e-5, doi.org/10.5061/dryad.zw3r22855). Regardless of linear or quadratic models, observed c statistics are greater than 0.8 for all models of time points. More specifically, each of the above models has the c statistic of 0.853, 0.849, 0.848, 0.850, 0.849, 0.847, and 0.845, respectively.

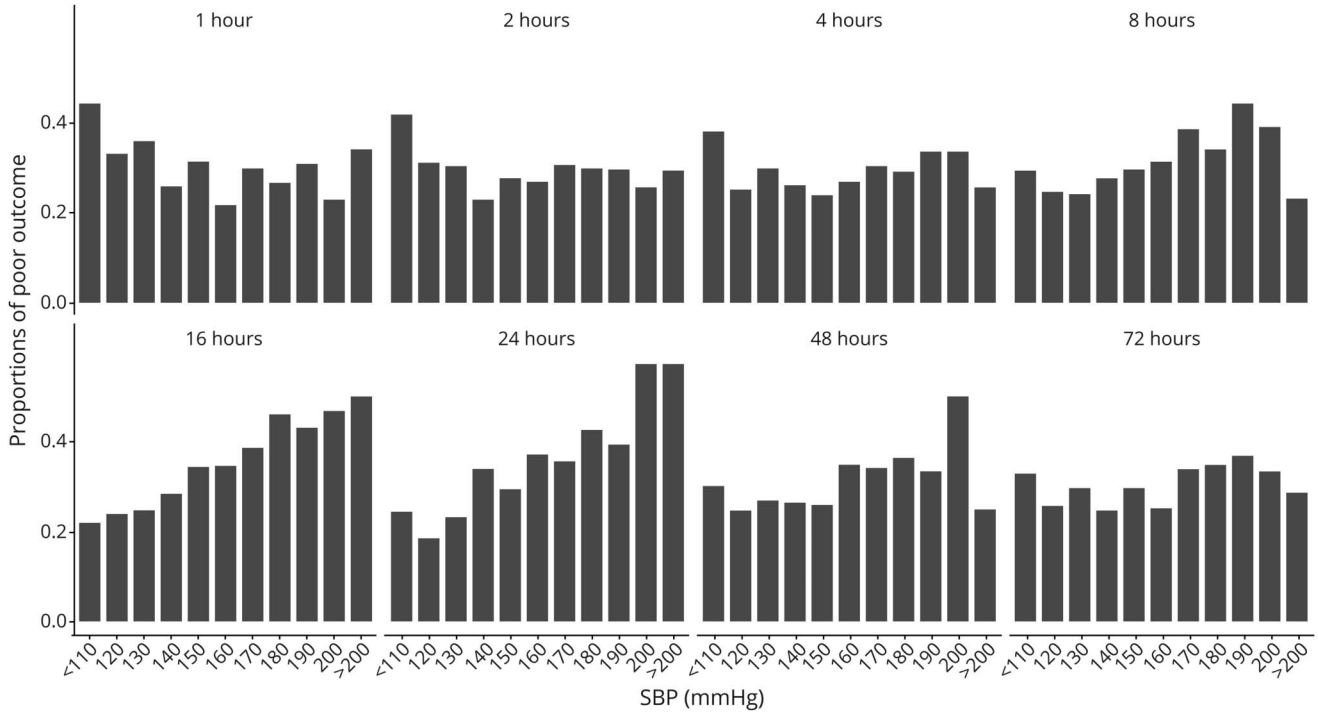
The results of our study and the previous study from the Virtual Stroke International Stroke Trial Archive (VISTA) Collaboration[6] were compared regarding the effects of SBP values on poor functional outcome at each time point under the assumption of a linear relationship and are presented in figure 4. In both studies, SBP affected the outcome significantly, except the initial 4 hours, and the point estimates of the OR increased during the initial 24 hours.

Discussion

The main finding of this study was that the relationship between acute SBP and functional outcome varies depending on the elapsed time from stroke onset. Immediately after stroke onset, the relationship between SBP and poor outcome was U-shaped. From several hours to 1 day after stroke onset, SBP and outcome exhibited a linear relationship. Over the course of 48–72 hours, a J-shaped relationship was observed.

This work combined fragmented results of previous studies of SBP in acute ischemic stroke. The U-shaped relationship with a nadir near 165 mm Hg at the hyperacute stage is in concordance with previous studies,[8,9,13] all of which also demonstrated a U-shaped relationship with the nadir at 180 mm Hg (median time from stroke onset to hospitalization, 7 hours),[13] 195 mm Hg (all participants hospitalized within 24 hours of onset),[8] and 150 mm Hg (>56% of patients admitted within 24 hours).[9] From 8 to 24 hours, SBP exhibited a linear relationship with functional outcome. Throughout the time window of the present study, the observed linear effect of SBP corresponded well to that in the previous study of the VISTA Collaboration (figure 4).[6] At 48 and 72 hours, when SBP was gradually stabilized, a J-shaped relationship was observed. The

Figure 2 Proportions of poor outcome (3-month modified Rankin Scale score 3–6) according to systolic blood pressure (SBP) at each time point



SBP value showing the best functional outcome was in patients with 123 mm Hg, which was in accord with a previous study reporting a J-shaped relationship with a nadir at 125–134 mm Hg in patients with ischemic stroke or TIA enrolled in the later time window.[26]

Mechanisms to explain these complex relationships were explored. The association between high SBP and poor outcome regardless of the timing of BP measurement could be explained by the fact that the high SBP observed in the acute stage of ischemic stroke consistently increased the risk of cerebral edema, hemorrhagic transformation, and early recurrence.[7,27–29]

Poorer outcome in patients with SBP values of <165 mm Hg at 1 and 2 hours after stroke (figure 3) onset might be explained by the fact that a certain SBP level is required to maintain cerebral perfusion and may provide a protective effect to brain tissue since cerebral autoregulation is transiently impaired due to acute ischemic injuries.[3,16] A recent study showed no difference in clinical outcome between intensive and guideline-recommended BP reduction in patients with acute ischemic stroke who were admitted within 6 hours and treated with alteplase, and this failure might be due to an inappropriate target BP (130–140 mm Hg).[30]

The linear association in the 8- to 24-hours time periods might be attributed to, at least partly, the effect of recanalization whether it is detected or not. Spontaneous or treatment-induced recanalization, which occurs frequently in this time window, can make BP decline more rapidly and to a greater extent, and also leads to good clinical outcome.[31]

After 48 hours from onset, when the BP nearly reached a plateau and most patients were stabilized neurologically, worse outcome in patients with SBP values <125 mm Hg (figure 3) may be explained by the fact that those with low SBP in this time window could have large infarct, cardiac failure, or deteriorated vital status, all of which lead to poor outcome. The association of low SBP values and coronary events in patients with acute ischemic stroke has been reported previously.[9,32] However, the underlying pathophysiologic mechanisms mentioned above are just postulated; they should be supported or verified by further research.

The SBP value at which the best outcome was observed decreased from 169 to 123 mm Hg as time elapsed in our study. The notion that the optimal SBP level varies depending on the elapsed time from stroke onset is supported by this finding and the previous studies reporting various nadirs ranging from 120 to 180 mm Hg.[8,9,13,32] Furthermore, neutral results of BP reduction trials in acute ischemic stroke might be attributable to a broad time window and a fixed target BP.[2]

This study has several limitations. The clinical data were acquired retrospectively, which can be a potential source of bias. Nonetheless, the covariates used in the analysis were collected prospectively with predetermined protocols, which reduced

Table 2 Comparisons of linear and quadratic regression models analyzing relationship between systolic blood pressure (SBP) and 3-month functional outcome at each time point

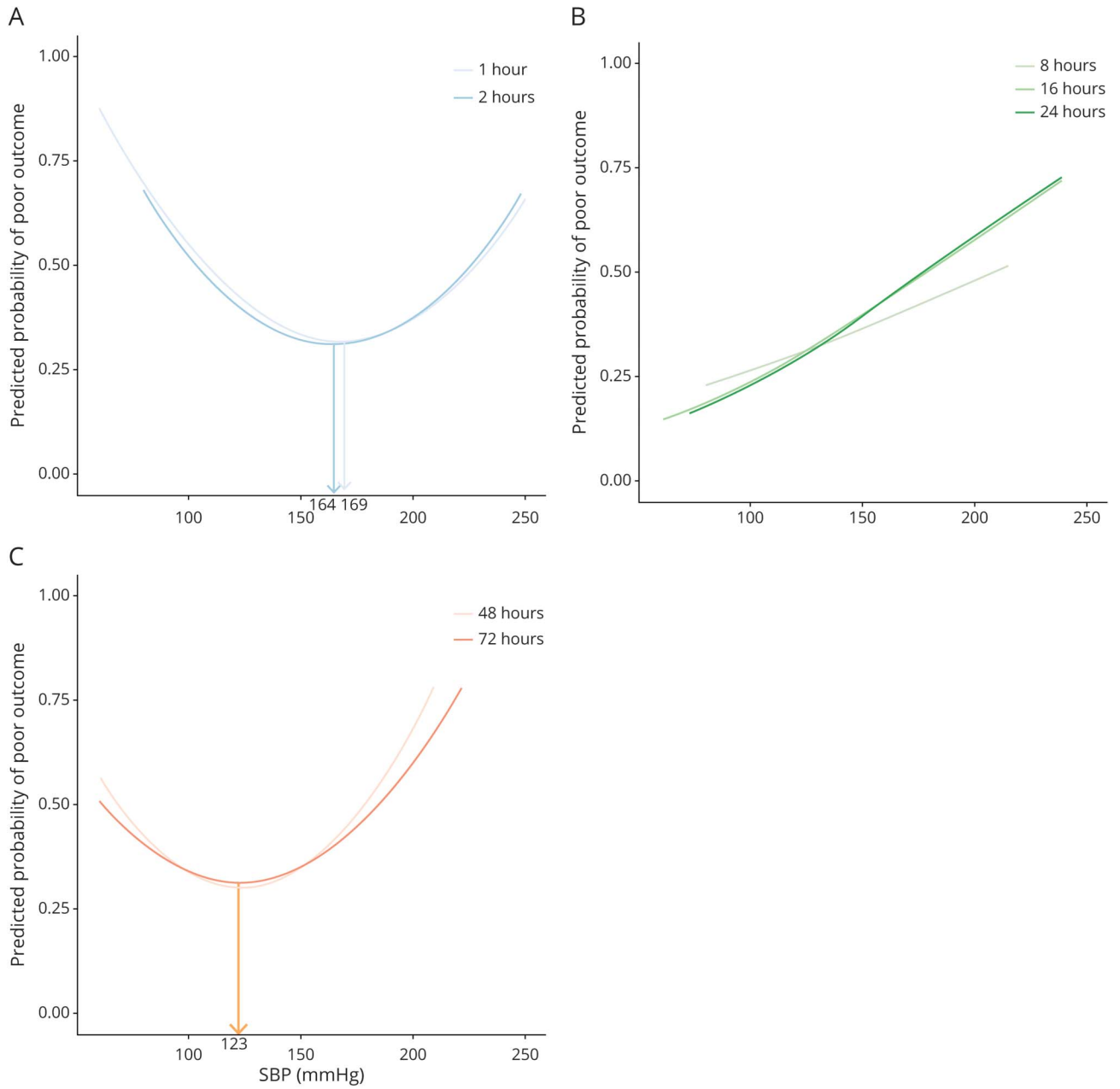
	1 hour (n = 1,022)	2 hours (n = 1,325)	4 hours (n = 2,251)	8 hours (n = 2,503)	16 hours (n = 2,538)	24 hours (n = 2,545)	48 hours (n = 2,533)	72 hours (n = 2,479)
***p* of β[c]**								
3-month mRS 0–2 (ref) vs 3–6								
Linear model								
SBP	0.23	0.31	0.40	<0.001	<0.001	<0.001	0.002	0.01
Quadratic model								
SBP	0.003	0.002	0.23	0.82	0.90	0.67	0.006	0.04
SBP^2	0.005	0.003	0.18	0.52	0.44	0.27	0.002	0.02
Model comparison								
△AIC (L − Q)[a]	6.01	6.67	−0.31	−1.60	−1.43	−0.80	8.00	3.79
***p* of △−2 LL[b]**	0.005	0.003	0.19	0.53	0.45	0.27	0.002	0.02
***p* of β[d]**								
3-month mRS ordinal scale 0–6								
Linear model								
SBP	0.89	0.31	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Quadratic model								
SBP	0.09	0.004	0.52	0.74	0.61	0.13	0.001	0.03
SBP^2	0.09	0.003	0.23	0.33	0.18	0.02	<0.001	0.01
Model comparison								
△AIC (L − Q)[a]	0.92	7.33	−0.37	−1.00	−0.14	3.56	11.16	4.70
***p* of △−2 LL[b]**	0.09	0.002	0.20	0.32	0.17	0.02	<0.001	0.01

Abbreviations: AIC = Akaike Information Criterion; L = linear; LL = log-likelihood; mRS = modified Rankin Scale; Q = quadratic.
Variables adjusted were age, sex, initial NIH Stroke Scale score, stroke subtype, and acute recanalization therapy.
[a] A lower AIC value indicates a better model fit. To calculate AIC differences, AIC in model with both linear and quadratic SBP term were subtracted from that containing linear term. A larger difference indicates a greater predictive power in the quadratic model.
[b] By likelihood ratio test between linear and quadratic models. The degree of freedom was 1. If *p* of −△ 2 LL is under 0.05, quadratic model is significantly better in model fit.
[c] By Wald test for significance of coefficients of SBP terms in logistic regression model.
[d] With ordinal logistic model under proportional odds assumption.

the likelihood of bias due to the retrospective nature of this study. The data were acquired from patients with clear-onset stroke, and who were admitted to a university hospital within 6 hours of stroke onset. Multicenter studies including patients hospitalized at later time windows are required to generalize our findings, although baseline characteristics of our study population were not different from those of a prospective, nationwide, multicenter stroke registry, the Clinical Research Collaboration for Stroke in Korea.[17,18,33] We had no information on changes of vessel status and perfusion during hospitalization, which could moderate the effect of BP on outcome.[12] However, the sensitivity analysis among patients who did not receive acute recanalization therapy yielded comparable results. We did not apply imputation techniques to missing SBP data. The stroke subtype was reported as a modifier of SBP effect on outcome, rather than a confounder.[34] We checked effect modification by stroke severity and subtype but there was no significant effect modification. Further research aiming to stratify stroke subtype or severity when exploring the relationship between SBP and outcome with sufficient sample size would be worth doing. We only compared linear and quadratic models based on previous studies reporting linear or J- or U-shaped associations, but we could not exclude the possibility that other models exist. Although we demonstrated that the fitted models differ at each time point, we could not provide information on the statistical significance of those differences quantitatively due to methodologic limitations. Therefore, this study should be interpreted cautiously and regarded as hypothesis-generating.

The conflicting reports of SBP and outcome in previous studies[6–9,11,12] may be attributable to the fact that the

Figure 3 Probability of poor outcome predicted by systolic blood pressure (SBP) at each time point

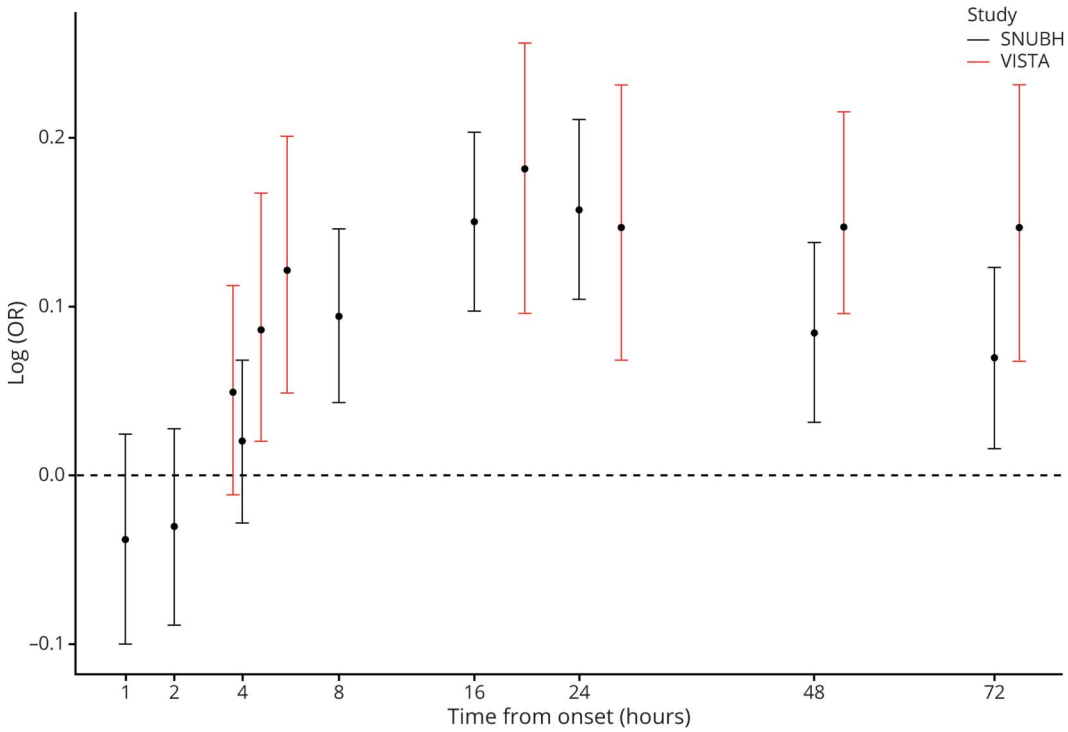


The predicted probability of poor outcome (3-month modified Rankin Scale score 3–6) according to the SBP values was calculated using the adjusted models at 1 and 2 hours (A), 8, 16, and 24 hours (B), and 48 and 72 hours (C). Variables adjusted were age, sex, initial NIH Stroke Scale score, stroke subtype, and acute recanalization therapy.

timing of BP measurements was discordant among studies and was not even considered in their design and analysis. Thus, our study may be novel as we evaluated the independent effect of BP on outcome at each time point only including patients whose stroke onset time was clear and using the time intervals from stroke onset rather than those from admission. A recent study reporting that there are distinct BP trajectory groups in acute stages of ischemic stroke and the fact that they differ in stroke characteristics and outcomes is consistent with the perspective of this study.[25]

With the lack of conclusive evidence on optimal BP management in acute ischemic stroke, the questions "when," "in whom," and "how" to initiate treatment for BP management are yet to be resolved.[35] Our findings suggest that a BP management strategy should consider the change of BP effect on outcome over time. Whether altering BP targets according to the elapsed time from stroke onset can improve outcome was not assessed in this hypothesis-generating study. An optimal BP at each time point should be identified to design a future randomized trial to evaluate the efficacy of targeting BP within a specific time window or with a changing BP target over time.

Figure 4 Log odds ratios (ORs) and 95% confidence intervals for poor outcome by systolic blood pressure (SBP) at several time points in Seoul National University Bundang Hospital (SNUBH) and Virtual Stroke International Stroke Trial Archive (VISTA)



Outcome variable was identical: poor functional outcome defined as 3-month modified Rankin Scale score 3–6. We added 3.7 hours to blood pressure measurement time for the results of VISTA because the average of time from onset to enrollment was 3.7 hours and their SBP measurement was started at entry into the trial.

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Name	Location	Contribution
Ji-Ah Shin	Seoul National University College of Medicine, Korea	Designed and conceptualized study, analyzed the data, interpreted the data, drafted the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Keon-Joo Lee, MD	Department of Neurology, Cerebrovascular Center, Seoul National University Bundang Hospital (SNUBH), Seongnam, Korea	Major role in the acquisition of data, revised the manuscript for intellectual content
Ji Sung Lee, PhD	Clinical Research Center, Asan Medical Center, Seoul, Korea	Analyzed the data
Jihoon Kang, MD	SNUBH, Seongnam, Korea	Role in the acquisition of data, revised the manuscript for intellectual content
Beom Joon Kim, MD	SNUBH, Seongnam, Korea	Role in the acquisition of data, revised the manuscript for intellectual content
Moon-Ku Han, MD	SNUBH, Seongnam, Korea	Role in the acquisition of data, revised the manuscript for intellectual content
Jun Yup Kim, MD	SNUBH, Seongnam, Korea	Role in the acquisition of data
Myung Suk Jang	SNUBH, Seongnam, Korea	Role in data management

Appendix *(continued)*

Name	Location	Contribution
Mi Hwa Yang	SNUBH, Seongnam, Korea	Role in data management
Juneyoung Lee, PhD	Department of Biostatistics, Korea University, Seoul	Statistical consultation on data interpretation, revised statistical analysis section of the manuscript
Philip B. Gorelick, MD MPH	Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL	Revised the manuscript for intellectual content
Hee-Joon Bae, MD, PhD	SNUBH, Seongnam, Korea	Interpreted the data, revised the manuscript for intellectual content

References

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46–e110.
2. Lee M, Ovbiagele B, Hong KS, et al. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. Stroke 2015;46:1883–1889.
3. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev 2014:CD000039.
4. Mistri AK, Robinson TG, Potter JF. Pressor therapy in acute ischemic stroke: systematic review. Stroke 2006;37:1565–1571.
5. Kang MJ, Yang JW, Lee YB, et al. The role of phenylephrine in patients with small deep subcortical infarct and progressive weakness. J Neurol Sci 2017;377:107–111.
6. Sare GM, Ali M, Shuaib A, Bath PM; VISTA Collaboration. Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA Collaboration. Stroke 2009;40:2098–2103.
7. Ishitsuka K, Kamouchi M, Hata J, et al. High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. Hypertension 2014;63:54–60.
8. Stead LG, Gilmore RM, Decker WW, Weaver AL, Brown RD Jr. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. Neurology 2005;65:1179–1183.
9. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; Group ISTC. Blood pressure and clinical outcomes in the international stroke trial. Stroke 2002;33:1315–1320.
10. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 2004;43:18–24.
11. Lin MP, Ovbiagele B, Markovic D, Towfighi A. Systolic blood pressure and mortality after stroke: too low, no go? Stroke 2015;46:1307–1313.
12. Martins AI, Sargento-Freitas J, Silva F, et al. Recanalization modulates association between blood pressure and functional outcome in acute ischemic stroke. Stroke 2016;47:1571–1576.
13. Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke 2004;35:520–526.
14. Wallace JD, Levy LL. Blood pressure after stroke. JAMA 1981;246:2177–2180.
15. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke 1986;17:861–864.
16. Petersen NH, Ortega-Gutierrez S, Reccius A, Masurkar A, Huang A, Marshall RS. Dynamic cerebral autoregulation is transiently impaired for one week after large-vessel acute ischemic stroke. Cerebrovasc Dis 2015;39:144–150.
17. Kim BJ, Han MK, Park TH, et al. Current status of acute stroke management in Korea: a report on a multicenter, comprehensive acute stroke registry. Int J Stroke 2014;9:514–518.
18. Kim BJ, Park JM, Kang K, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. J Stroke 2015;17:38–53.
19. Ko Y, Lee S, Chung JW, et al. MRI-based algorithm for acute ischemic stroke subtype classification. J Stroke 2014;16:161–172.
20. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–607.
21. Bagherzadeh-Khiabani F, Ramezankhani A, Azizi F, Hadaegh F, Steyerberg EW, Khalili D. A tutorial on variable selection for clinical prediction models: feature selection methods in data mining could improve the results. J Clin Epidemiol 2016;71:76–85.
22. Aho K, Derryberry D, Peterson T. Model selection for ecologists: the worldviews of AIC and BIC. Ecology 2014;95:631–636.
23. Myers J, Kei J, Aithal S, et al. Development of a diagnostic prediction model for conductive conditions in neonates using wideband acoustic immittance. Ear Hear 2018;39:1116–1135.
24. Lee KJ, Kim BJ, Han MK, et al. Predictive value of pulse pressure in acute ischemic stroke for future major vascular events. Stroke 2018;49:46–53.
25. Kim BJ, Cho YJ, Hong KS, et al. Trajectory groups of 24-hour systolic blood pressure after acute ischemic stroke and recurrent vascular events. Stroke 2018;49:1836–1842.
26. Xie X, Xu J, Gu H, et al. The J-curve association between systolic blood pressure and clinical outcomes in ischemic stroke or TIA: the BOSS study. Sci Rep 2017;7:14023.
27. Ogata J, Yutani C, Imakita M, et al. Hemorrhagic infarct of the brain without a reopening of the occluded arteries in cardioembolic stroke. Stroke 1989;20:876–883.
28. Vemmos KN, Tsivgoulis G, Spengos K, et al. Association between 24-h blood pressure monitoring variables and brain oedema in patients with hyperacute stroke. J Hypertens 2003;21:2167–2173.
29. Selim M, Fink JN, Kumar S, et al. Predictors of hemorrhagic transformation after intravenous recombinant tissue plasminogen activator: prognostic value of the initial apparent diffusion coefficient and diffusion-weighted lesion volume. Stroke 2002;33:2047–2052.
30. Anderson CS, Huang Y, Lindley RI, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet 2019;393:877–888.
31. Mattle HP, Kappeler L, Arnold M, et al. Blood pressure and vessel recanalization in the first hours after ischemic stroke. Stroke 2005;36:264–268.
32. Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 2004;255:257–265.
33. Kim JY, Kang K, Kang J, et al. Executive summary of stroke statistics in Korea 2018: a report from the epidemiology research council of the Korean stroke society. J Stroke 2019;21:42–59.
34. Ntaios G, Lambrou D, Michel P. Blood pressure changes in acute ischemic stroke and outcome with respect to stroke etiology. Neurology 2012;79:1440–1448.
35. Ntaios G, Bath P, Michel P. Blood pressure treatment in acute ischemic stroke: a review of studies and recommendations. Curr Opin Neurol 2010;23:46–52.