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Admission Blood Pressure in Relation to Clinical Outcomes and Successful Reperfusion After Endovascular Stroke Treatment

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BACKGROUND AND PURPOSE: Optimal blood pressure (BP) targets before endovascular treatment (EVT) for acute ischemic stroke are unknown. We aimed to assess the relation between admission BP and clinical outcomes and successful reperfusion after EVT.

METHODS: We used data from the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry, an observational, prospective, nationwide cohort study of patients with ischemic stroke treated with EVT in routine clinical practice in the Netherlands. Baseline systolic BP (SBP) and diastolic BP (DBP) were recorded on admission. The primary outcome was the score on the modified Rankin Scale at 90 days. Secondary outcomes included successful reperfusion (extended Thrombolysis in Cerebral Infarction score 2B-3), symptomatic intracranial hemorrhage, and 90-day mortality. Multivariable logistic and linear regression were used to assess the associations of SBP and DBP with outcomes. The relations between BPs and outcomes were tested for nonlinearity. Parameter estimates were calculated per 10 mmHg increase or decrease in BP.

RESULTS: We included 3180 patients treated with EVT between March 2014 and November 2017. The relations between admission SBP and DBP with 90-day modified Rankin Scale scores and mortality were J-shaped, with inflection points around 150 and 81 mmHg, respectively. An increase in SBP above 150 mmHg was associated with poor functional outcome (adjusted common odds ratio, 1.09 [95% CI, 1.04–1.15]) and mortality at 90 days (adjusted odds ratio, 1.09 [95% CI, 1.03–1.16]). Following linear relationships, higher SBP was associated with a lower probability of successful reperfusion (adjusted odds ratio, 0.97 [95% CI, 0.94–0.99]) and with the occurrence of symptomatic intracranial hemorrhage (adjusted odds ratio, 1.06 [95% CI, 0.99–1.13]). Results for DBP were largely similar.

CONCLUSIONS: In patients with acute ischemic stroke treated with EVT, higher admission BP is associated with lower probability of successful reperfusion and with poor clinical outcomes. Further research is needed to investigate whether these patients benefit from BP reduction before EVT.

Key Words: blood pressure ■ hypertension ■ ischemic stroke ■ reperfusion ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

BP	blood pressure
DBP	diastolic blood pressure
EVT	endovascular treatment
MR CLEAN	Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
SBP	systolic blood pressure
sICH	symptomatic intracranial hemorrhage

In patients with acute ischemic stroke and a proximal occlusion of an intracranial artery of the anterior circulation, endovascular treatment (EVT) increases the chance of a good functional outcome.^{1,2} Still, about half of the patients treated with EVT remain functionally dependent or die,³ in part, because of unsuccessful reperfusion or the occurrence of symptomatic intracranial hemorrhage (sICH). Further optimization of current treatment strategies is, therefore, warranted. A potential strategy for improving outcome after EVT is early blood pressure (BP) modification.

In the acute phase of stroke, hypertension is common^{4,5} and may serve as a compensatory mechanism to increase blood flow to the ischemic area.⁶ In general populations of patients with acute ischemic stroke and in those with a large vessel occlusion, J- and U-shaped curves have been described for the relation between BP and clinical outcomes, where both low and high systolic BPs (SBP) were associated with poor outcome.^{4,7,8} Given the wide range of reported optimum baseline SBP and diastolic BP (DBP) values, it is likely that optimal BP targets vary across patients and stroke subtypes.⁶ In some studies, higher SBP was associated with an increased risk of sICH.^{7,9}

In line with these uncertainties, BP management in the acute phase of ischemic stroke remains an unresolved and controversial issue, especially in the era of EVT.¹⁰ There is insufficient information on the relationship between BP and the probability of successful reperfusion after EVT. A previous study showed that the benefit of EVT is consistent across the entire range of SBP.⁷ However, there is no consensus on the optimal BP targets for patients with large vessel occlusion eligible for EVT. We aimed to assess the relationship of admission BP with clinical outcomes and successful reperfusion in patients with ischemic stroke treated with EVT in routine clinical practice.

METHODS

Study Protocol and Data Availability

We used data from the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry,³ a prospective, observational cohort study of consecutive patients with ischemic stroke undergoing EVT in the Netherlands. Registration started after the final randomization in March 2014 in the MR CLEAN trial.¹¹ The 17 intervention centers that participated in the MR CLEAN trial prospectively registered consecutive patients treated with EVT for acute ischemic stroke. Source data will not be made available since no patient approval was obtained for sharing anonymized data. However, detailed analytic methods and study materials, including output files of statistical analyses, will be made available to other researchers on request to the first author.

Patients

We included all consecutive patients treated with EVT between March 16, 2014, and November 1, 2017, who had a groin puncture within 6.5 hours after stroke onset, were aged 18 years or older, and had intracranial proximal arterial occlusion in the anterior circulation (intracranial carotid artery-T or middle [M1/M2] or anterior [A1/A2] cerebral artery), demonstrated by computed tomography angiography.

Clinical and Radiological Definitions

Admission SBP and DBP were defined as the first recorded noninvasive SBP and DBP measured as part of routine clinical care on admission to the emergency department. The type of BP measurement for each individual patient was not recorded in the electronic patient records, but the use of an automated sphygmomanometer is common practice in all participating centers. EVT was defined as a groin puncture in the angiography suite, and the method of EVT for each individual patient was left to the discretion of the treating interventionist. All imaging was assessed at an imaging core laboratory, consisting of 20 trained interventional neuroradiologists and one interventional neurologist blinded to clinical findings, except for the side of symptoms. Successful reperfusion was defined as a score on the extended Thrombolysis in Cerebral Infarction scale ≥ 2 B. The extended Thrombolysis in Cerebral Infarction scale ranges from 0 (no antegrade reperfusion of the occluded vascular territory) to 3 (complete antegrade reperfusion).¹²

Every intracerebral hemorrhage was assessed by the MR CLEAN Registry complication committee through evaluation of medical reports and imaging and scored as sICH based on the Heidelberg criteria.¹³

Outcome Measures

The primary outcome was the score on the modified Rankin Scale (mRS) at 90 days.¹⁴ The mRS is a measure of functional outcome after stroke, ranging from 0 (no symptoms) to 6 (death). Secondary outcomes were excellent (mRS score 0–1), good (mRS score 0–2), or favorable (mRS score 0–3) functional outcome at 90 days, mortality at 90 days, successful reperfusion after EVT, stroke severity (National Institutes of Health Stroke Scale [NIHSS] score) at 24 to 48 hours after the intervention, and the occurrence of an sICH.

Statistical Analysis

Baseline characteristics and outcomes of the study population were compared according to their admission SBP, dichotomized at the inflection value of the nonlinear relationship between BP and functional outcome. χ^2 tests were used for categorical variables and Wilcoxon rank-sum test or 2 sample *t* test for continuous variables.

To examine the relations between admission BP and clinical and radiographic outcomes, we tested which model best fitted the data by comparing the likelihood ratios of a univariable linear function with a model including restricted cubic splines or a quadratic term for the BP parameter. When model fit was not improved by transformation of the BP parameter, a linear model was chosen and regression analysis was performed on the whole population. When a nonlinear relationship between BP and the outcome measure was found, the inflection value of the nonlinear model was used as a reference point, and regression analyses were performed on 2 subgroups to estimate the differential effects of lower and higher ranges of BP on functional outcome. To assess which BP parameter (SBP or DBP) had the best correlation with the mRS at 90 days, we used the Akaike Information Criterion. The model that best fitted the relation of BP with functional outcome was used for further analysis.

We performed multivariable ordinal logistic regression, binary logistic regression, or linear regression analyses, as appropriate, for each outcome variable. We adjusted for a limited set of potential confounders, identified by a directed acyclic graph made by the authors specifically for the purpose of the current analyses.^{15,16} For functional outcome and mortality at 90 days and for the occurrence of sICH, we adjusted for age, history of hypertension, and NIHSS score at baseline (Figure 1 in the [Data Supplement](#)). Analyses for successful reperfusion were adjusted for age and NIHSS score. In a post hoc analysis, we also adjusted for the presence of ipsilateral carotid stenosis of 50% or greater or occlusion. In exploratory analyses, we assessed whether the relations of baseline SBP with mRS and sICH were modified by successful reperfusion, by adding an

interaction term to the multivariable logistic regression model or performing the analyses on subgroups. The association of baseline BP parameters with each clinical outcome were calculated per 10 mm Hg increase or decrease in BP and expressed as odds ratios, common odds ratios, or β coefficients with accompanying 95% CI.

Missing values, including missing BP values, were replaced with multiple imputation ($n=5$) based on relevant variables and outcomes using AregImpute. All descriptive analyses include patients with complete data, whereas all regression analyses were performed after multiple imputation. Statistical analyses were performed with R software (Version 3.6.1 R Foundation).¹⁷

Ethics Approval and Informed Consent

The institutional review board of the Erasmus Medical Center Rotterdam, the Netherlands, considered the MR CLEAN Registry as a registry study, and therefore, the requirement of written informed consent was waived. However, all patients were provided with information on the study in writing and orally and were given the opportunity to refuse participation. In case of refusal to participate, their data were deleted from the database.

RESULTS

Study Population

Of 3637 patients treated with EVT in the Netherlands during the study period, 3180 were included in the current analysis (Figure II in the [Data Supplement](#)). Admission SBP was available for 3092 patients (97%) and DBP for 3084 patients (97%). An mRS score at 90 days was available for 2968 patients (94%). Among those with known admission SBP, the median age was 72 (interquartile range, 61–81) years and 1482 (48%) were male. The mean admission SBP and DBP were 150 mm Hg (SD 25) and 82 mm Hg (SD 16), respectively.

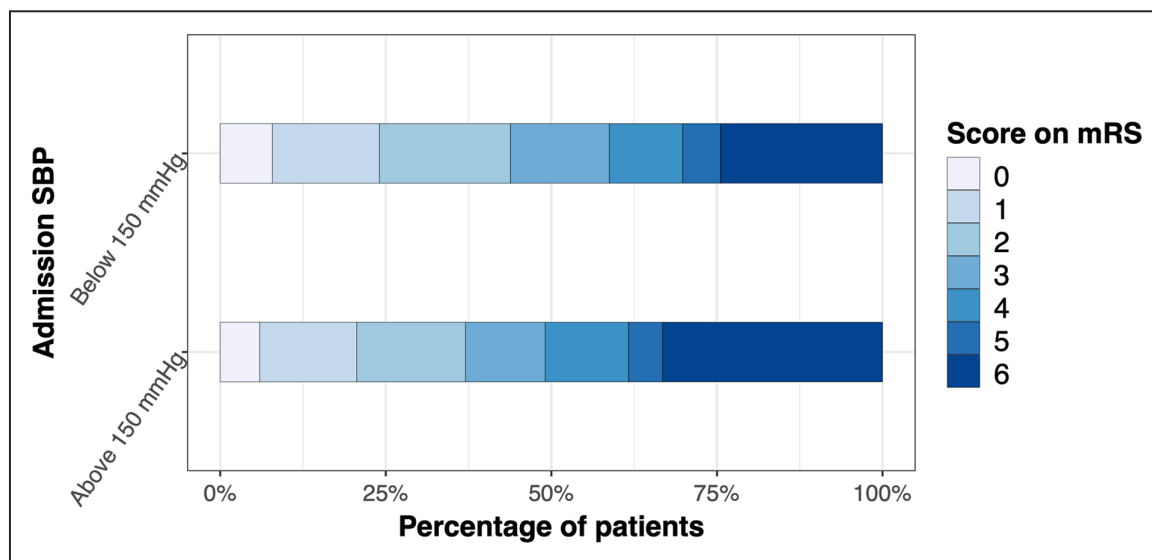


Figure 1. Distribution of scores on the modified Rankin Scale (mRS) at 90 d for patients with admission systolic blood pressure (SBP) above 150 mmHg and below 150 mmHg.

Table 1. Outcomes According to Admission SBP

	All patients,* n=3092	SBP<150 mmHg, n=1535/3092	SBP≥150 mmHg, n=1557/3092	P value†
Primary outcome				
mRS score at 90 d, median (IQR)	3 (2–6)	3 (2–5)	4 (2–6)	<0.001
Secondary outcomes				
mRS score 0–1 at 90 d, n (%)	663/2896 (23)	345/1435 (24)	301/1461 (21)	0.03
mRS score 0–2 at 90 d, n (%)	1200/2896 (41)	629/1435 (44)	541/1461 (37)	<0.001
mRS score 0–3 at 90 d, n (%)	1595/2896 (55)	843/1435 (59)	717/1461 (49)	<0.001
Mortality at 90 d, n (%)	836/2896 (29)	351/1435 (25)	485/1461 (33)	<0.001
Successful reperfusion, n (%)‡	1851/3011(62)	959/1498 (64)	892/1513 (59)	0.004
TICI score, n (%)				0.03
0	508/3011 (17)	231/1498 (15)	277/1513 (18)	
1	90/3011 (3)	37/1498 (3)	53/1513 (4)	
2A	563/3011 (19)	271/1498 (18)	292/1513 (19)	
2B	663/3011(22)	344/1498 (23)	324/1513 (21)	
2C	323/3011 (11)	158/1498 (11)	165/1513 (11)	
3	859/3011 (29)	457/1498 (31)	402/1513 (27)	
NIHSS at 24–48 h, median (IQR)	10 (4–17)	9 (3–16)	11 (4–17)	<0.001
Symptomatic intracranial hemorrhage, n (%)	184/3092 (6)	69/1535 (5)	115/1557 (7)	<0.001

IQR indicates interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and TICI, Thrombolysis in Cerebral Infarction.

*All patients with known SBP.

†P value for difference between the 2 SBP groups: SBP<150 vs SBP≥150.

‡Successful reperfusion indicates scores TICI 2B, 2C, or 3.

Compared with patients with an admission SBP <150 mmHg, patients with an admission SBP ≥150 mmHg were older, more frequently had a medical history of diabetes or hypertension or used antihypertensive medication, and smoked less often (Table I in the [Data Supplement](#)). Patients with SBP ≥150 mmHg had slightly longer onset-to-groin and onset-to-reperfusion times

compared with those with SBP <150 mmHg (190 versus 196 and 246 versus 255 minutes, respectively). Of the 1535 patients with SBP <150 mmHg, 835 (54%) were transferred from a primary stroke center to an intervention center versus 851 of 1557 (55%) of those with SBP ≥150 mmHg. Patients with admission SBP ≥150 mmHg had a higher median mRS score and a higher rate

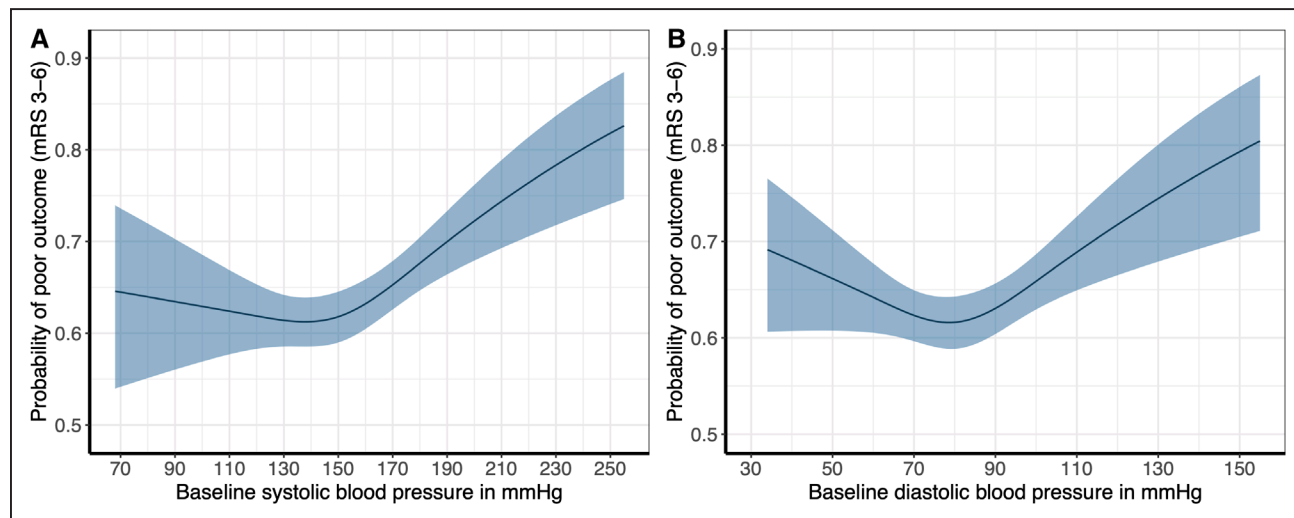


Figure 2. Relationship of baseline systolic (SBP) and diastolic blood pressure (DBP) with the probability of poor functional outcome (modified Rankin Scale [mRS] score 3–6) 90 d poststroke.

Both models fitted with a restricted cubic spline transformation with 3 knots and are adjusted for National Institutes of Health Stroke Scale (NIHSS) at baseline, age, and history of hypertension. The figures depict the probability of poor outcome (mRS score 3–6) with 95% CI, for each level of baseline SBP (A) and DBP (B). The depicted relationships are derived from the ordinal model with the full-range mRS score as the outcome variable. The ranges of the x-axes correspond to minimum and maximum values of SBP and DBP in the study (SBP: 68–255 mmHg, DBP: 34–155 mmHg).

Table 2. Association of Baseline SBP With Clinical and Radiographic Outcomes in Univariable and Multivariable Analysis

	SBP<150 mmHg		SBP≥150 mmHg	
	Unadjusted	Adjusted	Unadjusted	Adjusted
mRS score at 90 d (shift analysis towards poor outcome)*	0.89 (0.85 to 0.94)	1.00 (0.95 to 1.06)	1.15 (1.10 to 1.20)	1.09 (1.04 to 1.15)
mRS score 0–1 at 90 d*	1.08 (1.01 to 1.15)	1.00 (0.93 to 1.08)	0.89 (0.84 to 0.95)	0.92 (0.85 to 0.99)
mRS score 0–2 at 90 d*	1.11 (1.05 to 1.17)	0.97 (0.91 to 1.04)	0.87 (0.83 to 0.92)	0.92 (0.86 to 0.97)
mRS score 0–3 at 90 d*	1.10 (1.17 to 1.24)	1.02 (0.95 to 1.10)	0.86 (0.82 to 0.90)	0.92 (0.87 to 0.98)
mRS score 3–6 at 90 d*	0.90 (0.86 to 0.96)	1.03 (0.57 to 1.10)	1.15 (1.09 to 1.20)	1.09 (1.03 to 1.16)
Mortality at 90 d*	0.87 (0.82 to 0.93)	1.02 (0.94 to 1.10)	1.16 (1.10 to 1.21)	1.09 (1.03 to 1.16)
NIHSS at 24–48 h*	−0.31 (−0.09 to −0.54)	−0.02 (−0.25 to 0.20)	0.46 (0.27 to 0.65)	0.34 (0.15 to 0.53)
	SBP			
	Unadjusted	Adjusted		
Symptomatic intracranial hemorrhage†	1.07 (1.01 to 1.14)	1.06 (0.99 to 1.13)		
Successful reperfusion (eTICI score 2B-3)†	0.96 (0.93 to 0.98)	0.97 (0.94 to 0.99)		

eTICI indicates extended Thrombolysis in Cerebral Infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and SBP, systolic blood pressure.

*Adjusted β -coefficients, OR, and corresponding 95% CI per 10 mmHg increase in SBP above or decrease below the median value of 150 mmHg.

†Adjusted odds ratio and corresponding 95% CI per 10 mmHg increase in SBP.

of death at 90 days, as well as a higher NIHSS score at 24 to 48 hours, a higher rate of sICH, and a lower rate of successful reperfusion compared with patients with admission SBP <150 mmHg (Figure 1 and Table 1).

Baseline BP and 90-Day Functional Outcome

The association between admission SBP or DBP and functional outcome at 90 days (mRS shift analysis) was nonlinear. Univariable model fit was better with a restricted cubic spline for the BP parameter than with a linear BP term (likelihood ratio test $P=0.04$ for SBP; $P<0.001$ for DBP; Figure III in the [Data Supplement](#)). Model fit was most optimal for SBP (Akaike Information Criterion 11 528 for SBP, 11 566 for DBP). In the adjusted model, the nonlinear relationship between SBP and functional outcome was J-shaped, with an inflection point at the median value of SBP: 150 mmHg (Figure 2). For DBP, the relationship with functional outcome was also J-shaped with an inflection point at 81 mmHg, the median value of DBP (Figure 2).

In the analysis adjusted for age, history of hypertension and NIHSS at baseline, higher SBPs (above the median of 150 mmHg) were associated with increased odds of poor functional outcome (adjusted common odds ratio 1.09 per 10 mmHg [95% CI, 1.04–1.15]), but lower SBPs (below the median of 150 mmHg) were not (adjusted common odds ratio 1.00 per 10 mmHg [95% CI, 0.95–1.06]; Table 2). Similarly, higher but not lower DBPs from the median value of 81 mmHg were associated with increased odds of poor functional outcome (Table II in the [Data Supplement](#)). The relation between SBP and functional outcome (shift analysis) was not modified by successful reperfusion (P for interaction=0.47 and 0.73 for SPB<150 mmHg and SBP≥150 mmHg, respectively).

Admission BP and Mortality, 24 to 48 Hours NIHSS, sICH, and Successful Reperfusion

The relations of SBP with mortality and NIHSS at 24 to 48 hours were J-shaped with an inflection value at the median value of 150 mmHg, whereas the relations between SBP and sICH and successful reperfusion (extended Thrombolysis in Cerebral Infarction score 2B-3) were linear (Figure 3). Higher SBPs above the median value of 150 mmHg were associated with increased odds of mortality and a higher NIHSS after 24 to 48 hours, whereas lower SBPs below 150 mmHg were not (Table 2). Higher SBP was associated with a nonsignificant tendency towards an increased risk of sICH (Table 2). This association was not modified by successful reperfusion. Higher SBP was associated with decreased odds of achieving successful reperfusion (Table 2). This association persisted after adjustment for the presence of carotid stenosis of 50% or greater. Results for the relationship between DBP and secondary outcomes were similar (Table II and Figure IV in the [Data Supplement](#)).

DISCUSSION

In this prospective multicenter cohort study of 3180 patients treated with EVT for acute ischemic stroke in the anterior circulation, the relations of baseline SBP and DBP with poorer functional outcome followed J-shaped curves, with inflection points at the median values of 150 and 81 mmHg, respectively. Higher SBPs and DBPs above the median values were associated with increased odds of poor functional outcome and mortality at 90 days. In line with this, higher SBPs and DBPs were associated with a decreased probability of successful reperfusion and a tendency towards more frequent sICH.

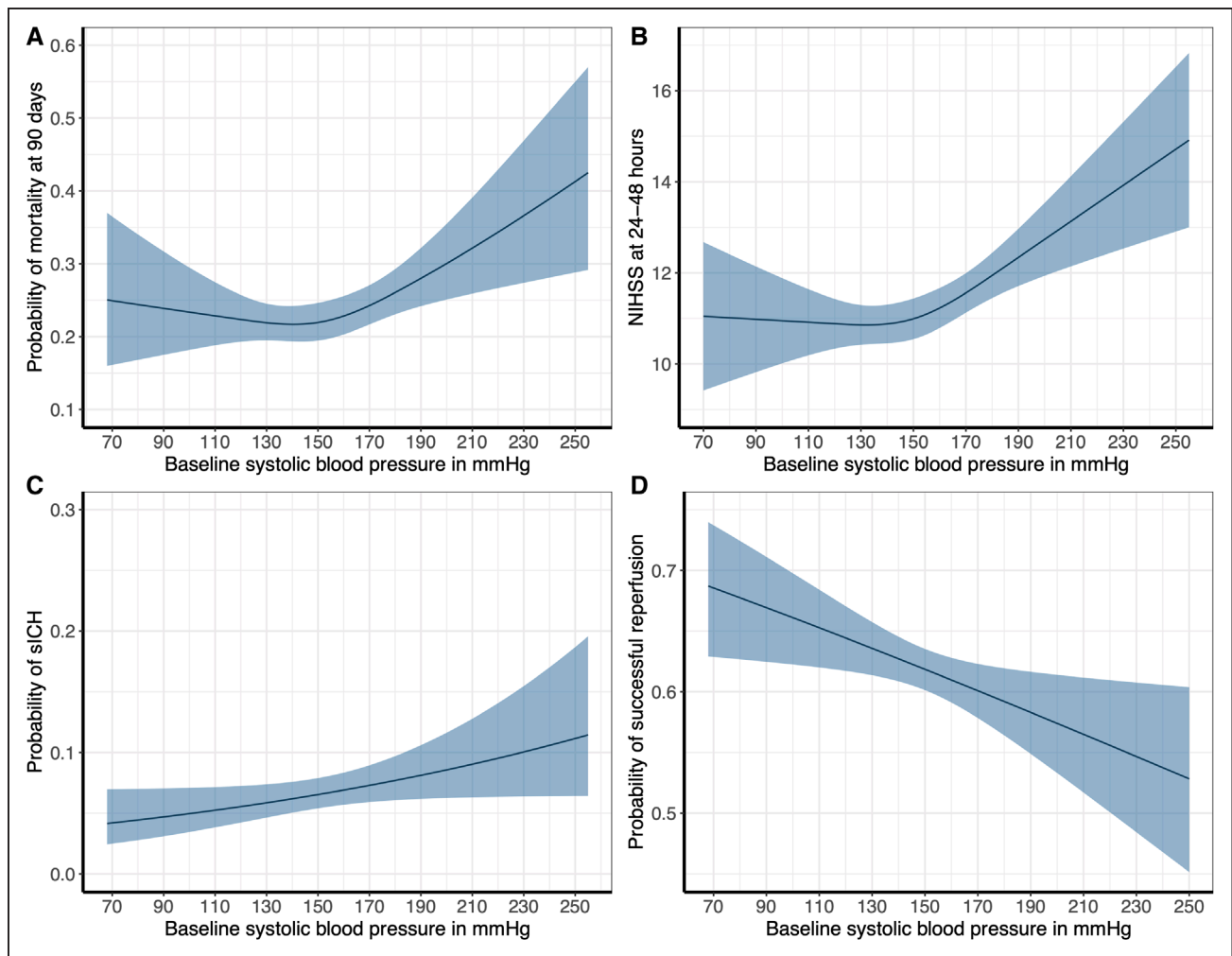


Figure 3. Relationship of baseline systolic blood pressure (SBP) with probability of mortality 90 d poststroke, National Institutes of Health Stroke Scale (NIHSS) at 24–48 h poststroke, probability of symptomatic intracranial hemorrhage (sICH), probability of successful reperfusion.

Models fitted with a restricted cubic spline transformation with 3 knots (**A** and **B**) or linear model (**C** and **D**). The figures depict the probability of 90-d mortality (**A**), NIHSS at 24–48 h poststroke (**B**), probability of sICH (**C**), and probability of successful reperfusion (**D**) with 95% CIs, for each level of baseline SBP. The ranges of the x-axes correspond to minimum and maximum values of SBP and diastolic blood pressure (DBP) in the study (SBP: 68–255 mmHg, DBP: 34–155 mmHg).

A French study of 1332 patients treated with EVT also reported a J-shaped relationship between SBP and mortality, with a nadir at 157 mmHg, and a nonlinear relationship between SBP and functional outcome, with a threshold of >177 mmHg for poor functional outcome.⁸ This study also found no relation between low SBP and functional outcome, but SBP <110 mmHg was associated with an increased risk of death. In various other studies, U-shaped relations of BP with clinical outcomes have been reported for patients with any ischemic stroke,^{4,7,18,19} with both extremes of BP associated with poorer outcome, although the reported optimum SBPs varied substantially between studies, ranging from 120 to 130 mmHg^{7,19} to 156 to 220 mmHg in another study.²⁰ Other types of relationships (eg, linear) have also been described.²¹ This is likely due to heterogeneity in inclusion criteria and stroke subtypes.

We found a tendency towards increased occurrence of sICH in patients with higher SBP, albeit not reaching statistical significance. In some previous studies of patients treated with intravenous alteplase or EVT, an association between high baseline SBP and the risk of sICH was found.^{7,9} The lack of statistical significance in our study might be due to lack of power since just 6% of the included patients had a sICH. Two other studies in patients treated with EVT or with ischemic stroke in general also failed to find an association between SBP and sICH.^{4,8}

In our study, higher BPs were associated with a lower probability of successful reperfusion after EVT. This finding is in line with 2 previous studies in patients with a large vessel occlusion, which demonstrated that higher SBPs were associated with poor reperfusion after EVT with the MERCI device (Mechanical Embolus Removal in Cerebral

Ischemia)²² or with intravenous thrombolysis.²³ While this may indicate that occlusions that are difficult to recanalize are associated with higher BP, it has also been hypothesized that clot removal may be more difficult due to the hydraulic forces imposed by higher BP.²² Patients with SBP \geq 150 had a higher rate of carotid stenosis \geq 50% or occlusion at the symptomatic carotid bifurcation, which may have increased the difficulty of the EVT procedure and thereby resulted in lower reperfusion rates. However, the relationship between SBP and lower reperfusion persisted after adjusting for the presence of carotid stenosis or occlusion, suggesting other factors are at play. Finally, we found slightly longer onset-to-groin and onset-to-reperfusion times for patients with SBP \geq 150 mmHg, which is most likely explained by either treatment of hypertension or a wait-and-see policy in patients with BPs of 185/110 mmHg or higher before the start of intravenous thrombolysis.

Whether the relationship between baseline BP and functional outcome is dependent on successful reperfusion remains unclear. High SBP could be deleterious in successfully reperfused patients due to higher incidence of sICH, or it could be beneficial in those patients due to improved collateral flow and prolonged penumbral sustenance before the procedure. In our study, reperfusion status did not modify the relation between SBP and functional outcome, and the same applies to the relation between SBP and sICH. This is in line with the French study mentioned above, in which the association of SBP with functional outcome did not depend on the occurrence of successful recanalization.⁸ A recent multicenter international study, including 306 patients with large vessel occlusion, found that the relationship between BP and functional outcome was modified by reperfusion status. In patients with successful reperfusion, high SBP was associated with less infarct growth and better functional outcome, possibly though improved collateral flow. This was not the case for those without successful reperfusion.²⁴ These results were contradictory to a recent multicenter international study of 1245 successfully recanalized patients, which found an association between high admission SBP on the one hand and a higher risk of sICH and a lower chance of good functional outcome on the other.²⁵ The latter study only included patients in whom successful reperfusion was achieved and therefore, effect modification by reperfusion status was not investigated, which limits the interpretation of this finding.

Most previous trials of BP lowering in patients with ischemic stroke have shown that treatment of hypertension in the first days after stroke onset does not reduce the risk of death or dependence.²⁶ However, these trials did not assess very early BP modification before reperfusion therapy, and most were performed before EVT was implemented in routine clinical practice. One recently published phase III trial, RIGHT-2 (Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial), investigated BP lowering in a prehospital setting with nitroglycerin. Although moderate BP lowering did not result in improved functional outcome,

this trial included patients with any ischemic stroke and only 2% of patients in the nitroglycerin group were eventually treated with mechanical thrombectomy.²⁷ While our findings imply that very early BP lowering may be beneficial in stroke patients eligible for EVT, it is important to stress that our results do not prove a direct causal relationship between high BP and poor clinical outcomes. However, it is worthwhile to further explore early BP modification in randomized trials. This is currently done in the trials MR ASAP (Multicentre Randomised Trial of Acute Stroke Treatment in the Ambulance With a Nitroglycerin Patch)²⁸ and INTERACT4 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial).²⁹

Three limitations of the current study are worth mentioning. First, no eligibility log was available to assess whether EVT was withheld for reasons related to baseline BP. Second, use of antihypertensive treatment in the emergency department was not documented, which limits our ability to assess the relationship of pre-EVT BP with outcomes. In addition, the documentation of a single SBP and DBP increases the risk of measurement error. The major strength of our study is the large dataset with detailed and near-complete data. Our results represent an unselected cohort of EVT-treated patients in routine clinical practice, which improves generalizability of our findings. A relatively large number of patients with poor or absent collaterals were treated, as well as patients with high baseline BPs, which emphasizes that patients with poor prognostic factors were not systemically deemed ineligible for EVT.

In summary, we found an association of higher admission SBPs and DBPs with poor clinical outcomes and lower probability of successful reperfusion in patients with ischemic stroke treated with EVT. Our results underscore the potential for early BP modification in patients eligible for EVT, which could be the focus of future randomized controlled trials.

ARTICLE INFORMATION

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the critical revision of the article. Drs van der Worp and Nederkoorn performed the study concept, interpretation of the results, critical revision of the article.

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Disclosures

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APPENDIX

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REFERENCES

- Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al; American Heart Association Stroke Council. 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. doi: 10.1161/STR.0000000000000158
- Jansen IGH, Mulder MJHL, Goldhoorn RB; MR CLEAN Registry Investigators. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949. doi: 10.1136/bmj.k949
- Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315–1320. doi: 10.1161/01.str.0000014509.11540.66
- Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, Divani AA, Reddi AS. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007;25:32–38. doi: 10.1016/j.ajem.2006.07.008
- Regenhardt RW, Das AS, Stapleton CJ, Chandra RV, Rabinov JD, Patel AB, Hirsch JA, Leslie-Mazwi TM. Blood pressure and penumbral substance in stroke from large vessel occlusion. *Front Neurol*. 2017;8:317. doi: 10.3389/fneur.2017.00317

7. Mulder MJHL, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lycklama À Nijeholt G, Emmer BJ, van der Worp HB, et al; Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) Investigators. Baseline blood pressure effect on the benefit and safety of intra-arterial treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands). *Stroke*. 2017;48:1869–1876. doi: 10.1161/STROKEAHA.116.016225
8. Maier B, Gory B, Taylor G, Labreuche J, Blanc R, Obadia M, Abrivard M, Smajda S, Desilles JP, Redjem H, et al; Endovascular Treatment in Ischemic Stroke (ETIS) Research Investigators. Mortality and disability according to baseline blood pressure in acute ischemic stroke patients treated by thrombectomy: a collaborative pooled analysis. *J Am Heart Assoc*. 2017;6:e006484. doi: 10.1161/JAHA.117.006484
9. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, Wahlgren N, Ahmed N; SITS Investigators. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. *Stroke*. 2012;43:1524–1531. doi: 10.1161/STROKEAHA.111.644815
10. Vitt JR, Trillanes M, Hemphill JC III. Management of blood pressure during and after recanalization therapy for acute ischemic stroke. *Front Neurol*. 2019;10:138. doi: 10.3389/fneur.2019.00138
11. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
12. Noser EA, Shaltoni HM, Hall CE, Alexandrov AV, Garami Z, Cacayorin ED, Song JK, Grotta JC, Campbell MS III. Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? *Stroke*. 2005;36:292–296. doi: 10.1161/01.STR.0000152331.93770.18
13. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CB, Marquering HA, Mazya MV, et al. The heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981–2986. doi: 10.1161/STROKEAHA.115.010049
14. 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. doi: 10.1161/01.str.19.5.604
15. Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. *Nephrol Dial Transplant*. 2015;30:1418–1423. doi: 10.1093/ndt/gfu325
16. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22:745. doi: 10.1097/EDE.0b013e318225c2be
17. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.
18. Bangalore S, Schwamm L, Smith EE, Hellkamp AS, Suter RE, Xian Y, Schulte PJ, Fonarow GC, Bhatt DL; Get With the Guidelines-Stroke Steering Committee and Investigators. Blood pressure and in-hospital outcomes in patients presenting with ischaemic stroke. *Eur Heart J*. 2017;38:2827–2835. doi: 10.1093/eurheartj/ehx330
19. Vemmos KN, Tsvigoulis G, Spengos K, Zakopoulos N, Syntetos A, Manios E, Konstantopoulou P, Mavrikakis M. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med*. 2004;255:257–265. doi: 10.1046/j.1365-2796.2003.01291.x
20. 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. doi: 10.1212/01.wnl.000180939.24845.22
21. Ishitsuka K, Kamouchi M, Hata J, Fukuda K, Matsuo R, Kuroda J, Ago T, Kuwashiro T, Sugimori H, Nakane H, et al; FSR Investigators. High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. *Hypertension*. 2014;63:54–60. doi: 10.1161/HYPERTENSIONAHA.113.02189
22. Nogueira RG, Liebeskind DS, Sung G, Duckwiler G, Smith WS; MERC1; Multi MERC1 Writing Committee. Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERC1) and Multi MERC1 Trials. *Stroke*. 2009;40:3777–3783. doi: 10.1161/STROKEAHA.109.561431
23. Tsvigoulis G, Saqqur M, Sharma VK, Lao AY, Hill MD, Alexandrov AV; CLOTBUST Investigators. Association of pretreatment blood pressure with tissue plasminogen activator-induced arterial recanalization in acute ischemic stroke. *Stroke*. 2007;38:961–966. doi: 10.1161/01.STR.0000257314.74853.2b
24. Hong L, Cheng X, Lin L, Bivard A, Ling Y, Butcher K, Dong Q, Parsons M; INSPIRE Study Group. The blood pressure paradox in acute ischemic stroke. *Ann Neurol*. 2019;85:331–339. doi: 10.1002/ana.25428
25. Anadani M, Orabi MY, Alawieh A, Goyal N, Alexandrov AV, Petersen N, Kodali S, Maier IL, Psychogios MN, Swisher CB, et al. Blood pressure and outcome after mechanical thrombectomy with successful revascularization. *Stroke*. 2019;50:2448–2454. doi: 10.1161/STROKEAHA.118.024687
26. Bath PMW, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev*. 2014;10:CD000039. doi: 10.1002/14651858.CD000039.pub3
27. RIGHT-2 Investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet*. 2019;393:1009–1020. doi: 10.1016/S0140-6736(19)30194-1
28. van den Berg SA, Dippel DWJ, Hofmeijer J, Fransen PSS, Caminada K, Siegers A, Kruyt ND, Kerkhoff H, de Leeuw FE, Nederkoorn PJ, et al; MR ASAP Investigators. Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP): study protocol for a randomised controlled trial. *Trials*. 2019;20:383. doi: 10.1186/s13063-019-3419-z
29. Anderson C. Intensive Ambulance-delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial (INTERACT4). ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03790800>. Accessed March 23, 2020.