


# Blood Pressure Variability in Thrombectomy for Acute Ischemic Stroke: *Post-Hoc* Analysis of the BP-TARGET trial

Walter W. Merriman<sup>a, d</sup> , Mikael Mazhigi<sup>b</sup>, David Z. Rose<sup>c</sup>, Adnan I. Qureshi<sup>a</sup>

## Abstract

**Background:** Factors associated with blood pressure variability (BPV) in acute ischemic stroke (AIS) patients undergoing thrombectomy have not been well established. Therefore, we performed a *post-hoc* analysis of the BP-TARGET trial, evaluating the relationship between BPV, post-procedural intraparenchymal hemorrhage (IPH), and functional independence at 90 days.

**Methods:** For 24 h after thrombectomy, blood pressure values were recorded and BPV was quantified by calculating the following indices: 24-h average real variability ( $AVR_{24}$ ), time rate index (TRI), successive variability (SV), standard deviation (SD), and range for systolic, diastolic, and mean arterial blood pressures. We assessed the effect of initial National Institutes of Health Stroke Scale (NIHSS) score, age, modified Thrombolysis in Cerebral Infarction (mTICI) score, and initial systolic blood pressure post-procedure on BPV, as well as the effect of BPV on IPH at 24 h and functional independence defined as modified Rankin Scale (mRS) of 0-2 at 90 days.

**Results:** A total of 193 AIS patients (mean age  $72.7 \pm 13.6$  years), with an average post-procedure systolic blood pressure of  $152.8 \pm 25.6$  mm Hg, were analyzed. An mTICI score of 2b (incomplete/subtotal recanalization), compared with mTICI score of 3 (full recanalization), predicted increased BPV (ARV:  $P = 0.014$ , TRI:  $P = 0.028$ , and SV:  $P = 0.030$ ). There was no association between BPV and functional independence at 90 days (ARV:  $P = 0.185$ , TRI:  $P = 0.657$ , and SV:  $P = 0.550$ ), or BPV and post-procedural IPH.

**Conclusion:** In this *post-hoc* analysis of the BP-TARGET trial, better recanalization was associated with decreased BPV in AIS patients post-

thrombectomy. Nevertheless, we found no association between BPV indices and functional independence at 90 days or post-procedural IPH.

**Keywords:** Ischemic stroke; Blood pressure; Thrombectomy; Cerebral hemorrhage; Recanalization

## Introduction

Intraparenchymal hemorrhage (IPH) after thrombectomy in patients with acute ischemic stroke (AIS) remains a major cause of death or disability [1]. Elevated systolic blood pressure (SBP) has been implicated in IPH pathophysiology after intravenous thrombolysis in AIS [2-6]. Subsequently, several clinical trials [7-10] have evaluated the role of SBP reduction in AIS patients undergoing thrombectomy. A meta-analysis of eight studies with 2,922 patients did not identify a difference in functional independence (defined as modified Rankin Scale (mRS) 0-2) at 90 days or IPH within 24 h in AIS patients with either intensive SBP reduction or moderate SBP reduction compared with standard SBP reduction post-thrombectomy [11]. Now, therefore, the focus may be shifting from absolute SBP values to blood pressure variability (BPV) as the most relevant biomarker associated with IPH and functional outcomes in AIS patients undergoing thrombectomy. Another meta-analysis demonstrated that increased variability of SBP in the acute phase, post-thrombectomy is associated with worse functional outcomes [12]. However, no consensus exists on which indices of BPV can or should be used for the purpose of quantifying increased BPV, or what magnitude of BPV is clinically relevant. The present study investigates the relationship between several indices of BPV and IPH and functional outcomes in AIS patients undergoing thrombectomy, and seeks to identify predictors of BPV, in a *post-hoc* analysis of a major multicenter randomized clinical trial [7].

## Materials and Methods

### Study population

We performed a *post-hoc* analysis of the BP-TARGET study, which was a multi-center trial that randomized AIS patients post-thrombectomy to either intensive SBP control (goal 100 - 129

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<sup>a</sup>Zeenat Qureshi Stroke Institutes and Department of Neurology, University of Missouri, Columbia, MO, USA

<sup>b</sup>Neurology Department, Hopital Lariboisiere, Paris, France

<sup>c</sup>Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA

<sup>d</sup>Corresponding Author: Walter Merriman, Zeenat Qureshi Stroke Institutes and Department of Neurology, University of Missouri, Columbia, MO 65201, USA. Email: [wmmn8y@umsystem.edu](mailto:wmmn8y@umsystem.edu)

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mm Hg) or standard control (goal 130 - 185 mm Hg) [7]. Briefly, all patients within the BP-TARGET trial underwent thrombectomy for large vessel occlusion (LVO) in either the internal carotid artery or proximal middle cerebral artery (M1) within 6 h of symptom onset and achieved a modified Thrombolysis in Cerebral Ischemia (mTICI) score of 2b or 3 [13]. Investigators were permitted to use any antihypertensive agent, with calcium channel blockers being the most frequent choice. SBP and diastolic blood pressure (DBP) were recorded at the completion of thrombectomy, then every 15 min for 2 h, then every 30 min for 6 h, and then every hour until the 24 h mark. We only excluded patients who were missing: 1) > 20% of blood pressure (BP) recordings; 2) an initial SBP measurement; or 3) IPH data.

**BP variables**

Mean arterial pressure (MAP) was calculated using Gauer’s method [14]. BPV was assessed for each patient by calculating the following indices: 24-h apparent real variability (ARV<sub>24</sub>), time rate index (TRI), successive variability (SV), standard deviation (SD), ranges for SBP and DBP, and MAPs over the first 24 h post-thrombectomy. In all cases of missing BP data, the time index of the missing data was removed and the next index with available BP data was used.

The ARV<sub>24</sub> is a time-weighted average of changes in BP, as previously described in the literature [15]. It is calculated by first multiplying the difference between two BP measurements (P) by the interval of time between them (w<sub>k</sub>), these values are then summated, and finally divided by the sum of the time intervals. The ARV<sub>24</sub> equation is:

$$ARV_{24} = \frac{1}{\sum w_k} \sum_{i=1}^N w_k |P_{i+1} - P_i|$$

$$w_k = t_{i+1} - t_i$$

The TRI is an average rate of change between individual BP measurements [16]. It is calculated by finding the difference between measurements, then dividing that difference by the time (t) interval between them, then taking the average of that quotient. The TRI equation is:

$$TRI = \frac{1}{N-1} \sum_{i=1}^{N-1} \left| \frac{P_{i+1} - P_i}{t_{i+1} - t_i} \right|$$

SV is an averaged squared difference between adjacent BP measurements [17]. It is calculated by finding the squared difference between sequential BP measurements, then taking the average of those differences, and finally the square root of the average. The difference between SV and SD is that the former compares adjacent values, and the latter compares values to the mean. The SV equation is:

$$SV = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N-1} (P_{i+1} - P_i)^2}$$

**Outcomes**

We analyzed the relationship of BPV variables with two out-

comes: 1) post-thrombectomy IPH, defined as any new intraparenchymal hyperdensity consistent with hemorrhage on computed tomography (CT) obtained between 24 and 36 h post-procedure and verified on CT at 72 h post-procedure (regardless of symptoms); and 2) functional independence at 90 days, defined by a mRS score of 0-2. The mRS scoring at 90 days post-thrombectomy was ascertained by independent qualified personnel who did not participate in the randomization or in-hospital treatment of the patients.

**Statistical analysis**

The baseline characteristics of the sample population were expressed as a number for categorical variables and as a mean ± SD for continuous variables. We used a Welch t-test of independent means to compare the means of ARV<sub>24</sub>, TRI, SV, range, and SD between those patients with and without post-thrombectomy IPH. We utilized a multiple linear regression to determine which factors predicted the systolic ARV, TRI, and SV among independent variables of initial National Institutes of Health Stroke Scale (NIHSS), age, initial SBP, and mTICI score. The initial NIHSS scores were first converted from a raw score into levels of scores 0 to 9, 10 to 19, and 20 or more and included as an ordinal variable. The TICI scores of 2b and 3 were included as an ordinal variable. The initial SBP and age were included as continuous variables. A P-value of < 0.05 was considered significant. All data reduction and calculations were performed using the statistical programming language R (R Core Team (2024). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria [18]).

The research and preparation of this manuscript was determined to not be human subject research by University of Missouri Internal Review Board, and therefore not subject to approval by the same. The research and preparation of this manuscript adhered to ethical guidelines of the institution at which it was performed.

**Results**

The BP-TARGET study recruited 318 patients. After applying our exclusion criteria, 193 patients were identified for this *post-hoc* analysis. The most common reason for exclusion was BP data missing values exceeding 20% (n = 77), followed by mRS data missing at 90 days (n = 24), initial BP value missing (n = 19), and/or missing IPH data (n = 5). The mean patient age was 73 ± 14 years and 91 patients were men and 102 were women. Clinical characteristics are listed in Table 1. The mean initial NIHSS score (± SD) was 16 ± 6. Post-procedure, 83 patients had a TICI score of 2b (incomplete/subtotal recanalization) and 110 had a score of 3 (complete recanalization). The mean initial SBP was 153 ± 26 mm Hg. Post-thrombectomy IPH was seen in 77 (39.9%) of 193 patients (42.2% with mTICI 2b and 38.1% with mTICI 3) and functional independence at 90 days was seen in 98 of 193 patients (38.8% with mTICI 2b and 50.8% with mTICI 3).

**Table 1.** Baseline Characteristics for 193 Patients With Successful Thrombectomy of a Large Arterial Occlusion According to the Presence or Absence of Intraparenchymal Hemorrhage in the First 24 h Post-Procedure in a *Post-Hoc* Analysis of BP-TARGET Trial Data

	Total	Post-procedure intracranial hemorrhage		P-value
		Yes, n = 77 (39.9%)	No, n = 116 (60.1%)	
IV thrombolysis, n (%)	103 (88.8)	41 (39.8)	62 (60.2)	0.566
Initial NIHSS, mean ± SD	15.7 ± 5.9	16.8 ± 5.5	15.0 ± 6.2	0.044
Initial systolic blood pressure, mm Hg ± SD	152.8 (25.6)	154.0 (28.7)	151.7 (23.2)	0.552
Male sex, n (%)	91 (47.2)	37 (40.6)	54 (59.3)	0.954
Age, mean ± SD	72.7 ± 13.6	71.6 ± 13.5	73.4 ± 13.7	0.368
mTICI grade after thrombectomy				0.681
mTICI 2b, n (%)	83 (43.0)	35 (42.2)	48 (57.8)	
mTICI 3, n (%)	110 (57.0)	42 (38.1)	68 (61.8)	
Functional Independence at 90 days				< 0.001
mRS 0-2, n (%)	98 (50.8)	30 (39.0)	68 (58.6)	
mTICI 2b, n (%)	38 (38.8)	12 (31.6)	26 (68.4)	
mTICI 3, n (%)	60 (61.2)	17 (28.3)	43 (71.6)	
mRS ≥ 3, n (%)	95 (49.2)	47 (61.0)	48 (41.4)	
Hypertension	132 (68.4)	52 (39.4)	80 (60.6)	0.777
Tobacco use	32 (16.6)	12 (37.5)	20 (62.5)	0.973
Diabetes mellitus	42 (21.9)	18 (42.9)	24 (57.1)	0.652
Premorbid antiplatelet therapy, n (%)	48 (25.0)	22 (45.8)	26 (54.2)	0.756
Premorbid anticoagulant therapy, n (%)	43 (22.3)	12 (27.9)	31 (72.1)	0.353

IV: intravenous; mRS: modified Rankin Scale; mTICI: modified Thrombolysis in Cerebral Ischemia; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation.

### Predictors of BPV

A multiple linear regression was performed to identify factors that predicted systolic BPV. Among ARV<sub>24</sub>, TRI, and SV, a mTICI score of 3 (P = 0.014, P = 0.028, and P = 0.030, respectively) predicted a lower systolic BPV (Table 2). Pre-procedural NIHSS was also found to predict lower systolic BPV in TRI only (P = 0.028). Post-procedural initial SBP and age were not found to be significant predictors of BPV.

### BP variables and post-thrombectomy IPH

Both a higher initial NIHSS (16.8 vs. 15.0, P = 0.044) and a lower rate of functional independence at 90 days (39.0% vs. 58.6%, P < 0.001) were found in patients with post-thrombectomy IPH compared to those without IPH (Table 1).

Calculations of ARV<sub>24</sub>, TRI, SV, range, and SD were performed for SBP, DBP, and MAPs for all patients. No significant deviations from the planned analysis were required. No significant relationship between indices of BPV and IPH was found in this analysis (Table 3).

### BP variables and functional independence at 90 days

None of the indices of BPV tested were found to predict functional independence at 90 days (Table 4).

### Discussion

The relationship between mTICI grades and three separate indices of BPV was evaluated in our *post-hoc* analysis of the BP-TARGET study, which was a multi-center trial that randomized AIS patients post-thrombectomy to either intensive SBP control (goal 100 - 129 mm Hg) or standard control (goal 130 - 185 mm Hg). A previous study showed that an incomplete revascularization (mTICI score < 3) is associated with greater BPV [19]. This is in keeping with the idea that to support retrograde flow through collateral blood vessels, and augment cerebral perfusion pressure (CPP), such incomplete reperfusion drives higher systemic pressure values and by extension increases BPV [11].

In a recent meta-analysis of 11 studies comprising 3,520 patients, BPV was correlated to functional outcome but intrac-

**Table 2.** Multiple Linear Regression Model Results for 193 Patients With Successful Thrombectomy of a Large Arterial Occlusion for Prediction of Apparent Real Variability, Time Rate Index, and Successive Variability of Systolic Blood Pressure in the First 24 h Post-Procedure in a Post-Hoc Analysis of BP-TARGET Trial Data

Coefficients	Estimate	Standard error	t-value	P-value
<b>ARV</b>				
Intercept	13.56	1.948	6.960	0.000
Pre-procedural NIHSS	-0.578	0.353	-1.638	0.103
Post-procedural SBP, mm Hg	0.004	0.010	-0.825	0.652
mTICI grade 3	-1.402	0.500	-2.473	0.014
Age, years	-0.010	0.019	-0.530	0.597
<b>TRI</b>				
Intercept	0.401	0.060	6.645	0.000
Pre-procedural NIHSS	-0.024	0.011	-2.216	0.028
Post-procedural SBP, mm Hg	0.000	0.000	0.304	0.762
mTICI grade 3	-0.040	0.015	-2.577	0.011
Age, years	0.000	0.001	-0.187	0.852
<b>SV</b>				
Intercept	16.44	2.434	6.752	0.000
Pre-procedural NIHSS	-0.786	0.441	-1.783	0.076
Post-procedural SBP, mm Hg	0.008	0.012	0.655	0.513
mTICI grade 3	-1.900	0.624	-3.044	0.030
Age, years	-0.003	0.023	-0.128	0.898

ARV<sub>24</sub>: 24-h average real variability; mm Hg: millimeters of mercury; mTICI: modified Thrombolysis in Cerebral Ischemia; NIHSS: National Institutes of Health Stroke scale; SBP: systolic blood pressure; SV: successive variability; TRI: time rate index.

ranial hemorrhage was not [12]. In that analysis, SD (odds ratio (OR) 0.854;  $P = 0.02$ ), SV (OR 0.41;  $P = 0.00$ ), and coefficient of variation (OR 0.572;  $P = 0.04$ ) of SBP were associated with lower odds of good functional outcome at 3 months ( $mRS \leq 2$ ). As in our study, no difference was found between BPV for patients with intracranial hemorrhage versus those without. The studies included in the meta-analysis differed from the present study in several ways: first, regarding the occluded vessels, some studies included extracranial and posterior circulation vessels, whereas others (like our study) did not; secondly, our study, unlike some of the observational studies included in the meta-analysis, was based on pre-defined BP targets and standardized BP data ascertainment; third, some studies included any intracranial hemorrhage while others included only IPH, and whether or not it was symptomatic. Therefore, unfortunately, high degree of heterogeneity in the meta-analysis and the results of our study highlight the uncertainty about BPV as a predictor of both IPH and/or functional outcomes ( $mRS$  0-2) at 90 days.

Several limitations on the present study are worthy of mention. First is the lack of mechanistic justification for the choice of specific indices of BPV utilized. Common statistical measures of variability such as SD and range are more frequently utilized compared to more sophisticated measures such as AVR<sub>24</sub>, TRI, and SV across this and other studies, which are more rarely used. Their utility and applicability of AVR<sub>24</sub>, TRI, and SV to AIS, thrombectomy, and their compli-

cations remain unarticulated. Furthermore, all indices of BPV are calculated *post-hoc*, requiring some interval of time for the accumulation of the data and calculation, making them unfit and impractical as treatment targets with current technology at the bedside in the neuro-intensive care unit or emergency department. Another limitation is the mixing of both standard and intensive SBP reduction groups from the BP-TARGET trial. The relationships sought in the present study are those between BPV and outcomes, irrespective of the source of that variability or lack thereof. Nevertheless, there could be differences in those relationships if they were divided into subgroups based on their treatment group assignment in the original trial. There is also the consideration that the topography of ICH has been shown to affect several measures of clinical outcome and the original study did not make a distinction based on where the hemorrhage occurred [20]. Finally, the BP data have an inconsistent time basis and small sample size; the time between measurements varies both systematically due to the design of the trial and at random due to missingness. In our study, we mitigated this by excluding patients with more than 20% missing data, but this only decreases the effect of missing data and comes at the expense of decreasing the sample size. Regardless, our analysis adds to the growing body of literature showing that despite recanalization post-thrombectomy for AIS is associated with decreased BPV, there remains a lack of clear association between BPV and IPH or 90-day independence in this setting. This ultimately underscores the need for

**Table 3.** Measures and Significance of Indices of Blood Pressure Variability for 193 Patients With Successful Thrombectomy of a Large Arterial Occlusion According to the Presence or Absence of Intraparenchymal Hemorrhage in the First 24 h Post-Procedure in a *Post-Hoc* Analysis of BP-TARGET Trial Data

	Post-procedural intracranial hemorrhage				Δ	95% Confidence interval	P-value
	Yes, n = 77 (39.9%)		No, n = 116 (60.1%)				
	Mean	SD	Mean	SD			
<b>SBP</b>							
Range, mm Hg	64.66	19.02	70.57	25.16	-5.91	-12.19, 0.380	0.065
SD, mm Hg	15.10	4.50	15.96	4.93	-0.85	-2.21, 0.502	0.215
TRI, mm Hg/min	0.32	0.09	0.35	0.12	-0.03	-0.06, 0.001	0.061
ARV <sub>24</sub> , mm Hg	11.61	3.42	11.61	3.49	0.00	-1.00, 0.998	0.996
SV, mm Hg	14.18	3.92	15.10	4.61	-0.92	-2.14, 0.297	0.137
<b>DBP</b>							
Range, mm Hg	52.79	18.76	54.81	24.25	-2.02	-8.14, 4.108	0.517
SD, mm Hg	11.60	3.81	12.04	4.79	-0.45	-1.67, 0.779	0.473
TRI, mm Hg/min	0.30	0.12	0.29	0.14	0.01	-0.03, 0.042	0.778
ARV <sub>24</sub> , mm Hg	9.87	4.03	9.83	4.01	0.04	-1.13, 1.21	0.943
SV, mm Hg	13.34	5.13	13.56	5.72	-0.22	-1.78, 1.340	0.783
<b>MAP</b>							
Range, mm Hg	49.32	14.36	51.57	19.58	-2.25	-7.08, 2.572	0.358
SD, mm Hg	11.17	3.16	11.64	4.08	-0.47	-1.50, 0.563	0.371
TRI, mm Hg/min	0.26	0.09	0.26	0.11	0.00	-0.03, 0.025	0.813
ARV <sub>24</sub> , mm Hg	8.77	2.97	8.70	3.10	0.07	0.81, 0.948	0.874
SV, mm Hg	11.32	3.71	11.66	4.26	-0.35	1.49, 0.796	0.550

ARV<sub>24</sub>: 24-h average real variability; DBP: diastolic blood pressure; Δ: difference; MAP: mean arterial pressure; mm Hg: millimeters of mercury; mTICI: modified Thrombolysis in Cerebral Ischemia; NIHSS: National Institutes of Health Stroke Scale; SBP: systolic blood pressure; SD: standard deviation; SV: successive variability; TRI: time rate index.

further research in this area that may define other biomarkers to improve outcomes.

**Conclusions**

We observed that full recanalization is associated with decreased BPV post-thrombectomy for AIS. However, we found no evidence that increased BPV is associated with IPH in the

24 h post-procedure or functional independence at 90 days. Our results highlight the need for additional data prior to adoption of reduction in BPV as a therapeutic target post-thrombectomy in AIS patients.

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**Table 4.** Multiple Linear Regression Model Results for 193 Patients With Successful Thrombectomy of a Large Arterial Occlusion for Prediction of Functional Independence at 90 days Based on Blood Pressure Variability Indices in the 24 h Post-Procedure, in a *Post-Hoc* Analysis of BP-TARGET Trial Data

Coefficients	Estimate	Standard error	t-value	P-value
ARV	-0.032	0.024	-1.331	0.185
TRI	0.293	0.659	0.445	0.657
SV	0.017	0.028	0.590	0.550
Range	-0.003	0.004	-0.823	0.412
SD	0.017	0.017	0.996	0.321

ARV<sub>24</sub>: 24-h average real variability; SD: standard deviation; SV: successive variability; TRI: time rate index.

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## Financial Disclosure

This study was unfunded.

## Conflict of Interest

Dr. Walter Merriman has no disclosures to declare. Dr. Adnan Qureshi is cofounder of DyQure, QureVasc, and Qureshi Medica LLC and has received grant support from Chiesi USA. Dr. David Rose has received honoraria/grant funding from Atricure, Boston Scientific, Chiesi, CSL-Behring, Medtronic and Viz. Dr. Mikayel Mazhigi has no disclosures to declare.

## Informed Consent

All subjects included in the study on which this work was based were provided with written informed consent.

## Author Contributions

Dr. Walter Merriman performed the data analysis and creating the draft of the manuscript. Dr. Mikayel Mazhigi contributed to the conception and the revising of the manuscript for important intellectual content. Dr. David Rose contributed to the analysis of the results and revised the manuscript for important intellectual content. Dr. Adnan Qureshi contributed to the conception, design, and revision of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

## Abbreviations

AIS: acute ischemic stroke; ARV<sub>24</sub>: 24-hour average real variability; BPV: blood pressure variability; DBP: diastolic blood pressure; Δ: difference; IPH: intraparenchymal hemorrhage; IV: intravenous; LVO: large vessel occlusion; M1: proximal middle cerebral artery; MAP: mean arterial pressure; mm Hg: millimeters of mercury; mRS: modified Rankin Scale; mTICI: modified Thrombolysis in Cerebral Ischemia; NIHSS: National Institutes of Health Stroke Scale; SBP: systolic blood pressure; SD: standard deviation; SV: successive variability; TRI: time rate index

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