Blood Pressure After Endovascular Thrombectomy
Modeling for Outcomes Based on Recanalization Status

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Background and Purpose—The optimal level for blood pressure after endovascular thrombectomy in acute ischemic stroke is not well established. We sought to evaluate the association of post-endovascular thrombectomy systolic blood pressure (SBP) levels with clinical outcomes.

Methods—We included endovascular thrombectomy–treated patients registered from 2014 to 2017 in the Safe Implementation of Treatments in Stroke International Thrombectomy Registry. The mean 24-hour SBP after endovascular thrombectomy treatment was analyzed both as a continuous variable and in intervals. The primary outcome was 3-month functional independence (modified Rankin Scale score of 0–2). The secondary outcomes were symptomatic intracerebral hemorrhage (SICH) and 3-month mortality. The SBP interval with the highest proportion of functional independence was chosen as reference. All analyses were performed for successful or unsuccessful recanalization (modified Treatment in Cerebral Ischemia score ≥2b or <2b, respectively). The results were adjusted for known confounders in logistic regression models.

Results—In the multivariable analyses, a higher SBP value as a continuous variable was associated unfavorably with all outcomes in patients with successful recanalization (n=2920) and with more SICH in patients with unsuccessful recanalization (n=711). SBP interval ≥160 mm Hg was associated with less functional independence (adjusted odds ratio, 0.28 [95% CIs, 0.15–0.53]) and more SICH (adjusted odds ratio, 6.82 [95% CIs, 1.53–38.09]) compared with reference 100 to 119 mm Hg in patients with successful recanalization. SBP ≥160 mm Hg was associated with more SICH (adjusted odds ratio, 6.62 [95% CIs, 1.07–51.05]) compared with reference 120 to 139 mm Hg in patients with unsuccessful recanalization.

Conclusions—Higher SBP values were associated with less functional independence at 3 months in patients with successful recanalization and with more SICH regardless of recanalization status. **(*Stroke*. 2020;51:519-525. DOI: 10.1161/STROKEAHA.119.026914.)**

Key Words: blood pressure ■ brain ischemia ■ humans ■ odds ratio ■ thrombectomy

Endovascular thrombectomy (EVT) is an effective treatment for acute ischemic stroke (AIS) caused by a large artery occlusion.[1–6] A meta-analysis of EVT treatment with or without pretreatment with intravenous thrombolysis (IVT) confirmed that EVT leads to better functional outcomes at 90 days compared with standard treatment that largely included IVT monotherapy.[7] Despite these positive results, there are many aspects to EVT treatment that still remain unclear.

The role of blood pressure (BP) in the post-EVT treatment setting is not well understood, while higher values of BP at baseline before EVT have been associated with worse functional outcome.[8] BP has been shown to decrease significantly after successful recanalization with intraarterial treatment.[9] In patients with unsuccessful recanalization, BP decreases as well but at a later time point.[9] Systolic BP (SBP) has been shown to have a linear correlation to functional outcome in successfully recanalized patients, where lower SBP values were associated with a better functional outcome.[10] In contrast, in patients with unsuccessful recanalization, SBP had a J-shaped relationship with good functional outcome.[10] Higher peak values of SBP after EVT treatment have been shown to be associated with a worse 90-day functional

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outcome and an increased risk of hemorrhagic complications.[11] The existing guideline recommendations from the American Heart Association/American Stroke Association recommend maintaining a BP level of <180/105 during and for 24 hours after EVT, which is solely based on observational studies.[12] Owing to the scarcity of data, it is left to the judgement of the operating interventional neuroradiologist and attending neurologist to determine which BP levels to maintain. We aimed to investigate the potential association of BP levels with clinical outcomes in EVT-treated AIS patients with and without successful recanalization in an explorative analysis.

Methods

We used the Safe Implementation of Treatments in Stroke (SITS) International Thrombectomy Registry (SITS-TBYR). Data related to the current study are derived from the SITS International Stroke Thrombolysis Register (ISTR). Requests to access the anonymized data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author (M. Matusevicius), and access may be given on reasonable request and approval by the SITS Scientific Committee. AIS patients with large artery occlusion receiving EVT treatment with or without prior IVT recorded in the SITS-TBYR during January 1, 2014, to December 31, 2017, were eligible for the study. The process of data entry for the SITS registries has been described previously.[13] Centers in the SITS-TBYR commit to report all consecutive cases treated with EVT. Baseline and demographic characteristics, stroke severity per National Institutes of Health Stroke Scale (NIHSS), medical history, imaging data, and follow-up evaluation is collected in the registry. Imaging studies, neurological status, and follow-up evaluation is performed according to local routines at each individual study center. Symptomatic intracranial hemorrhage (SICH) events were established based on locally read imaging data and clinical data entered into the registry. To ensure high data quality and completeness, the study population consisted of cases from centers recording at least 10 patients in the registry in addition to at least 70% available data for 3-month outcome.

Outcomes

The primary outcome was functional independence at 3 months defined as modified Rankin Scale (mRS) score of 0 to 2. The secondary outcomes were excellent outcome defined as mRS score 0 to 1 at 3 months, 3-month mortality, in addition to SICH by mSITS-MOST (modified SITS-Monitoring Study) criteria. mSITS-MOST was defined as local or remote parenchymal hemorrhage type 2 or any subarachnoid hemorrhage on radiological findings on follow-up radiology at 22 to 36 hours poststroke, in combination with a neurological deterioration ≥4 NIHSS points or leading to death within 24 hours. In the analyses of mRS 0 to 2 and mRS 0 to 1 at 3 months, we excluded patients with a premorbid function defined as baseline mRS of >2 and >1, respectively.

Statistical Analysis

Data on BP were collected in the SITS-TBYR at several time points after EVT treatment: at the end of EVT procedure and at 2, 4, 12, and 24 hours post-EVT treatment. We calculated the mean BP value during the initial 24 hours post-EVT treatment for each patient using the available time points. For inclusion in the analysis, patients were required to have values at 12 and 24 hours post-treatment. The mean SBP values were then analyzed as both a continuous independent variable and categorized into intervals, while diastolic BP (DBP) was analyzed only as a continuous independent variable.

BP as a continuous independent variable was analyzed in multivariable logistic regression models. We chose to include BP as a predictor in linear, quadratic, and restricted cubic spline models based on previously described modeling.[14] Akaike Information Criterion (AIC) was used to test different number of knots for the primary outcome in restricted cubic spline, with the best model being compared with the linear and quadratic models. The difference in ΔAIC was used to compare multivariate logistic regression models, where a smaller AIC value indicated a better fit with the data and hence a superior multivariate logistic regression model.

SBP was first categorized into 20 mm Hg increment half-open intervals from 100 to 180 mm Hg and the intervals <100 and ≥180 mm Hg. SBP intervals with <30 patients were merged with an adjacent interval to maintain sufficient power in the analyses. The interval with the highest percentage of functional independence was chosen as the reference for the analyses. SBP as a categorical independent variable was analyzed in multivariate logistic regression models.

Additionally, we included an explorative analysis of change in SBP from end of EVT procedure to mean 24 hours value. We used the same BP intervals as described previously. The resulting increase, decrease, or remainder within similar SBP values was then used to further stratify the patients, using a ±10 mm Hg cutoff for an increase or decrease in SBP from the end of EVT procedure.

All analyses were performed separately after stratification of patients by dichotomized recanalization status defined by the modified Treatment in Cerebral Ischemia score (Table I in the online-only Data Supplement).[15] Recanalization status was deemed as either successful (modified Treatment in Cerebral Ischemia score 2b–3) or unsuccessful (modified Treatment in Cerebral Ischemia score 0–2a). To test our assumption of a strong effect of recanalization status on SBP and outcome, we performed a sensitivity analysis including all patients and used recanalization status as an independent predictor in the multivariate logistic regression models for SBP. Additionally, we performed an ANCOVA with dichotomized modified Treatment in Cerebral Ischemia as a predictor with the same covariates as in the multivariate analyses (described below) and SBP as the outcome.

Baseline characteristics and demographics were described for each recanalization strata. Adjusted odds ratios (aORs) for the outcomes were obtained using multivariate logistic regression models. Visual representations of the aORs were presented using error bars for the log aORs. Known clinical variables were selected as covariates for the multivariate logistic regression models. Independent variables chosen for inclusion in the models were age, sex, NIHSS score at baseline, glucose at baseline, SBP at baseline, history of hyperlipidemia, history of congestive heart failure, history of smoking, and IVT treatment. We chose not to include history of hypertension in the regression models because of the potential collinearity between hypertension and SBP at baseline but presented it with the baseline and demographic characteristics.

$P<0.05$ was considered to be statistically significant. All analyses were performed in R v3.5.0 (cran.r-project.org).

Ethics Committee Approval

The current study was approved by the Stockholm Regional Ethical Board through the framework of SITS-Monitoring Study II. Ethical approval or written patient consent for participation in SITS differed among participating countries. Ethical approval or patient consent were obtained in countries that required this, while other countries approved the register for conduct as an anonymized audit.

Results

In total, 9380 patients treated with EVT were registered in the SITS-TBYR. The final study population consisted of 3631 patients after exclusion of patients from centers with <10 patients or 70% data completeness at 3 months (Figure I in the online-only Data Supplement). Successful recanalization was achieved in 2920 patients, who had a mean age of 69 years, median baseline NIHSS score of 16 points, mean baseline SBP of 149 mm Hg, and 52% male sex (Table 1). Recanalization was not successful in 711 patients, who had

Table 1. Baseline and Demographic Characteristics

	mTICI 2b–3 (n=2920)	mTICI 0–2a (n=711)
Age, y	69.0 (13.4)	70.8 (13.4)
NIHSS	16 (11–21)	16 (11–20)
Sex, male	52 (1524/2920)	50 (359/711)
SBP baseline	149.2 (25.7)	152.3 (27.0)
Glucose baseline	7.5 (4.3)	7.6 (2.7)
Prestroke mRS	0 (0–0)	0 (0–1)
Platelet aggregation inhibitor treatment	29 (835/2895)	31 (221/704)
Oral anticoagulant treatment	19 (554/2898)	21 (145/705)
Hypertension	67 (1943/2910)	71 (504/707)
Diabetes mellitus	18 (530/2410)	19 (138/708)
Hyperlipidemia	32 (933/2885)	33 (229/707)
Smoking	24 (663/2796)	26 (172/670)
Previous stroke	11 (330/2896)	12 (84/710)
Transitory ischemic attack	3 (94/2904)	4 (28/709)
Atrial fibrillation	29 (852/2900)	30 (214/710)
Congestive heart failure	10 (289/2893)	12 (82/707)
IVT treatment	64 (1873/2920)	60 (425/711)

For continuous variables, mean values with SD within parentheses. For ordinal variables, median values with interquartile range within parentheses. For categorical variables, percentage of that variable with number of patients with that variable per total number of patients with recorded data for that variable in parentheses. IVT indicates intravenous thrombolysis; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

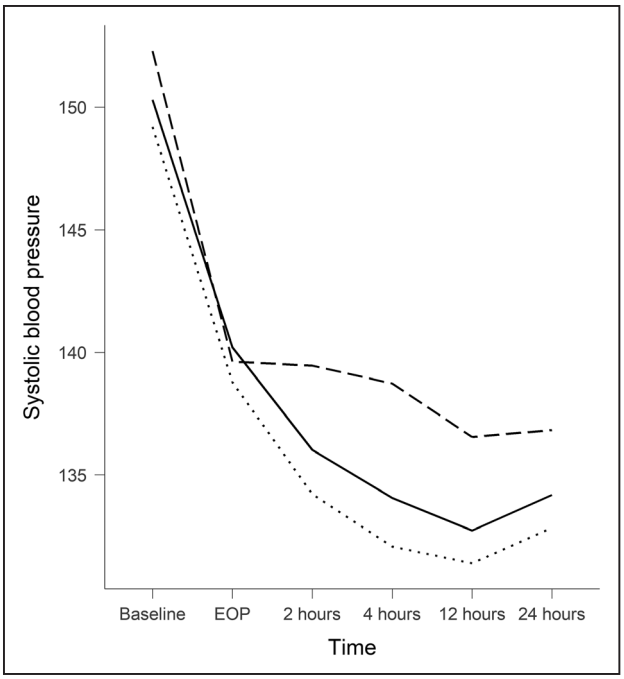

Figure 1. Systolic blood pressure at different time points. Lines represent all patients (solid line), patients with successful recanalization (dotted line), and patients with unsuccessful recanalization (dashed line). EOP indicates end of endovascular thrombectomy procedure.

a mean age of 71 years, median baseline NIHSS score of 16 points, mean baseline SBP of 152 mm Hg, and 50% male sex. In the sensitivity analysis, successful reperfusion was significantly associated with all outcomes except SICH in all regression models, supporting dichotomization in the following multivariate logistic regression models (Table II in the online-only Data Supplement). The ANCOVA analysis showed that successful recanalization was significantly associated with lower changes of higher mean 24-hour SBP values (aOR, 0.05 [95% CI, 0.01–0.29]).

There was a clear trend of decreasing SBP from baseline to end of EVT procedure to the measurement at 24 hours post-EVT, regardless of recanalization status (Figure 1). A similar trend was seen with DBP (Figure II in the online-only Data Supplement).

Patients within SBP range of 100 to 119 mm Hg had the highest percentages of functional independence (63%) for patients with successful recanalization and SBP range of 120 to 139 mm Hg for patient with unsuccessful recanalization (31%; Table III in the online-only Data Supplement). These were chosen as reference intervals in the multivariable analyses of SBP in 20-mm Hg intervals. Because of the low number of patients with SBP ≥180 mm Hg, we used the SBP ≥160 mm Hg as the upper cutoff regardless of recanalization status and SBP <120 mm Hg as the lower cutoff for patients with unsuccessful recanalization.

SBP as a continuous independent variable in the multivariate logistic regression models showed that higher SBP values in the linear model were independently associated with less functional independence (aOR, 0.987 [95% CI, 0.980–0.995]) and more SICH (aOR, 1.027 [95% CI, 1.007–1.047]) and mortality (aOR, 1.018 [95% CI, 1.008–1.028]) in patients with successful recanalization (Table 2). In patients with unsuccessful recanalization, higher SBP values were associated with more SICH (aOR, 1.040 [95% CI, 1.008–1.075]) but not with functional independence (aOR, 1.003 [95% CI, 0.985–1.022]). The multivariate logistic regression models showed that patients with successful recanalization had lower mean SBP for favorable outcomes than patients with unsuccessful recanalization (Figure 2). When comparing the multivariate logistic regression models for patients with successful recanalization, the quadratic models showed best fit for all outcomes except for death at 3 months based on ΔAIC (Table IV in the online-only Data Supplement). The linear models showed the worst fit with the data. Interestingly, the nonlinear models' shape suggests that with decreasing SBP, there is an increased chance of favorable outcome that flips to being unfavorable after a certain point. For patients with unsuccessful recanalization, the linear models showed best fit for all outcomes except mRS of 0 to 1.

In the multivariate logistic regression models of DBP as continuous variable, the linear model showed that an increase in DBP was associated with less functional independence (odds ratio [OR], 0.987 [95% CI, 0.975–0.998]) and more SICH (OR, 1.033 [95% CI, 1.001–1.066]) and death (OR, 1.029 [95% CI, 1.013–1.045]) for patients with successful recanalization (Table 2). For patients with unsuccessful

Table 2. Adjusted ORs of SBP and DBP as Continuous Linear Predictors

	mRS 0–2 at 3 mo	mRS 0–1 at 3 mo	SICH by mSITS	Death at 3 mo
SBP linear model				
mTICI 2b–3	0.987 (0.980–0.995)	0.994 (0.986–1.002)	1.027 (1.007–1.047)	1.017 (1.007–1.028)
mTICI 0–2a	1.003 (0.985–1.022)	0.985 (0.960–1.009)	1.040 (1.008–1.075)	1.006 (0.989–1.023)
DBP linear model				
mTICI 2b–3	0.987 (0.975–0.998)	0.997 (0.985–1.009)	1.033 (1.001–1.066)	1.029 (1.013–1.045)
mTICI 0–2a	1.004 (0.975–1.034)	0.994 (0.956–1.033)	1.072 (1.010–1.142)	0.992 (0.966–1.019)

In parentheses, 95% CI. ORs for every increase of 1 mm Hg. DBP indicates diastolic blood pressure; mRS, modified Rankin Scale; mSITS, modified Safe Implementation of Treatment in Stroke; mTICI, modified Treatment in Cerebral Ischemia; OR, odds ratio; SBP, systolic blood pressure; and SICH, symptomatic intracerebral hemorrhage.

recanalization, there was no association with functional independence (OR, 1.004 [95% CI, 0.975–1.034]) but an increased risk of SICH (OR, 1.072 [95% CI, 1.010–1.142]). The multivariate logistic regression models for DBP showed that based on ΔAIC, the linear models had best fit for all outcomes regardless of recanalization status, except for death at 3 months for patients without successful recanalization, where the quadratic model had best fit (Table V in the online-only Data Supplement). Visually, almost all nonlinear models followed a near-linear pathway for patients with successful recanalization, further emphasizing the linear trend (Figure III in the online-only Data Supplement).

In our explorative analysis of SBP change from end of EVT procedure to mean 24 hours SBP, we found a trend of increased proportion of history of hypertension, higher age, and higher SBP at baseline with an SBP increase beyond 10 mm Hg for patients with successful recanalization (Table VI in the online-only Data Supplement) and for patients with unsuccessful recanalization (Table VII in the online-only Data Supplement).

In the multivariate logistic regression models of SBP as interval categorical variable for patients with successful recanalization, the log ORs were visually observed to resemble a U shape (Figure 3). Compared with the reference interval of 100 to 119 mm Hg, SBP intervals of 140 to 159 and ≥160 mm Hg were associated with less 3-month functional independence (aOR, 0.65 [95% CI, 0.43–0.97]; aOR, 0.28 [95% CI, 0.14–0.53]) and more SICH for ≥160 mm Hg (aOR, 6.82 [95% CI, 1.53–38.09]), whereas SBP of 120 to 139 mm Hg was associated with less 3-month mortality (aOR, 0.61 [95% CI, 0.38–0.998]; Table VIII in the online-only Data Supplement). For patients with unsuccessful recanalization, only excellent outcome visually resembled a U shape (Figure 3). Compared with the reference interval of 120 to 139 mm Hg, SBP interval ≥160 mm Hg was associated with more SICH (aOR, 6.62 [95% CI, 1.07–51.05]). There was no association for any interval with the other outcome parameters (Table IX in the online-only Data Supplement).

Discussion

In this large multinational, multicenter study of patients with AIS due to large artery occlusion treated with EVT in routine clinical practice, we found that SBP after EVT treatment has a complex association with outcomes, which differs based on recanalization status. Our results suggest that for patients with successful recanalization, a linear model may not be the best way to describe the associations with outcomes. We found a better fit for SBP as a continuous variable with outcomes in quadratic multivariate logistic regression models than in the linear models for patients with successful recanalization. This suggests that a more complex relationship between SBP and outcomes is present, but this was not further improved by the addition of restricted cubic spline models. Previous studies on BP after stroke primarily focus on describing linear trends.[10,11,16] Our results suggest that for patients with successful recanalization, a linear model may not be the best way to describe the associations with outcomes. On the contrary, the linear models showed a consistently better fit with patients with unsuccessful recanalization and with DBP regardless of recanalization status.

Our sensitivity analysis showed that recanalization status was strongly associated with SBP after EVT, which is in line with what recent studies are suggesting.[10,11,16,17] Previous studies investigating the relationship of SBP and outcome by recanalization status after EVT treatment show decreased odds of functional independence with increased SBP in patients with successful recanalization.[10,11,16] Studies have also shown that during the initial 24 hours after EVT treatment, an increase in maximum SBP by 10 mm Hg and high peak SBP values were associated with less functional independence in recanalized patients.[11,16] Our results for unsuccessful recanalization are somewhat in contrast to results of recent studies. Higher maximum values of SBP during the initial 24 hours after EVT treatment were found to be associated with worse functional outcomes in unsuccessfully recanalized patients,[17] whereas another study found a quadratic association with a J shape for functional outcome in EVT- or IVT-treated patients.[10] Our results suggest that a linear association was the best fit for patients with unsuccessful recanalization, showing significant increase in SICH over 160 mm Hg but not with other outcomes. These discrepancies could partly be due to differences in methodology in the studies or due to the relatively smaller sample of patients with unsuccessful recanalization. On the contrary, our study had 4× more patients in our unsuccessfully recanalized subpopulation than in the previous studies combined.

Differences of our findings between recanalized and nonrecanalized patients could be explained by pathophysiology of cerebral ischemia. After successful recanalization, a higher SBP is probably not required. On contrary, for patients with

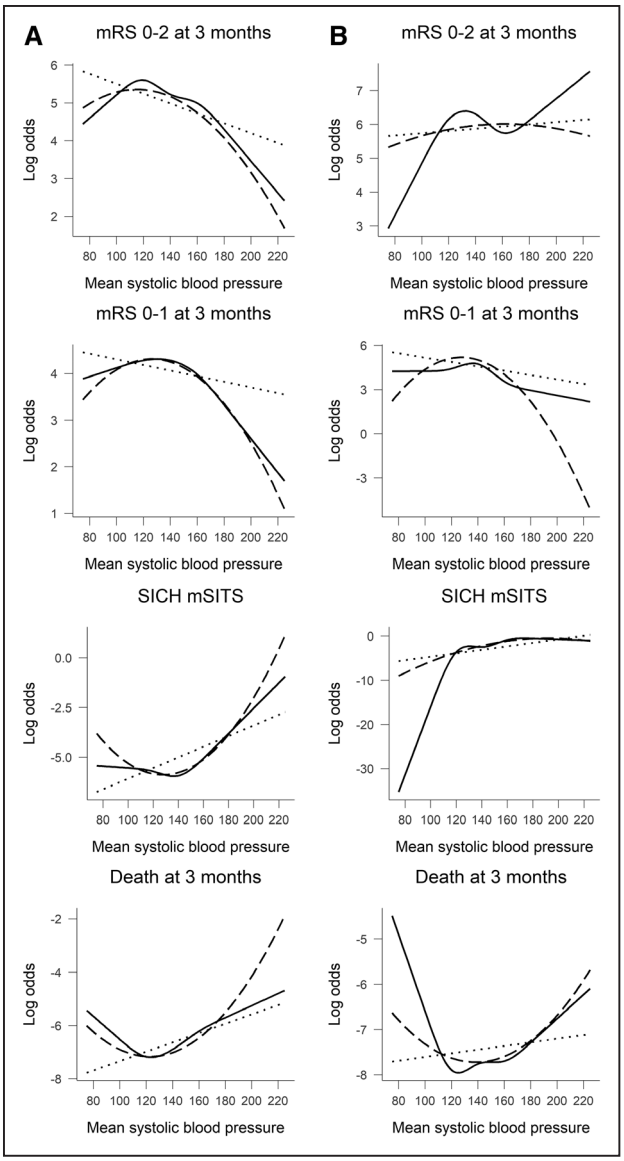

Figure 2. Multivariate logistic regression models of systolic blood pressure. Shown for patients with successful recanalization (**A**) and patients with unsuccessful recanalization (**B**). Regression models include linear model (dotted line), quadratic model (dashed line), and restricted cubic spline model with 3 knots (solid line). mRS indicates modified Rankin Scale; and SICH mSITS, symptomatic intracerebral hemorrhage by mSITS-MOST (modified SITS-Monitoring Study) criteria.

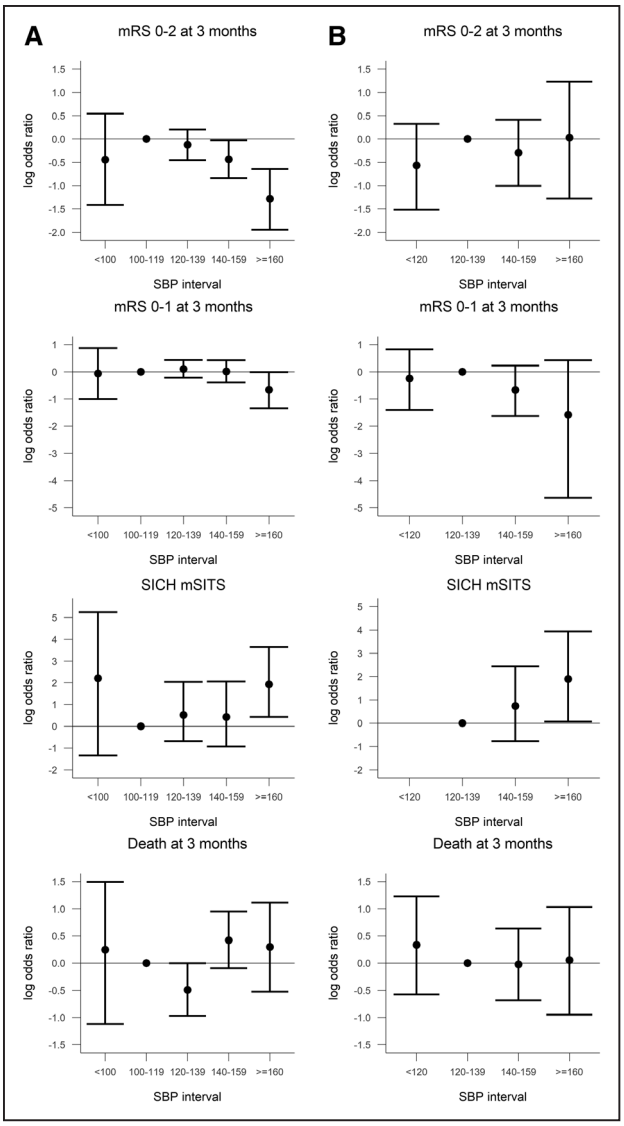

Figure 3. Adjusted log odds ratios of the outcomes in interval analysis of systolic blood pressure (SBP). Adjusted log odds ratios (point) and 95% CIs (error bars) of outcomes as per 20 mm Hg SBP intervals for (**A**) patients with successful recanalization and (**B**) patients with unsuccessful recanalization. SBP interval 100 to 119 mm Hg used as reference for successful recanalization and SBP interval 120 to 139 mm Hg for unsuccessful recanalization. Too few events for analysis for symptomatic intracerebral hemorrhage (SICH) modified Treatment in Cerebral Ischemia 0 to 2a <120 mm Hg. mRS indicates modified Rankin Scale; and SICH mSITS, SICH by mSITS-MOST (modified SITS-Monitoring Study) criteria.

unsuccessful recanalization, cerebral autoregulation would try to keep a higher SBP to improve cerebral blood flow in the ischemic area. This may explain the association of more SICH with high SBP values but no association with functional independence in patients with unsuccessful recanalization. This is further supported by the general trend of our nonlinear multivariate logistic regression models, which showed that the ORs for favorable outcomes were shifted toward lower SBP values for patients with successful recanalization as compared with patients with unsuccessful recanalization. On the contrary, our nonlinear models seem to diverge significantly at the extreme values of SBP, possibly because of the lower patient numbers in these regions. Therefore, strong assumptions about these extreme values may be difficult to draw from our data.

In terms of nonlinear associations of BP, a J- or U-shaped association with unfavorable outcome has previously been observed in general acute stroke patients,[18–20] as well as in successfully and unsuccessfully recanalized patients separately.[10] In our analyses, we graphically observed a similar J/U-shaped pattern for the point estimates of the log aORs of the outcomes regardless of recanalization status. However, differences in study populations and method of analysis could affect the comparability of these studies to our results. Martins et al[10] included patients treated with IVT, EVT, or both and used 3 modalities to define recanalization status (conventional angiography, transcranial doppler, and computed tomographic angiography), whereas 2 other studies analyzed only changes

in SBP during the initial 24 hours post-EVT treatment rather than specific SBP values.[11,16,17]

Our finding of higher SBP with more SICH regardless of recanalization status is in line with a previous report of EVT in AIS[11] and a recent meta-analysis evaluating the association of BP levels with outcomes in AIS patients treated with IVT.[21] On the contrary, previous randomized controlled trials on BP lowering in acute stroke did not show any significant benefit of BP-lowering treatment on long-term clinical outcomes,[22–24] although these studies were not designed to study BP-lowering treatment based on recanalization status. Additionally, a recent randomized controlled trial reported lower SICH rates in IVT-treated AIS patients who were randomized to an intensive BP-lowering regimen, despite not translating into improved long-term outcome.[25]

There are currently little data to describe the BP course after EVT treatment, despite EVT intrinsically providing valuable data on recanalization status, which are not otherwise readily available after IVT treatment. Our explorative analysis suggests, perhaps unsurprisingly, that history of hypertension and higher SBP at baseline were associated with increasing in SBP after the end of EVT procedure, regardless of recanalization status. Additionally, higher age was also associated with an increase in SBP for primarily patients with successful recanalization. Unfortunately, we did not have data on NIHSS directly after EVT, which could have been an important factor affecting both SBP course and mean SBP during 24 hours after EVT. It is of importance to further investigate what factors may affect BP course, to help clinicians understand what BP changes to expect, and how to handle these changes.

This study has certain limitations, including the retrospective design with its inherent limitations. We chose to include centers that had good 3-month follow-up data, which could lead to a potential selection bias. We did not have data on individual SBP targets for each patient or study centers' local guidelines. Therefore, we do not know how successfully BP was managed at that level or the details of the BP-lowering treatment regimens. We do not have data on which guidelines, international or local, each study center follows. We had scarce data on patients with mean SBP <100 mm Hg and >180 mm Hg, limiting our conclusions for these patients.

Conclusions

In conclusion, we found that SBP interval ≥160 mm Hg was associated with less functional independence at 3 months in patients with successful recanalization, but no SBP interval had any association with functional independence in unsuccessful recanalization. A higher SBP value as a continuous independent variable and SBP interval ≥160 mm Hg was associated with more SICH regardless of recanalization status. Our nonlinear models showed better fit for patients with successful recanalization, with predicted favorable outcomes at much lower SBP than current guidelines. While awaiting future randomized controlled trials investigating SBP management after EVT treatment, our results may serve as an important indication that lower SBP targets may be warranted for future guidelines and trials.

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Disclosures

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