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Original Article

Higher Blood Pressure during Endovascular Thrombectomy in Anterior Circulation Stroke Is Associated with Better Outcomes

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Background and Purpose Reports investigating the relationship between in-procedure blood pressure (BP) and outcomes in patients undergoing endovascular thrombectomy (EVT) due to anterior circulation stroke are sparse and contradictory.

Methods Consecutive EVT-treated adults (modern stent retrievers, BP managed in line with the recommendations, general anesthesia, invasive BP measurements) were evaluated for associations of the rate of in-procedure systolic BP (SBP) and mean arterial pressure (MAP) excursions to >120%/<80% of the reference values (serial measurements at anesthesia induction) and of the reference BP/weighted in-procedure mean BP with post-procedure imaging outcomes (ischemic lesion volume [ILV], hemorrhages) and 3-month functional outcome (modified Rankin Scale [mRS], score 0 to 2 vs. 3 to 6).

Results Overall 164 patients (70.7% pharmacological reperfusion, 80.5% with good collaterals, 73.8% with successful reperfusion) were evaluated for ILV (range, 0 to 581 cm^3) and hemorrhages (incidence 17.7%). Higher rate of in-procedure SBP/MAP excursions to >120% was independently associated with lower ILV, while higher in-procedure mean SBP/MAP was associated with lower odds of hemorrhages. mRS 0-2 was achieved in 75/155 (48.4%) evaluated patients (nine had missing mRS data). Higher rate of SBP/MAP excursions to >120% and higher reference SBP/MAP were independently associated with higher odds of mRS 0-2, while higher ILV was associated with lower odds of mRS 0-2. Rate of SBP/MAP excursions to <80% was not associated with any outcome.

Conclusions In the EVT-treated patients with BP managed within the recommended limits, a better functional outcome might be achieved by targeting in-procedure BP that exceeds the pre-procedure values by more than 20%.

Keywords Stroke; Mechanical thrombolysis; Blood pressure; Anesthesia, general

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Introduction

Critical blood pressure (BP) values in the acute ischemic stroke patients undergoing reperfusion treatment are based on the exclusion criteria in the pivotal Phase III trials of recombinant human tissue plasminogen activator (rtPA).[1,2] These BP limits were applied in the most recent endovascular thrombectomy (EVT) studies.[3] However, there have been no randomized controlled trials specifically evaluating the proposed BP limits and there is uncertainty whether BP level of 185/105 mm Hg as an exclusionary criterion for reperfusion treatments can be generalized.[4] Notably, studies in hypertensive patients demonstrated a shift of the limits of functional cerebral blood flow autoregulation to higher values in patients with higher pre-stroke BP levels.[5,6] Thus, keeping BP at a certain universally defined level during the most vulnerable phase of acute cerebral ischemia seems counterintuitive. In animals models of stroke, cerebral blood flow in moderately under-perfused tissue depends on systemic BP and any significant drop in BP is likely to compromise penumbra viability.[7] However, BP beyond the proposed limits could be detrimental due to higher risk of post-reperfusion hemorrhages after EVT.[8] Oscillations in systolic blood pressure (SBP) after EVT may also be associated with poorer outcomes.[9] Earlier studies suggested U-shaped associations between on-admission BP and favorable clinical outcomes in ischemic stroke patients, but also poorer outcomes in patients with generally higher BP throughout hospitalizations.[10-12] One recent analysis reported an association between higher maximum in-procedure SBP and poor 30-day outcomes, while several others suggested the opposite—associations between poorer outcomes and indicators of BP dips.[13-16] Thus, we hypothesized that during EVT it would be reasonable to target individualized BP values. We therefore investigated the relationship between in-procedure SBP and mean arterial pressure (MAP) excursions to above or below the limits defined in respect to their pre-procedure values and (1) post-procedure imaging findings: ischemic lesion volume (ILV) and visible hemorrhages; (2) 3-month functional outcomes; in a cohort of adults with anterior circulation ischemic stroke treated with EVT.

Methods

Design

This is a retrospective analysis of a single-center prospective database comprising adults (age ≥18 years) with a symptomatic acute ischemic stroke due to occlusion of the internal carotid artery and/or middle cerebral artery treated with EVT using modern stent retrievers (a few patients received thrombus aspiration only) over a 5-year period (January 1, 2012 to December 31, 2016). It was approved by the Ethics Committee of Bundesland Salzburg. Figure 1A depicts the flow: patients underwent EVT under general anesthesia (GA) with or without intravenous rtPA, which individually required measures for BP reduction;[4] the analysis was restricted to patients with invasive BP measurement; serial BP values taken immediately before the start of EVT/induction of anesthesia were considered a "reference BP" for the period of the procedure; patients underwent post-procedure computed tomography (CT) imaging to assess hemorrhages and ILV, and were evaluated for the functional outcome at 3 months post-stroke (modified Rankin Scale

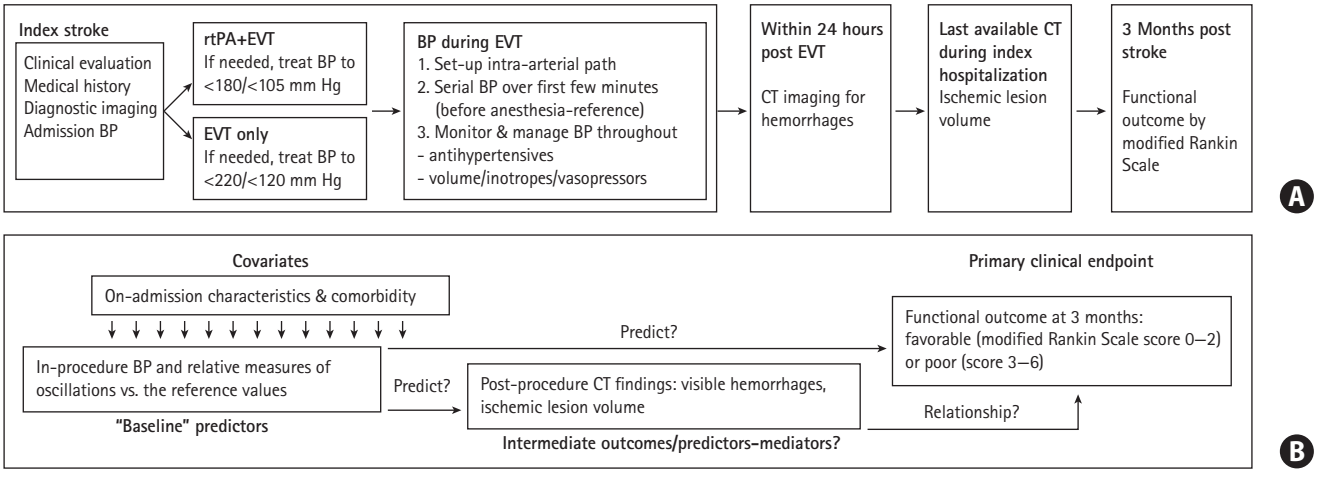

Figure 1. (A) Patient flow. (B) Steps in data analysis. We analyzed relationships between blood pressure (BP) during endovascular thrombectomy (EVT) with or without recombinant tissue plasminogen activator (rtPA) with (1) post-procedure computed tomography (CT) findings: ischemic lesion volume (ILV) and visible hemorrhages; (2) functional outcome at 3 months. We explored a possibility of a mediated association: in-procedure BP → ILV/visible hemorrhage → 3-month functional outcome.

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[mRS]). We explored the associations between in-procedure BP oscillations defined in relative terms versus the "reference value" and (1) post-procedure ILV and visible hemorrhages; (2) favorable 3-month functional outcome (mRS 0-2) (Figure 1B).

Clinical evaluations

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Indication for EVT was made in line with continuously updated standards, while indication for rtPA was in accordance with the Safe Implementation of Thrombolysis in Stroke-Monitoring Study.[2,17] At discharge, stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[18] Functional outcome at 3 months was assessed at scheduled visits or by a telephone interview with the patient or a proxy.

Radiological evaluations

CT or magnetic resonance was used to identify the vessel(s) portions occluded and to evaluate leptomeningeal collaterals on CT-angiography. Collaterals were graded as good when ≥50% were present as compared to the unaffected side. Post-procedure CT was used to evaluate presence of hemorrhages and last available CT during the index hospitalization to determine ILV.[19] The reperfusion success was graded by the Thrombolysis in Cerebral Infarction (TICI) scale: grades 2b (perfusion >50% of the vascular distribution of the occluded artery) and 3 (full perfusion with filling of all distal branches) were considered a success, grades 0-2a were considered a failure.[20]

BP measurements and management

During EVT, BP was measured invasively every minute (except in two patients: every 2 or 5 minutes) and recordings were saved by the MetaVision® software (iMDsoft, Düsseldorf, Germany). Otherwise, it was measured regularly (cuff technique) and recorded in the patient charts. The in-house algorithm for acute stroke patients has been constantly in agreement with the respective guidelines, particularly in respect to the use of rtPA and EVT.

BP indicators

We determined the following BP indicators: (1) "reference" SBP/MAP as the mean of 3 to 5 measurements taken immediately before the start of EVT (induction of anesthesia); (2) individual values ±20% of the reference were determined and number of in-procedure excursions to values >120% or to <80% of the reference was counted to calculate their rates (episodes/10 minutes); (3) weighted mean in-procedure SBP/MAP by dividing area under the curve of BP over time (first to last in-procedure measurement) by the time period covered. We also determined rates of any excursions exceeding ±20% of the reference, and absolute (by linear interpolation) and relative (percent) time of the procedure with SBP/MAP >120% or <80% of the reference values.

Data analysis

We first evaluated associations of in-procedure BP with post-procedure ILV and hemorrhages, and then with 3-month mRS 0-2 (Figure 1B). General linear models were fitted to ln-transformed ILV (effects are geometric mean ratio [GMR], exponents of coefficient obtained with logarithms) and logistic models were fitted to hemorrhages and mRS 0-2. We considered rates of excursions to >120% and to <80% of the reference (analyzed jointly due to potential off-setting effects) to be the primary indicators of BP oscillations, as they were determined directly. Analyses based on derived indicators (absolute/relative time) provided virtually identical results, and are not shown. Analyses of the rate of any excursions exceeding ±20% provided no additional information (also not shown).

Several models were fitted to each outcome starting with larger ("full") models (default and selected effects [stepwise selection with P<0.200 to enter/stay] with sequential tests of interactions: excursion rates*reference BP, excursion rates*TICI grade, reference BP/in-procedure mean BP*TICI grade), from which "reduced" models (to avoid overfitting) were derived (effects of primary interest and biologically/statistically plausible adjustments). In the analysis of 3-month mRS, intermediate outcomes (ILV, hemorrhages) were introduced as adjustments into the "reduced" models, so model selection included a further step to "final" models. Figure 2 outlines the model selection procedure. For details on multivariate model building and selection see Supplementary Methods. Mediation analysis[21] evaluated possibility that the effects of BP on the functional outcome were mediated "through" the effects on ILV/hemorrhages. We used SAS version 9.4 statistical software (SAS Inc., Cary, NC, USA).

Results

Patients

Of the 202 admitted patients, 20 did not undergo EVT and 18 did not have invasive BP monitoring. The cohort analyzed for ILV and hemorrhages comprised 164 patients, while 155 were analyzed for 3-month mRS (nine patients lacked data) (Figure 3).

Patient characteristics are summarized in Table 1 (Supplementary Table 1 for laboratory tests). Both on-admission and reference SBP/MAP varied greatly. Reference values appeared

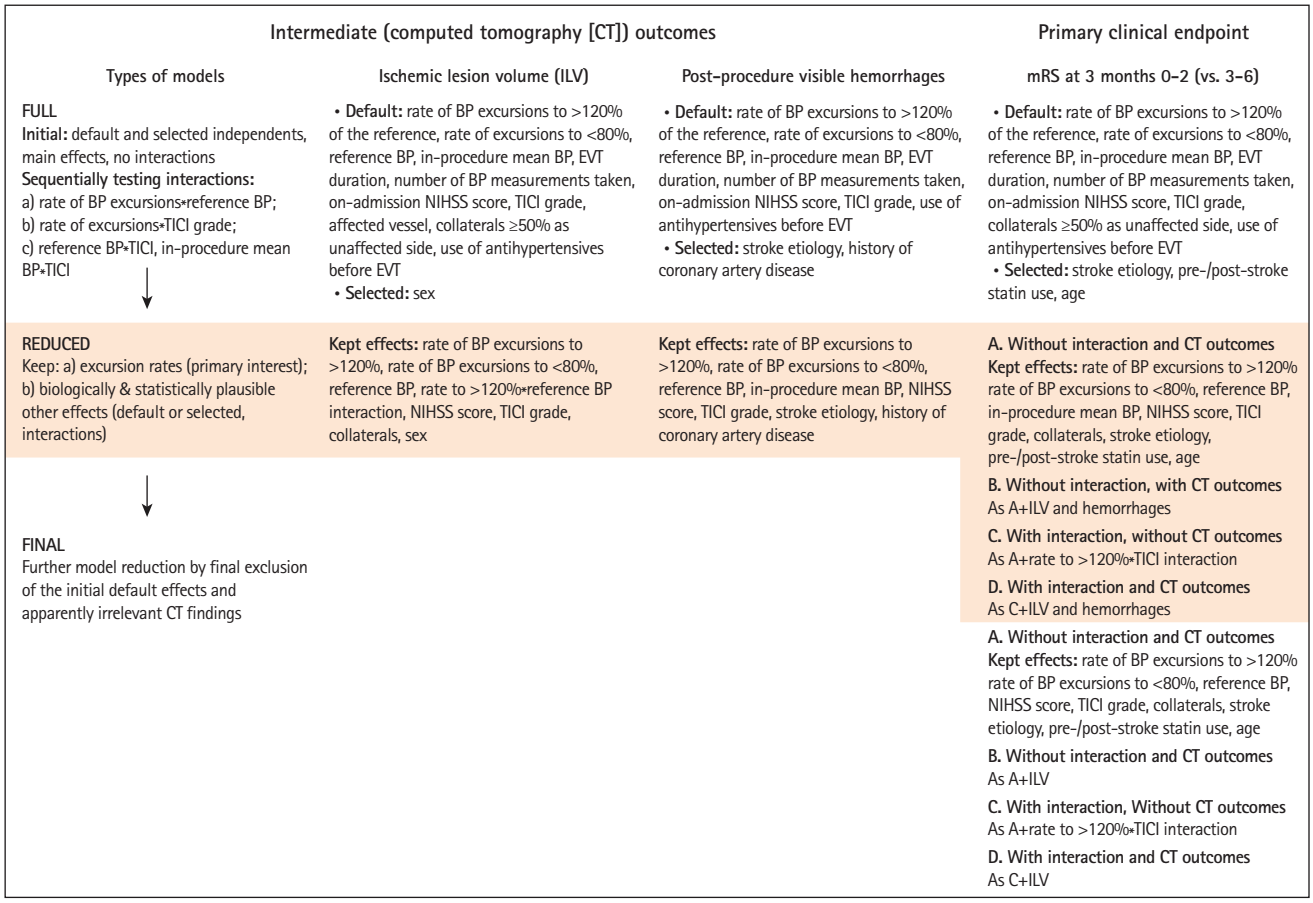

Figure 2. Model selection strategy. All models were fitted separately for systolic blood pressure (BP) and mean arterial pressure. TICI, Thrombolysis in Cerebral Infarction; EVT, endovascular thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

considerably lower than on-admission values, although intra-individual differences extended from substantial reduction to a substantial increase (Table 1). A total of 16 patients received antihypertensives between admission and EVT and two received sympathomimetics. Procedure lasted 12 to 587 minutes with 13 to 230 BP measurements, and 77 (46.9%) patients received sympathomimetics during EVT (Table 1). Overall, 38/164 (23.2%) patients had no excursions exceeding ±20% of the reference SBP/MAP, 68 and 70 (41.5% and 43.6% for SBP and MAP, respectively) experienced exclusively excursions to >120%, 37 and 31 (22.6% and 18.9%) exclusively excursions to <80%, and 21 and 25 (12.8% and 15.2%) experienced both. Data are summarized in Table 1 (see also Supplementary Table 2 and Supplementary Figure 1; for absolute/relative time >120% and <80% of the reference). Additional BP analysis (Supplementary Analysis of Blood Pressure) indicated that BP-related procedures were guided by the intention to keep BP within the recommended limits, and not by the presenting stroke characteristics.

Relationship between in-procedure BP and ILV/post-procedure hemorrhages

Of the 164 patients, 132 (80.5%) had good collaterals, 121 (73.8%) achieved successful reperfusion, ILV ranged 0 to 518 cm^3 and 29 (17.7%) patients had visible hemorrhages (Table 1). Full models were fitted to each outcome (see Supplementary Tables 3 and 4 for complete models). Independent variables consistently not associated with the outcomes were consecutively removed (Figure 2). Reduced models are shown in Table 2. Higher rate of in-procedure SBP excursions to >120% of the reference was associated with lower ILV, more so at higher reference values (rate*reference interaction) (Table 2). As an illustration, with reference SBP <120 mm Hg (n=62) the adjusted GMR=0.89 (interquartile range [IQR], 0.74 to 1.08), with reference SBP >135 mm Hg (n=60), GMR=0.34 (IQR, 0.15 to 0.74). The effect of SBP excursions was consistent in patients with TICI 0-2a (n=43) and TICI 2b-3 (n=121) (Supplementary Table 3). SBP excursions to <80% of the reference were not associated with ILV. Higher admission NIHSS score and male sex were associated with higher ILV; TICI grade 2b-3 and good collaterals were associated with

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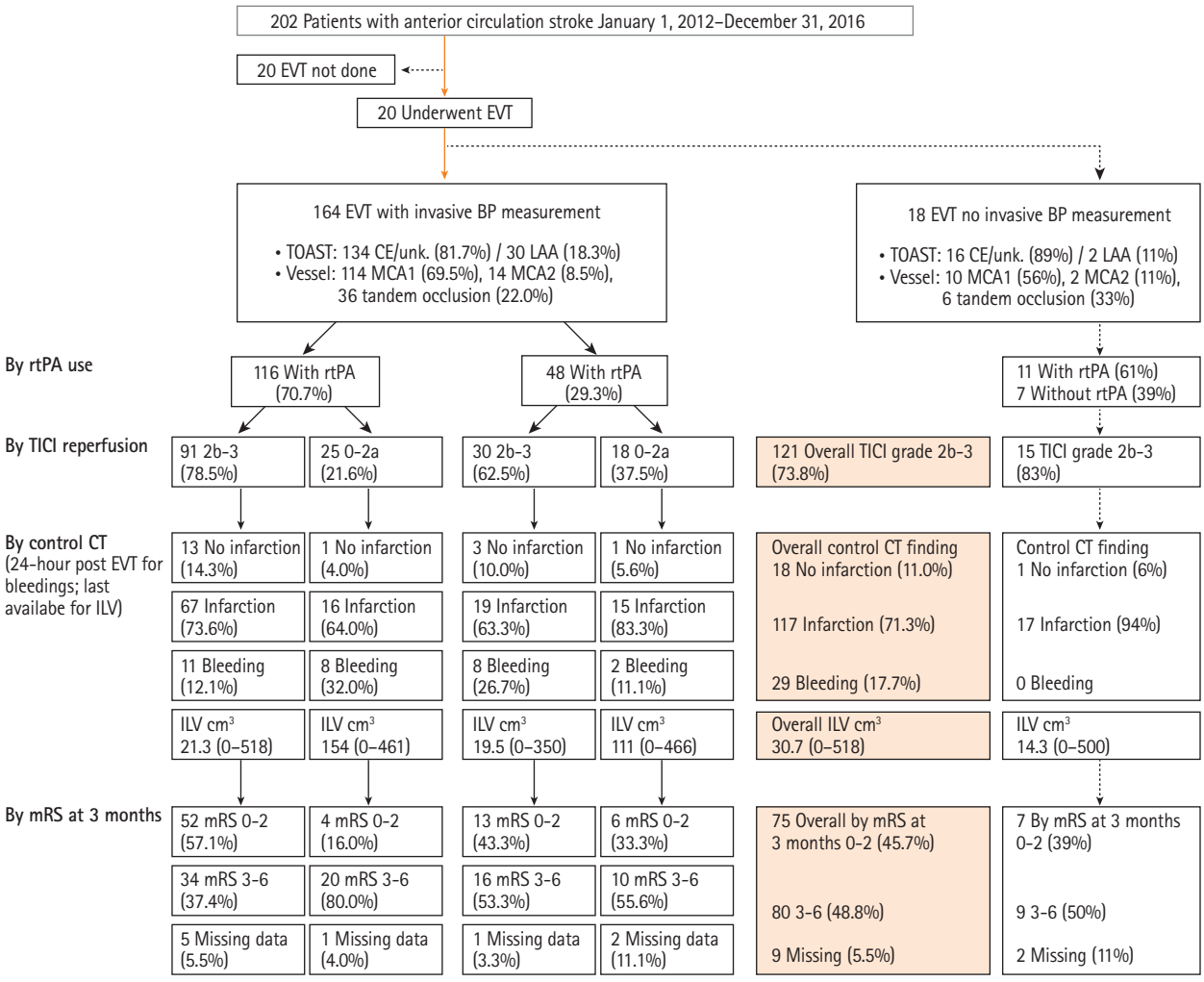

Figure 3. Disposition of patients. EVT, endovascular thrombectomy; BP, blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification; CE, cardioembolic; unk., unknown etiology; LAA, large artery atherosclerosis; MCA, middle cerebral artery, segment 1, segment 2; rtPA, recombinant human tissue plasminogen activator; TICI, Thrombolysis in Cerebral Infarction; CT, computed tomography; ILV, ischemic lesion volume; mRS, modified Rankin Scale.

lower ILV. Similar associations were observed for MAP, except for the excursions*reference interaction (Table 2).

In-procedure BP oscillations assessed by BP excursions were not associated with the post-procedure hemorrhages, higher reference SBP/MAP tended towards higher odds, while higher in-procedure mean SBP/MAP was associated with lower odds of hemorrhages (Table 2 and Supplementary Table 4). Higher in-procedure SBP/MAP was determined mainly by the higher reference SBP/MAP (Supplementary Analysis of Blood Pressure, Table F). Further analysis demonstrated that higher reference SBP/MAP was indirectly (via in-procedure mean) associated with lower odds of post-procedure hemorrhages: the indirect effect was practically identical in size to the direct effect (Table 2); hence, the total effect was close to zero (Supplementary Analysis of Post-Procedure Hemorrhages).

Relationship between in-procedure BP and 3-month functional outcome

Patients with mRS 0-2 (75/155, 48.4%) appeared younger, were more commonly men, and less commonly suffered comorbidities than the patients with mRS 3-6 (Table 1). They were more frequently pre-index stroke statin users, and less frequently antiplatelets or anticoagulants users (Table 1). On-admission NIHSS score, prevalence of cardioembolic/unknown etiology and of tandem occlusions were lower while the use of rtPA was more common and the onset-to-EVT time was shorter in patients with mRS 0-2 (Table 1). Average on-admission and reference SBP/MAP appeared similar between the two subsets and similarly low numbers of patients received antihypertensives between admission and EVT. BP decline between admission and EVT appeared somewhat greater in patients with mRS 3-6 (Table 1). Weighted mean in-proce-

Table 1. Patient and procedure characteristics, overall and by 3-month functional outcome*

Characteristic	All patients	mRS 0–2	mRS 3–6	Missing mRS
Number	164	75	80	9
Age (yr)	74 (20–92)	67 (20–91)	79 (44–92)	74 (52–89)
Male sex	73 (44.5)	37 (49.3)	31 (38.8)	5 (55.6)
Atrial fibrillation	64 (39.0)	23 (30.7)	36 (45.0)	5 (55.6)
Previous stroke	18 (11.0)	8 (11.0)	8 (10.0)	2 (22.2)
Peripheral artery disease	11 (6.7)	4 (5.3)	7 (8.8)	0 (0)
Ischemic heart disease	35 (21.3)	9 (12.0)	25 (31.3)	1 (11.1)
Carotid stenosis ≥50%	17 (10.4)	8 (10.7)	8 (10.0)	1 (11.1)
Hypertension	106 (64.6)	41 (54.7)	59 (73.8)	6 (66.7)
Diabetes mellitus	21 (12.8)	7 (9.3)	13 (16.3)	1 (11.1)
Chronic heart failure	26 (16.2)	8 (11.0)	18 (22.8)	0 (0)
Chronic renal failure	16 (9.9)	4 (56.42)	12 (15.2)	0 (0)
Pre-admission statins	135 (82.8)	68 (90.7)	60 (75.0)	1 (87.5)
Pre-admission antiplatelets	45 (27.4)	15 (20.0)	28 (35.0)	2 (22.2)
Pre-admission anticoagulants	29 (17.7)	9 (12.0)	18 (22.5)	2 (22.2)
On-admission systolic BP (mm Hg)	150 (83–223)	150 (100–210)	154 (83–223)	148 (110–192)
On-admission MAP (mm Hg)	107 (56–174)	106 (67–143)	108 (56–174)	106 (70–135)
NIHSS at presentation	18 (3–32)	16 (3–31)	20 (3–32)	18 (7–24)
Onset to first vessel imaging (min)	189 (98–900)	181 (98–374)	208 (99–639)	165 (111–900)
TOAST: cardioembolic or unknown	134 (81.7)	54 (72.0)	72 (90.0)	8 (88.9)
rtPA used	116 (70.7)	56 (74.7)	54 (67.5)	6 (66.7)
Middle cerebral artery segment 1	114 (69.5)	52 (69.3)	55 (68.8)	7 (77.8)
Middle cerebral artery segment 2	14 (8.5)	8 (10.7)	4 (5.0)	2 (22.2)
Tandem occlusion	36 (22.0)	15 (20.0)	21 (26.3)	0 (0)
Procedure duration (min)	83 (12–587)	65 (12–202)	109 (17–587)	72 (17–188)
BP measurements/procedure (n)	83 (13–230)	66 (13–203)	108 (18–230)	73 (18–189)
BP measurements/minute	1.0 (0.2–2.4)	1.0 (0.5–2.4)	1.0 (0.2–1.6)	1.0 (1.0–1.0)
SBP reference (mm Hg)	125 (73–203)	125 (93–203)	124 (73–191)	132 (98–182)
SBP Δ reference–admission (mm Hg)	–23 (–126 to 66)	–19 (–88 to 43)	–28 (–126 to 66)	–23 (–53 to 37)
MAP reference (mm Hg)	88 (56–136)	91 (61–136)	87 (56–134)	84 (64–123)
MAP Δ reference–admission (mm Hg)	–17 (–101 to 50)	–15 (–56 to 46)	–18 (–101 to 50)	–22 (–55 to 21)
BP treatment admission-to-procedure				
None	146 (89.0)	68 (90.7)	69 (86.3)	9 (100)
BP-lowering (urapidil, clonidine)	16 (9.8)	7 (9.3)	9 (11.3)	0 (0)
BP-increasing (sympathomimetics)	2 (1.2)	0 (0)	2 (2.5)	0 (0)
Procedure mean SBP (mm Hg)	128 (69–192)	126 (83–168)	126 (67–192)	142 (106–158)
Procedure mean MAP (mm Hg)	91 (43–125)	92 (56–117)	89 (43–125)	96 (66–112)
Rates of BP excursions vs. ref. (n/10 min)†				
SBP >120%	1.09 (0–9.26)	1.21 (0–9.26)	0.93 (0–8.41)	1.63 (0–8.19)
MAP >120%	1.19 (0–9.74)	1.31 (0–8.92)	1.03 (0–9.74)	1.95 (0–8.75)
SBP <80%	0.97 (0–9.20)	1.26 (0–9.04)	0.82 (0–9.20)	0.66 (0–0.98)
MAP <80%	0.79 (0–8.91)	1.08 (0–8.91)	0.66 (0–8.22)	0.11 (0–0.11)
Inotropes during procedure	77 (46.9)	33 (44.0)	38 (47.5)	6 (66.7)

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Table 1. Continued

Characteristic	All patients	mRS 0–2	mRS 3–6	Missing mRS
Leptomeningeal collaterals				
Poor (<50% as on unaffected side)	32 (19.51)	6 (8.0)	24 (30.0)	2 (22.2)
Good (≥50% as on unaffected side)	132 (80.5)	69 (92.0)	56 (70.0)	7 (77.8)
Reperfusion success (TICI class 2b–3)	121 (73.8)	65 (86.7)	50 (62.5)	6 (66.7)
Control CT				
No infarction, no hemorrhage	18 (11.0)	11 (14.7)	6 (7.5)	1 (11.1)
Infarction only, no hemorrhage	117 (71.3)	53 (70.6)	56 (70.0)	8 (88.9)
Hemorrhage visible	29 (17.7)	11 (14.7)	18 (22.5)	0 (0)
Ischemic lesion volume (cm^3)	30.7 (0–518)	10.9 (0–466)	102 (0–518)	9.1 (0–127)
Post-procedure statin use	110 (67.5)	43 (57.3)	62 (77.5)	5 (62.5)

Values are presented as median (interquartile range) or number (%).
mRS, modified Rankin Scale; BP, blood pressure; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment classification; rtPA, recombinant human tissue plasminogen activator; SBP, systolic blood pressure; TICI, Thrombolysis in Cerebral Infarction; CT, computed tomography.
*mRS score: favorable (score 0 to 2) or poor (score 3 to 6); †Geometric mean ratio (interquartile range).

dure SPB/MAP appeared comparable, while rates of excursions to >120% or to <80% of the reference appeared higher in patients with mRS 0-2. Similar proportions of patients received sympathomimetics during EVT (Table 1). Patients with mRS 0-2 more frequently had good collaterals, were more frequently successfully reperfused, their ILV was lower and visible hemorrhages were less frequent. They were less frequently post-stroke statin users, likely due to confounding by indication (Table 1).

Full, reduced and final models were fitted to the outcome (see Supplementary Table 5 for complete models). Independent variables consistently not associated with mRS were consecutively removed (Figure 2). Final models are shown in Table 3. The rate of SBP/MAP excursions to <80% of the reference was not associated with the outcome (Table 3). When not accounting for ILV, higher rate of SBP/MAP excursions to >120%, TICI grade 2b-3, good collaterals and pre-index stroke statin use were associated with mRS 0-2 (Table 3, Model A). Higher on-admission NIHSS score, cardioembolic/unknown stroke etiology, post-index stroke statin use and older age were associated with lower odds of mRS 0-2 (Table 3, Model A). When accounted for, higher ILV was associated with lower odds of mRS 0-2 (Table 3, Model B). At the same time, the effects of SBP/MAP excursions, TICI grade and of collaterals were reduced to include unity (Table 3, Model B). Mediation analysis (Figure 4) showed an indirect (via ILV) association between higher rates of SBP/MAP excursions to >120% and mRS 0-2 (the same was shown for TICI 2b-3 and good collaterals).

Several models (Supplementary Table 5) indicated an interaction between the rate of SBP/MAP excursions to >120% and TICI grade: (1) a strong association between higher rates and mRS 0-2 in patients with TICI 2b-3 (n=115) and none in patients with TICI 0-2a (n=40) with point-estimates <1.0; (2) no association between TICI 2b-3 and mRS 0-2 in patients with zero excursion rates, with clear-cut associations between TICI 2b-3 and higher odds of mRS 0-2 at rates around 1.0/10 minutes and higher (Supplementary Table 5, Models final C, D). We consider final models without the interaction (Table 3) to more generally describe the data than the models with this (uncertain) interaction that did not indicate harms ascribable to SPB/MAP excursions (for the full rationale, see Supplementary Methods).

Discussion

We found that in anterior circulation stroke patients treated with EVT/rtPA, in whom BP was generally kept within the recommended limits, higher in-procedure SBP/MAP was associated with a better 3-month functional outcome. The findings are supported by the association of higher rates of in-procedure SBP/MAP excursions to >120% of the reference values, and of higher reference BP with mRS 0-2. The fact that no such association was observed for (higher) in-procedure mean BP is likely due to aliasing by the effects of a higher number of excursions over a high(er) reference value. A stronger association between BP excursions and in-procedure mean BP at higher reference BP supports such a view. Data also suggest associations between a higher rate of SBP/MAP excursions to >120% and lower ILV. Higher ILV was associated with lower odds of mRS 0-2, and mediation analysis that differentiates effects identifying indirect paths[21] plausible in a temporal and pathophysiological sense disclosed its mediator role: BP excursions

Table 2. Relationship between BP/BP excursions during endovascular thrombectomy to values exceeding ±20% of the reference BP and control computed tomography findings

Variable	Systolic blood pressure		Mean arterial pressure	
	GMR or OR (95% CI)	*P*	GMR or OR (95% CI)	*P*
Ischemic lesion volume				
Default independent variables[†,‡]				
Rate of BP >120% of reference (by 1/10 min)	0.72 (0.60–0.87)	<0.001	0.75 (0.63–0.90)	0.002
Rate of BP <80% of reference (by 1/10 min)	1.06 (0.91–1.25)	0.443	1.10 (0.93–1.31)	0.265
Reference BP (by 10 mm Hg)	1.01 (0.85–1.19)	0.911	0.86 (0.69–1.07)	0.181
Rate of BP excursions >120%*reference BP	0.86 (0.78–0.96)	0.006	0.95 (0.86–1.04)	0.264
On-admission NIHSS score (by 1 point)	1.06 (1.01–1.11)	0.014	1.06 (1.01–1.10)	0.021
TICI grade 2b-3 (vs. 0-2a)	0.36 (0.20–0.67)	0.001	0.36 (0.20–0.67)	0.042
Affected vessel: MCA1 vs. other	0.65 (0.36–1.17)	0.153	0.72 (0.40–1.29)	0.270
Collaterals ≥50% as unaffected side (vs. no)	0.33 (0.16–0.68)	0.002	0.33 (0.16–0.67)	0.003
Selected independent variables				
Men (vs. women)	1.84 (1.07–3.17)	0.028	1.78 (1.03–3.07)	0.038
Post-procedure visible hemorrhages[†,§]				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.03 (0.72–1.48)	0.855	1.10 (0.82–1.50)	0.479
Rate of BP <80% of reference (by 1/10 min)	0.80 (0.58–1.11)	0.183	0.77 (0.53–1.12)	0.178
Reference BP (by 10 mm Hg)	1.48 (0.99–2.28)	0.056	1.86 (1.00–3.47)	0.051
Procedure mean BP (by 10 mm Hg)	0.65 (0.40–0.96)	0.032	0.52 (0.26–0.95)	0.034
TICI grade 2b-3 (vs. 0-2a)	0.62 (0.25–1.53)	0.298	0.61 (0.25–1.50)	0.280
Selected independent variables				
Cardioembolic/unknown etiology (vs. LAA)	3.61 (0.81–28.8)	0.095	3.51 (0.64–19.4)	0.149
History of coronary heart disease	2.58 (1.04–6.42)	0.041	2.56 (1.03–6.38)	0.043

BP, blood pressure; GMR, geometric mean ratio; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; MCA, middle cerebral artery (segment 1 or 2); LAA, large artery atherosclerosis.
*The asterisk is a part of the interaction term; [†]Reduced models; [‡]GMR (95% CI); [§]OR (95% CI).

are directly associated with lower ILV, lower ILV is directly associated with a better functional outcome, excursions affect functional outcome "through" the effects on ILV.

The analysis has limitations common to similar recent reports on the topic[13-16]—it did not account for the post-procedural BP; it did not test specific BP targets but evaluated spontaneously occurring patterns, where some, otherwise possible patterns, might not have occurred. Also, data on the initial infarct volume were not available. This leaves space for the assumption that patients with a larger initial infarct volume might have been managed at lower BP levels (to avoid hemorrhagic transformation), while a less stringent BP management might have been in place in patients with lower volumes, thus spuriously "grouping" poorer outcomes and lower BP (large initial volume), and better outcomes and higher BP (smaller initial volume). However, all observed associations were adjusted for on-admission NIHSS and use of antihypertensives between admission and EVT. It is reasonable to consider that these two variables to a large extent subsumed the "impact" of the initial infarct volume: if higher on-admission NIHSS (a "proxy" for larger infarct volume) would "go" together with higher on-admission BP, it would be associated also with immediate use of antihypertensives. However, our data showed that (1) higher on-admission BP but not NIHSS was associated with antihypertensive use; (2) BP reduction from admission to EVT (adjusted for on-admission BP) was similar in patients treated and not treated with antihypertensives; (3) neither on-admission NIHSS nor the use of antihypertensives were associated with reference BP or with in-procedure mean BP. Taken together, the findings suggest that the observed BP patterns were likely a consequence of the intended management within the recommended limits, and were not driven by the initial stroke severity (i.e., initial infarct volume). Furthermore, we consider invasive frequent BP recordings, inclusion of unselected patients, uniform anesthesia, and accounting for a number of confounders to be the study strengths.

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Table 3. Relationship between BP/BP excursions during endovascular thrombectomy to values exceeding ±20% of the reference value and 3-month modified Rankin Scale score 0-2 (final models)

Variable	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Model A: without imaging outcomes				
Default independents				
Rate of BP >120% of reference (by 1/10 min)	1.33 (1.01–1.76)	0.038	1.30 (1.01–1.66)	0.029
Rate of BP <80% of reference (by 1/10 min)	0.85 (0.67–1.08)	0.174	0.85 (0.65–1.10)	0.218
Reference BP (by 10 mm Hg)	1.37 (1.06–1.77)	0.013	1.49 (1.06–2.08)	0.016
On-admission NIHSS score (by 1 point)	0.85 (0.78–0.93)	<0.001	0.86 (0.80–0.94)	<0.001
TICI grade 2b-3 (vs. 0-2a)	3.96 (1.34–11.7)	0.009	3.72 (1.26–11.0)	0.013
Collaterals ≥50% as unaffected side (vs. no)	4.62 (1.45–11.2)	0.007	4.71 (1.44–15.4)	0.006
Selected independents				
Cardioembolic/unknown etiology (vs. LAA)	0.25 (0.07–090)	0.026	0.22 (0.06–0.84)	0.018
Pre-index stroke statin use	5.88 (1.55–22.3)	0.005	4.71 (1.27–17.5)	0.013
Post-index stroke statin use	0.32 (0.12–0.82)	0.015	0.34 (0.13–0.87)	0.020
Age (by 10 yr)	0.69 (0.50–0.96)	0.020	0.72 (0.52–0.99)	0.039
Model B: including ischemic lesion volume				
Default independents				
Rate of BP >120% of reference (by 1/10 min)	1.25 (0.95–1.71)	0.114	1.22 (0.95–1.61)	0.115
Rate of BP <80% of reference (by 1/10 min)	0.88 (0.69–1.11)	0.291	0.89 (0.67–1.15)	0.371
Reference BP (by 10 mm Hg)	1.33 (1.02–1.77)	0.034	1.37 (0.97–1.97)	0.071
On-admission NIHSS score (by 1 point)	0.87 (0.79–0.95)	0.002	0.88 (0.81–0.96)	0.003
TICI grade 2b-3 (vs. 0-2a)	2.73 (0.89–9.10)	0.079	2.55 (0.83–8.46)	0.101
Collaterals ≥50% as unaffected side (vs. no)	2.95 (0.88–11.2)	0.080	3.04 (0.91–11.5)	0.071
Ischemic lesion volume (by 2.718-fold)	0.65 (0.50–0.83)	<0.001	0.66 (0.50–0.84)	<0.001
Selected independents				
Cardioembolic/unknown etiology (vs. LAA)	0.19 (0.05–0.69)	0.011	0.16 (0.04–0.62)	0.007
Pre-index stroke statin use	3.94 (1.08–16.8)	0.037	3.48 (0.97–14.8)	0.057
Post-index stroke statin use	0.34 (0.12–0.88)	0.026	0.33 (0.12–0.87)	0.025
Age (by 10 yr)	0.63 (0.43–0.87)	0.005	0.65 (0.45–0.90)	0.010

BP, blood pressure; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; LAA, large artery atherosclerosis.

Present findings apparently disagree with a similar recent report.[13] Individual in-procedure BP indicators (maximum, minimum, dips) were evaluated for association with 30-day mRS in 147 EVT-treated patients. In multivariate models (13 independents), higher maximum SBP was associated with lower odds of mRS 0-2. The only other significant effect was admission NIHSS, while collaterals, stroke etiology, ILV were not considered.[13] The cohort differed from ours in respect to anesthesia (46% GA), less common rtPA use (35.8%), fewer reperfusion successes (50%), lower mRS 0-2 achievement (17%), and fewer BP recordings (every 5 minutes).[13] The apparently discordant results might be due to these methodological and cohort differences.

Three further similar studies indirectly support the present findings but also oppose them in a way.[14-16] All three studies suggest benefits of "higher" in-procedure BP, but imply this indirectly by recognizing detrimental consequences of low(er) MAP, i.e., in-procedure MAP dips, which we could not confirm. In one study (EVT under GA), at least one episode of MAP decline >40% from the baseline value was associated with 3-month mRS 3-6, but time spent at this MAP level was not.[14] Another (smaller) analysis (EVT under GA) reported no association between the largest in-procedure MAP decline from the baseline value and 3-month mRS. However, lower (vs. baseline) average in-procedure MAP was associated with poorer mRS, while higher average MAP was associated with better mRS,[15]

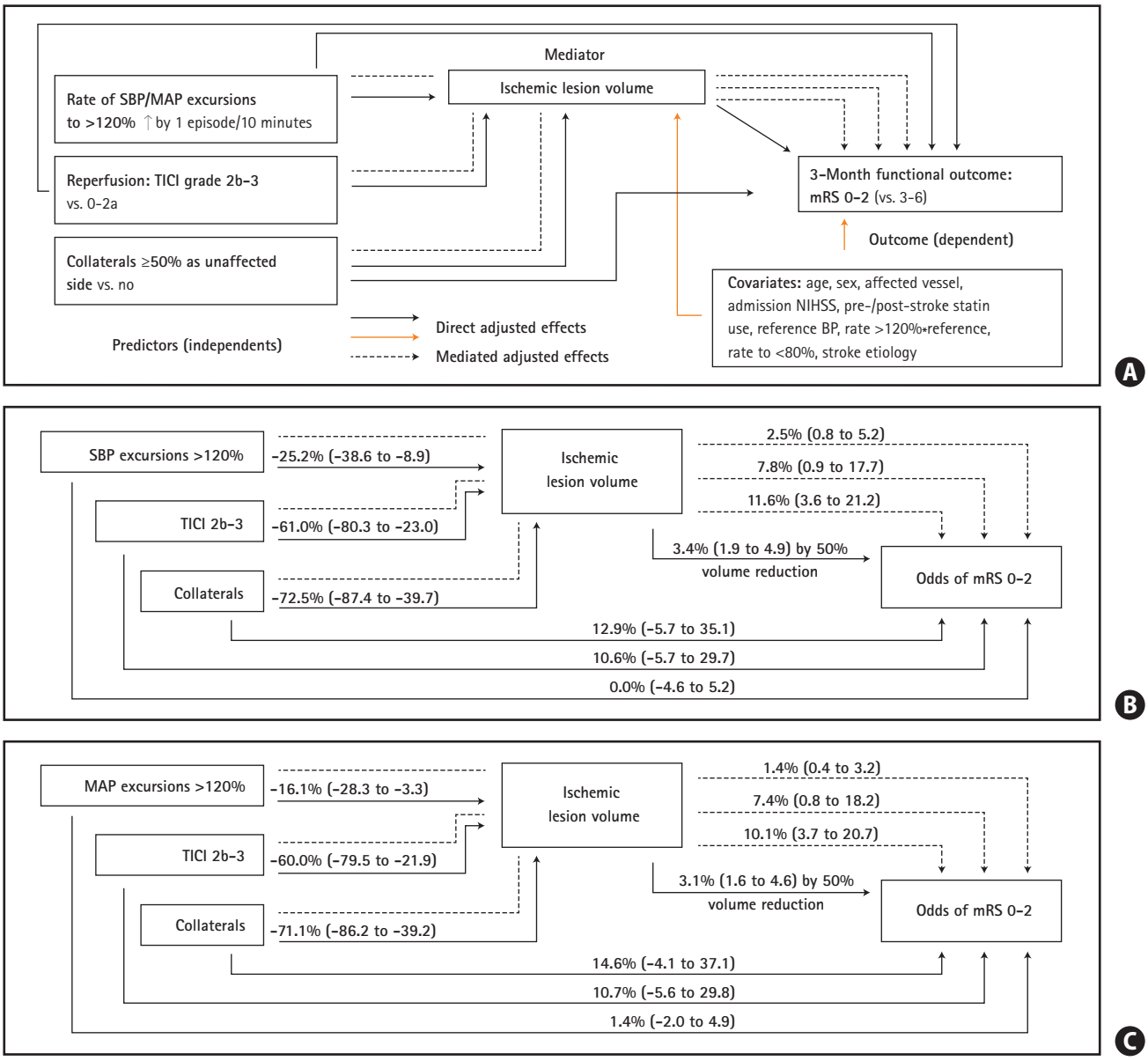

Figure 4. Mediation analysis: association of in-procedure systolic blood pressure (SBP) and mean arterial pressure (MAP) excursions to >120% of their reference values with 3-month modified Rankin Scale (mRS) score 0-2 is mediated through their association with the ischemic lesion volume (ILV). (A) Outline of associations. All associations are adjusted for all other model effects. Effects are from models analyzing ILV (Table 2) and mRS (Table 3). (B) Mediation model for SBP. (C) Mediation model for MAP. Higher rate of blood pressure (BP) excursions, Thrombolysis in Cerebral Infarction (TICI) scale grade 2b-3 and good collaterals are each directly associated with lower ILV; lower ILV is directly associated with higher odds of mRS 0-2; direct association of these predictors with mRS 0-2 is uncertain; each is associated with mRS 0-2 indirectly, via ILV. Effects are expressed as percent change in ILV or odds of mRS 0-2 with 95% confidence interval. NIHSS, National Institute of Stroke Scale.

thus being in line with present results. Detrimental effect of low(er) in-procedure MAP was suggested also in EVT under conscious sedation—lowest in-procedure MAP <100 mm Hg was associated with 3-month mRS 3-6.[16]

Despite methodological differences between the present and previous reports, there is evidence of detrimental consequences of low in-procedure MAP.[14-16] This is in apparent disagreement with the reported association between high(er) SBP during the first 24 hours post-EVT and poor functional outcomes.[9,22] It seems that management of BP in anterior circulation acute stroke patients undergoing EVT requires different strategies: one focused on in-procedure targets and prevention of excessive dips, the other focused on the post-procedural period targeting lower levels with a prompt management of excessive peaks.

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Conclusions

In the EVT-treated acute anterior circulation stroke patients in whom BP is managed within the currently recommended limits, a better functional outcome might be achieved by targeting in-procedure BP that exceeds the pre-procedure values by more than 20%.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2018.01305.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary Table 1. Routine laboratory test results taken on admission or within 24 hours, overall and by mRS score at 3 months

Variable	All patients	mRS 0–2	mRS 3–6	Missing mRS
Number	164	75	80	9
Serum creatinine (μmol/L)	77 (16–249)	76 (40–126)	85 (16–249)	73 (50–93)
Serum glucose (mmol/L)	6.6 (4.5–15.5)	6.2 (4.5–10.3)	7.1 (5.3–15.5)	6.4 (4.8–9.7)
Total cholesterol (mmol/L)	4.1 (2.0–7.8)	4.3 (2.5–6.4)	3.7 (2.0–7.8)	4.7 (2.8–5.2)
HDL-C (mmol/L)	1.1 (0.31–2.8)	1.1 (0.47–2.4)	1.1 (0.31–2.2)	1.7 (0.80–2.3)
LDL-C (mmol/L)	2.4 (0.52–4.7)	2.8 (0.59–4.5)	2.1 (0.52–4.7)	2.2 (1.7–3.9)
Triglycerides (mmol/L)	1.17 (0.34–4.55)	1.12 (0.46–4.55)	1.23 (0.34–3.23)	1.16 (0.56–2.08)
Fibrinogen (μmol/L)	9.9 (2.9–23.1)	9.9 (3.7–17.0)	10.0 (2.9–23.1)	10.3 (7.5–11.6)
C-reactive protein (mg/L)	0.36 (0.01–9.85)	0.29 (0.01–8.65)	0.46 (0.04–9.85)	0.38 (0.07–1.79)
Red blood cells ($\times 10^{12}$/L)	4.4 (2.8–5.7)	4.5 (3.4–5.4)	4.2 (2.8–5.7)	4.6 (3.9–5.1)
Hematocrit (%)	39.1 (24.8–52.1)	39.5 (24.9–46.4)	37.9 (24.6–52.1)	41.1 (35.4–45.6)
Platelets ($\times 10^{9}$/L)	220 (67–572)	229 (67–572)	212 (101–431)	224 (174–286)
White blood cells ($\times 10^{9}$/L)	8.1 (3.0–70.9)	8.2 (3.0–70.9)	8.4 (3.2–27.2)	7.4 (6.0–10.1)

Values are presented as median (interquartile range).
mRS, modified Rankin Scale; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Supplementary Table 2. Absolute (minutes) and relative (%) time spent with SBP and MAP >120% or <80% of the reference value, overall and by mRS score at 3 months

Variable	All patients	mRS 0–2	mRS 3–6	Missing mRS
Number	164	75	80	9
SBP >120% of reference (min)	8.6 (0–158)	8.6 (0–84)	8.6 (0–158)	7.3 (0–59)
MAP >120% of reference (min)	9.5 (0–223)	9.2 (0–127)	9.7 (0–223)	10.7 (0–63)
SBP <80% of reference (min)	8.9 (0–152)	9.0 (0–143)	8.9 (0–152)	7.6 (0–9)
MAP <80% of reference (min)	7.2 (0–160)	7.8 (0–75)	7.3 (0–160)	1 (0–1)
SBP >120% of reference (%)	10.9 (0–93)	12.1 (0–93)	9.3 (0–84)	16.3 (0–82)
MAP >120% of reference (%)	11.9 (0–97)	13.1 (0–89)	10.3 (0–97)	19.5 (0–88)
SBP <80% of reference (%)	9.6 (0–92)	12.3 (0–90)	8.2 (0–92)	6.6 (0–9.6)
MAP <80% of reference (%)	7.8 (0–89)	10.6 (0–89)	6.6 (0–82)	1 (0–1)

Values are presented as geometric mean (range).
SBP, systolic blood pressure; MAP, mean arterial pressure; mRS, modified Rankin Scale.

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Supplementary Table 3. Relationship between BP/BP excursions during EVT to values exceeding ±20% of the reference value and ischemic lesion volume (computed tomography scans)

Model	Systolic blood pressure		Mean arterial pressure	
	GMR (95% CI)	*P*	GMR (95% CI)	*P*
Full A: no interactions				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	0.78 (0.62–0.96)	0.021	0.79 (0.66–0.93)	0.006
Rate of BP <80% of reference (by 1/10 min)	1.02 (0.83–1.26)	0.845	1.11 (0.89–1.39)	0.342
Reference BP (by 10 mm Hg)	1.00 (0.76–1.31)	0.989	0.79 (0.53–1.17)	0.242
Procedure mean BP (by 10 mm Hg)†	0.92 (0.70–1.20)	0.538	1.06 (0.71–1.57)	0.772
Procedure duration (by 10 min)	1.01 (0.95–1.08)	0.764	1.02 (0.95–1.08)	0.639
BP measurements taken (by 10)	1.07 (0.98–1.17)	0.119	1.08 (0.99–1.17)	0.098
On-admission NIHSS score (by 1 point)	1.05 (1.00–1.11)	0.037	1.05 (1.00–1.10)	0.036
TICI grade 2b-3 (vs. 0-2a)	0.46 (0.24–0.91)	0.026	0.51 (0.26–0.98)	0.044
Affected vessel: MCA1 vs. MCA2	0.71 (0.25–1.98)	0.508	0.81 (0.29–2.23)	0.677
Affected vessel: MCA1 vs. tandem occlusion	0.70 (0.34–1.42)	0.316	0.73 (0.37–1.45)	0.371
Collaterals ≥50% as unaffected side (vs. no)	0.35 (0.17–0.74)	0.006	0.37 (0.18–0.76)	0.007
Antihypertensives before EVT (vs. no)	1.41 (0.55–3.56)	0.471	1.30 (0.53–3.23)	0.565
Selected independent variables‡				
Men (vs. women)	1.89 (1.08–3.32)	0.026	1.93 (1.11–3.34)	0.020
Model fit statistics (-2ResLL, AIC, BIC)	682.44, 712.44, 757.60		674.54, 704.54, 749.70	
Full B: with excursion*reference interactions				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	0.73 (0.57–0.92)	0.008	0.74 (0.58–0.93)	0.011
Rate of BP <80% of reference (by 1/10 min)	1.11 (0.81–1.52)	0.500	1.16 (0.87–1.54)	0.317
Reference BP (by 10 mm Hg)	0.88 (0.66–1.16)	0.358	0.75 (0.49–1.14)	0.178
Rate of BP excursions >120%*reference BP	0.86 (0.77–0.96)	0.008	0.96 (0.87–1.06)	0.404
Rate of BP excursions <80%*reference BP	0.98 (0.92–1.04)	0.492	0.98 (0.91–1.07)	0.710
Procedure mean BP (by 10 mm Hg)†	0.99 (0.75–1.29)	0.919	1.11 (0.74–1.67)	0.616
Procedure duration (by 10 min)	1.01 (0.95–1.07)	0.800	1.01 (0.95–1.08)	0.682
BP measurements taken (by 10)	1.06 (0.97–1.16)	0.171	1.07 (0.98–1.17)	0.109
On-admission NIHSS score (by 1 point)	1.05 (1.00–1.10)	0.041	1.05 (1.00–1.10)	0.052
TICI grade 2b-3 (vs. 0-2a)	0.47 (0.24–0.92)	0.027	0.51 (0.26–0.99)	0.046
Affected vessel: MCA1 vs. MCA2	0.86 (0.31–2.40)	0.874	0.85 (0.30–2.37)	0.748
Affected vessel: MCA1 vs. tandem occlusion	0.61 (0.30–1.24)	0.170	0.73 (0.36–1.45)	0.367
Collaterals ≥50% as unaffected side (vs. no)	0.37 (0.18–0.77)	0.008	0.37 (0.18–0.76)	0.007
Antihypertensives before EVT (vs. no)	1.50 (0.60–3.76)	0.380	1.33 (0.53–3.32)	0.539
Selected independent variables‡				
Men (vs. women)	1.88 (1.08–3.29)	0.026	1.91 (1.09–3.34)	0.024
Model fit statistics (-2ResLL, AIC, BIC)	693.63, 727.63, 778.58		691.64, 725.64, 776.59	
Full C: with excursions*TICI interactions				
Rate of BP >120% of reference*TICI grade	1.04 (0.75–1.44)	0.818	1.09 (0.81–1.48)	0.550
Rate of BP >120% at TICI 0-2a	0.71 (0.50–1.02)	-	0.85 (0.63–1.15)	-
Rate of BP >120% at TICI 2b-3	0.73 (0.57–0.94)	-	0.77 (0.65–0.93)	-
Rate of BP <80% of reference*TICI grade	0.87 (0.64–1.18)	0.365	0.87 (0.61–1.25)	0.456
Rate of BP <80% at TICI 0-2a	0.95 (0.70–1.27)	-	1.00 (0.70–1.42)	-
Rate of BP <80% at TICI 2b-3	1.06 (0.85–1.33)	-	1.15 (0.90–1.46)	-

Supplementary Table 3. Continued

Model	Systolic blood pressure		Mean arterial pressure	
	GMR (95% CI)	*P*	GMR (95% CI)	*P*
TICI grade 2b-3 (vs. 0-2a)	0.45 (0.23–0.90)	0.023	0.50 (0.25–0.96)	0.039
Reference BP (by 10 mm Hg)	1.01 (0.77–1.32)	0.961	0.80 (0.54–1.20)	0.284
Procedure mean BP (by 10 mm Hg)† (other effects were closely similar to A and B)	0.92 (0.70–1.21)	0.539	1.04 (0.70–1.55)	0.827
Model fit statistics (-2ResLL, AIC, BIC)	685.14, 719.14, 770.09		676.94, 710.94, 761.89	
Full D: with BP*TICI interactions				
Rate of BP >120% of reference (by 1/10 min)	0.72 (0.57–0.92)	0.009	0.79 (0.66–0.94)	0.007
Rate of BP <80% of reference (by 1/10 min)	1.00 (0.83–1.27)	0.809	1.11 (0.88–1.39)	0.372
TICI grade 2b-3 (vs. 0-2a)	0.48 (0.25–0.94)	0.033	0.51 (0.26–1.00)	0.050
Reference BP*TICI grade	0.92 (0.67–1.26)	0.619	0.91 (0.56–1.47)	0.704
Reference BP at TICI 0-2a	0.95 (0.68–1.33)	-	0.75 (0.46–1.22)	-
Reference BP at TICI 2b-3	1.03 (0.77–1.39)	-	0.82 (0.52–1.28)	-
Procedure mean*BP TICI grade	1.02 (0.66–1.58)	0.916	1.00 (0.54–1.86)	0.998
Procedure mean BP at TICI 0-2a	0.93 (0.61–1.41)	-	1.05 (0.59–1.86)	-
Procedure mean BP at TICI 2b-3 (other effects were closely similar to A and B)	0.91 (0.67–1.22)	-	1.05 (0.67–1.63)	-
Model fit statistics (-2ResLL, AIC, BIC)	694.74, 728.74, 779.69		685.49, 719.49, 770.44	
Reduced§				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	0.72 (0.60–0.87)	<0.001	0.75 (0.63–0.90)	0.002
Rate of BP <80% of reference (by 1/10 min)	1.06 (0.91–1.25)	0.443	1.10 (0.93–1.31)	0.265
Reference BP (by 10 mm Hg)	1.01 (0.85–1.19)	0.911	0.86 (0.69–1.07)	0.181
Rate of BP excursions >120%*reference BP	0.86 (0.78–0.96)	0.006	0.95 (0.86–1.04)	0.264
On-admission NIHSS score (by 1 point)	1.06 (1.01–1.11)	0.014	1.06 (1.01–1.10)	0.021
TICI grade 2b-3 (vs. 0-2a)	0.36 (0.20–0.67)	0.001	0.36 (0.20–0.67)	0.042
Affected vessel: MCA1 vs. other	0.65 (0.36–1.17)	0.153	0.72 (0.40–1.29)	0.270
Collaterals ≥50% as unaffected side (vs. no)	0.33 (0.16–0.68)	0.002	0.33 (0.16–0.67)	0.003
Selected independent variables‡				
Men (vs. women)	1.84 (1.07–3.17)	0.028	1.78 (1.03–3.07)	0.038
Model fit statistics (-2ResLL, AIC, BIC)	666.00, 688.00, 721.41		666.27, 688.27, 721.68	

Two types of models (each separately for systolic and mean arterial pressure) were fitted: "full" (with different interaction terms) and "reduced" (effects based on biological and statistical plausibility). Effects are GMRs (lesion volume was ln-transformed). GMRs for the interaction terms indicate whether the BP excursion effects were conditional on reference BP; or whether BP excursion effects and the effects of reference and procedure mean BP were conditional on the level of reperfusion (TICI grade).

BP, blood pressure; EVT, endovascular thrombectomy; GMR, geometric means ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; MCA, middle cerebral artery (segment 1 or 2); -2ResLL, 2 residual logarithmic likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion.

*The asterisk is a part of the interaction term; †Weighted mean as area under the BP-time curve divided by the time period covered; ‡By stepwise selection procedure (*P*<0.200 to enter/stay) among: age, sex, comorbidities, use of sympathomimetics during EVT, stroke etiology, time since symptom onset till the first vessel image, use of recombinant tissue plasminogen activator, pre-index stroke statin, antiplatelet or anticoagulant use; §Reduced model excluded interaction terms if no indication of moderation (for either systolic BP or mean arterial pressure), use of antihypertensives before EVT (highly insignificant and small number of treated patients), procedure mean BP (highly insignificant, determined by excursion rates, see Supplementary Analysis of Blood Pressure), procedure duration and number of BP measurements taken (highly insignificant). Affected vessel was dichotomized (MCA1/other).

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Supplementary Table 4. Relationship between BP/BP excursions during EVT to values exceeding ±20% of the reference value and finding of hemorrhages on post-procedure computed tomography scans

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Full A: no interactions				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.07 (0.72–1.52)	0.714	1.14 (0.82–1.57)	0.412
Rate of BP <80% of reference (by 1/10 min)	0.78 (0.55–1.06)	0.118	0.74 (0.49–1.06)	0.101
Reference BP (by 10 mm Hg)	1.56 (1.03–2.45)	0.036	2.00 (1.05–4.10)	0.034
Procedure mean BP (by 10 mm Hg)†	0.62 (0.38–0.94)	0.026	0.50 (0.24–0.94)	0.030
Procedure duration (by 10 min)	0.98 (0.67–1.08)	0.794	0.98 (0.67–1.08)	0.814
BP measurements taken (by 10)	1.05 (0.92–1.57)	0.561	1.04 (0.91–1.55)	0.585
On-admission NIHSS score (by 1 point)	1.02 (0.94–1.11)	0.629	1.02 (0.94–1.11)	0.567
TICI grade 2b-3 (vs. 0-2a)	0.76 (0.28–2.10)	0.590	0.74 (0.28–2.04)	0.560
Use of rtPA (vs. no)	0.76 (0.29–2.04)	0.572	0.78 (0.30–2.10)	0.609
Collaterals ≥50% as unaffected side (vs. no)	0.65 (0.23–1.92)	0.425	0.61 (0.22–1.79)	0.355
Antihypertensives before EVT (vs. no)	1.52 (0.31–5.87)	0.576	1.59 (0.32–6.14)	0.539
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	4.15 (0.91–35.1)	0.068	3.94 (0.87–33.9)	0.079
History of coronary artery disease	2.40 (0.92–6.19)	0.074	2.40 (0.91–6.22)	0.075
Model fit statistics (LL, AIC, BIC)	−68.059, 164.11, 207.52		−68.578, 165.15, 208.55	
Full B: with excursions*reference interactions				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.27 (0.82–1.90)	0.265	1.29 (0.81–1.98)	0.265
Rate of BP <80% of reference (by 1/10 min)	0.94 (0.55–1.53)	0.821	0.97 (0.59–1.49)	0.900
Reference BP (by 10 mm Hg)	1.61 (1.04–2.59)	0.033	2.31 (1.19–4.87)	0.014
Rate of BP excursions >120%*reference BP	1.20 (0.94–1.64)	0.153	1.05 (0.87–1.32)	0.641
Rate of BP excursions <80%*reference BP	0.94 (0.84–1.04)	0.269	0.86 (0.63–1.02)	0.088
Procedure mean BP (by 10 mm Hg)†	0.56 (0.33–0.87)	0.009	0.46 (0.21–0.90)	0.023
Procedure duration (by 10 min)	0.99 (0.67–1.08)	0.868	0.99 (0.65–1.08)	0.832
BP measurements taken (by 10)	1.06 (0.92–1.59)	0.467	1.06 (0.92–1.61)	0.474
On-admission NIHSS score (by 1 point)	1.03 (0.95–1.12)	0.528	1.03 (0.95–1.12)	0.489
TICI grade 2b-3 (vs. 0-2a)	0.71 (0.26–2.03)	0.529	0.76 (0.28–2.08)	0.583
Use of rtPA (vs. no)	0.85 (0.32–2.35)	0.748	0.85 (0.33–2.34)	0.748
Collaterals ≥50% as unaffected side (vs. no)	0.75 (0.26–2.31)	0.599	0.66 (0.23–1.98)	0.444
Antihypertensives before EVT (vs. no)	1.28 (0.25–5.16)	0.745	1.66 (0.32–6.71)	0.512
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	4.82 (0.94–47.4)	0.061	5.31 (1.04–53.3)	0.045
History of coronary artery disease	2.45 (0.93–6.42)	0.059	2.70 (1.01–7.21)	0.036
Model fit statistics (LL, AIC, BIC)	−66.167, 164.33, 213.93		−66.931, 165.86, 215.46	
Full C: with excursions*TICI interactions				
Rate of BP >120% of reference*TICI grade	1.69 (0.82–5.34)	0.170	1.41 (0.77–3.70)	0.303
Rate of BP >120% at TICI 0-2a	0.71 (0.30–1.67)	-	0.84 (0.40–1.80)	-
Rate of BP >120% at TICI 2b-3	1.21 (0.82–1.77)	-	1.19 (0.86–1.65)	-
Rate of BP <80% of reference*TICI grade	0.87 (0.54–1.41)	0.558	0.61 (0.25–1.13)	0.122
Rate of BP <80% at TICI 0-2a	0.86 (0.57–1.31)	-	0.96 (0.60–1.52)	-
Rate of BP <80% at TICI 2b-3	0.75 (0.51–1.11)	-	0.59 (0.32–1.09)	-

Supplementary Table 4. Continued

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
TICI grade 2b-3 (vs. 0-2a)	0.97 (0.32–2.95)	0.958	0.89 (0.30–2.64)	0.828
Reference BP (by 10 mm Hg)	1.51 (0.99–2.40)	0.053	1.91 (0.99–3.97)	0.052
Procedure mean BP (by 10 mm Hg)† (other effects were closely similar to A and B)	0.63 (0.38–0.95)	0.029	0.53 (0.25–0.99)	0.048
Model fit statistics (LL, AIC, BIC)	−66.756, 165.51, 215.11		−66.285, 164.56, 214.17	
Full D: with BP*TICI interactions				
Rate of BP >120% of reference (by 1/10 min)	1.06 (0.71–1.51)	0.763	1.09 (0.78–1.52)	0.582
Rate of BP <80% of reference (by 1/10 min)	0.79 (0.55–1.09)	0.159	0.77 (0.49–1.11)	0.172
TICI grade 2b-3 (vs. 0-2a)	0.87 (0.31–2.45)	0.799	0.91 (0.32–2.58)	0.853
Reference BP*TICI grade	0.77 (0.45–1.26)	0.296	0.62 (0.26–1.37)	0.241
Reference BP at TICI 0-2a	1.78 (1.07–2.95)	-	2.45 (1.07–5.60)	-
Reference at TICI 2b-3	1.36 (0.83–2.23)	-	1.53 (0.69–3.39)	-
Procedure mean BP*TICI grade	1.28 (0.66–2.64)	0.465	2.20 (0.79–7.32)	0.136
Procedure mean BP at TICI 0-2a	0.55 (0.29–1.01)	-	0.32 (0.12–0.87)	-
Procedure mean BP at TICI 2b-3 (other effects were closely similar to A and B)	0.70 (0.42–1.17)	-	0.70 (0.32–1.54)	-
Model fit statistics (LL, AIC, BIC)	−67.499, 166.99, 216.60		−67.439, 166.88, 216.48	
Reduced§				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.03 (0.72–1.48)	0.855	1.10 (0.82–1.50)	0.479
Rate of BP <80% of reference (by 1/10 min)	0.80 (0.58–1.11)	0.183	0.77 (0.53–1.12)	0.178
Reference BP (by 10 mm Hg)	1.48 (0.99–2.28)	0.056	1.86 (1.00–3.47)	0.051
Procedure mean BP (by 10 mm Hg)†	0.65 (0.40–0.96)	0.032	0.52 (0.26–0.95)	0.034
TICI grade 2b-3 (vs. 0-2a)	0.62 (0.25–1.53)	0.298	0.61 (0.25–1.50)	0.280
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	3.61 (0.81–28.8)	0.095	3.51 (0.64–19.4)	0.149
History of coronary heart disease	2.58 (1.04–6.42)	0.041	2.56 (1.03–6.38)	0.043
Model fit statistics (LL, AIC, BIC)	−69.109, 154.22, 179.02		−69.792, 155.58, 180.38	

Two types of models (each separately for systolic and mean arterial pressure) were fitted: "full" (with different interaction terms) and "reduced" (effects based on biological and statistical plausibility). Effects are ORs. ORs for the interaction terms indicate whether the BP excursion effects were conditional on reference BP; or whether BP excursion effects and the effects of reference and procedure mean BP were conditional on the level of reperfusion (TICI grade).
BP, blood pressure; EVT, endovascular thrombectomy; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; rtPA, recombinant tissue plasminogen activator; LAA, large artery atherosclerosis; LL, logarithmic likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion.
*The asterisk is a part of the interaction term; †Weighted mean as area under the BP-time curve divided by the time period covered; ‡By stepwise selection procedure (P<0.200 to enter/stay) among age, sex, comorbidities, use of sympathomimetics during EVT, stroke etiology, time since symptom onset till the first vessel image, type of affected vessel, pre-index stroke statin, antiplatelet or anticoagulant use; §Reduced model excluded interaction terms (no indication of qualitative moderation), use of antihypertensives before EVT (small number of treated patients & highly insignificant), existence of collaterals, use of rtPA, procedure duration and number of BP measurements taken since consistently highly insignificant.

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Supplementary Table 5. Relationship between BP/BP excursions during EVT to values exceeding ±20% of the reference value and favorable functional outcome at 3 months (mRS, score 0-2)

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Full A: without interactions				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.49 (1.05–2.23)	0.024	1.57 (1.12–2.35)	0.007
Rate of BP <80% of reference (by 1/10 min)	0.78 (0.54–1.07)	0.129	0.73 (0.47–1.05)	0.098
Reference BP (by 10 mm Hg)	1.63 (1.06–2.74)	0.023	2.29 (1.16–5.64)	0.014
Procedure mean BP (by 10 mm Hg)†	0.78 (0.46–1.18)	0.262	0.59 (0.23–1.17)	0.145
Procedure duration (by 10 min)	0.84 (0.41–1.05)	0.321	0.77 (0.36–1.03)	0.205
BP measurements taken (by 10)	1.10 (0.85–2.28)	0.743	1.18 (0.84–2.54)	0.610
On-admission NIHSS score (by 1 point)	0.86 (0.78–0.94)	<0.001	0.87 (0.79–0.94)	<0.001
TICI grade 2b-3 (vs. 0-2a)	3.14 (1.03–10.7)	0.043	2.74 (0.88–9.43)	0.082
Collaterals ≥50% as unaffected side (vs. no)	4.89 (1.48–19.1)	0.008	4.81 (1.44–18.9)	0.009
Antihypertensive before EVT (vs. no)	0.81 (0.19–3.23)	0.763	0.81 (0.19–3.27)	0.767
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.23 (0.06–0.82)	0.022	0.19 (0.04–0.72)	0.013
Pre-index stroke statin use	5.73 (1.58–25.1)	0.007	4.66 (1.27–20.5)	0.019
Post-index stroke statin use	0.30 (0.10–0.79)	0.014	0.30 (0.11–0.79)	0.015
Age (by 10 yr)	0.74 (0.51–1.04)	0.101	0.78 (0.54–1.09)	0.143
Model fit statistics (LL, AIC, BIC)	−71.406, 172.81, 218.46		−70.405, 170.81, 216.46	
Full B: with excursions*reference interaction				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.55 (1.01–2.47)	0.043	1.59 (1.03–2.64)	0.034
Rate of BP <80% of reference (by 1/10 min)	0.89 (0.55–1.40)	0.624	0.74 (0.44–1.15)	0.192
Reference BP (by 10 mm Hg)	1.72 (1.09–3.01)	0.017	2.30 (1.13–5.84)	0.019
Rate of BP excursions >120%*reference BP	1.00 (0.85–1.18)	0.995	1.01 (0.84–1.24)	0.948
Rate of BP excursions <80%*reference BP	0.97 (0.89–1.05)	0.409	1.00 (0.89–1.13)	0.969
Procedure mean BP (by 10 mm Hg)†	0.76 (0.44–1.17)	0.228	0.59 (0.23–1.18)	0.150
Procedure duration (by 10 min)	0.81 (0.38–1.04)	0.291	0.77 (0.36–1.04)	0.216
BP measurements taken (by 10)	1.14 (0.85–2.44)	0.672	1.18 (0.84–2.55)	0.616
On-admission NIHSS score (by 1 point)	0.86 (0.78–0.94)	<0.001	0.87 (0.79–0.94)	<0.001
TICI grade 2b-3 (vs. 0-2a)	3.16 (1.03–10.8)	0.043	2.73 (0.88–9.48)	0.084
Collaterals ≥50% as unaffected side (vs. no)	5.53 (1.61–23.0)	0.006	4.84 (1.43–19.4)	0.011
Antihypertensive before EVT (vs. no)	0.78 (0.18–3.15)	0.728	0.81 (0.19–3.29)	0.768
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.24 (0.06–0.85)	0.027	0.19 (0.04–0.74)	0.015
Pre-index stroke statin use	5.70 (1.59–24.4)	0.007	4.67 (1.27–20.7)	0.019
Post-index stroke statin use	0.29 (0.10–0.78)	0.003	0.30 (0.11–0.80)	0.015
Age (by 10 yr)	0.74 (0.51–1.04)	0.087	0.78 (0.54–1.09)	0.148
Model fit statistics (LL, AIC, BIC)	−71.059, 176.12, 227.86		−70.402, 174.80, 226.54	
Full C: with excursions*TICI interaction				
Rate of BP >120% of reference*TICI grade	7.72 (1.12–53.3)	0.038	2.44 (0.84–6.63)	0.080
Rate of BP >120% at TICI 0-2a	0.27 (0.04–1.75)	-	0.74 (0.28–1.99)	-
Rate of BP >120% at TICI 2b-3	2.10 (1.25–3.51)	-	1.81 (1.19–2.75)	-
Rate of BP <80% of reference*TICI grade	1.15 (0.70–1.89)	0.589	1.06 (0.57–1.96)	0.865

Supplementary Table 5. Continued

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Rate of BP <80% at TICI 0-2a	0.71 (0.41–1.22)	-	0.74 (0.39–1.40)	-
Rate of BP <80% at TICI 2b-3	0.82 (0.55–1.20)	-	0.78 (0.51–1.17)	-
Reference BP (by 10 mm Hg)	1.62 (1.02–2.79)	0.038	2.12 (1.08–5.12)	0.028
Procedure mean BP (by 10 mm Hg)†	0.78 (0.45–1.21)	0.292	0.65 (0.26–1.28)	0.238
TICI grade 2b-3 (vs. 0-2a) (other effects were closely similar to A and B)	7.36 (1.15–47.1)	0.035	3.67 (0.97–13.9)	0.056
Model fit statistics (LL, AIC, BIC)	−66.396, 166.79, 218.53		−67.909, 169.82, 221.56	
Full D: with BP*TICI interaction				
Rate of BP >120% of reference (by 1/10 min)	1.56 (1.03–2.38)	0.037	1.62 (1.08–2.41)	0.019
Rate of BP <80% of reference (by 1/10 min)	0.77 (0.53–1.11)	0.182	0.74 (0.49–1.12)	0.153
TICI grade 2b-3 (vs. 0-2a)	3.60 (1.09–11.8)	0.035	3.17 (0.93–10.8)	0.065
Reference BP*TICI grade	0.71 (0.42–1.19)	0.191	0.51 (0.21–1.21)	0.125
Reference BP at TICI 0-2a	2.16 (1.09–4.29)	-	3.97 (1.29–12.3)	-
Reference BP at TICI 2b-3	1.53 (0.92–2.55)	-	2.02 (0.88–4.61)	-
Procedure mean BP*TICI grade	1.45 (0.71–1.99)	0.310	2.76 (0.85–8.98)	0.093
Procedure mean BP at TICI 0-2a	0.57 (0.26–1.29)	-	0.26 (0.07–1.01)	-
Procedure mean BP at TICI 2b-3 (other effects were closely similar to A and B)	0.84 (0.50–1.39)	-	0.72 (0.30–1.73)	-
Model fit statistics (LL, AIC, BIC)	−70.385, 174.77, 226.51		−68.755, 171.51, 223.25	
Reduced A: no interactions, no CT findings§				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.44 (1.04–2.06)	0.026	1.38 (1.03–1.83)	0.023
Rate of BP <80% of reference (by 1/10 min)	0.78 (0.57–1.05)	0.101	0.84 (0.64–1.10)	0.193
Reference BP (by 10 mm Hg)	1.58 (1.07–2.48)	0.022	1.75 (1.00–3.07)	0.042
Procedure mean BP (by 10 mm Hg)†	0.84 (0.56–1.21)	0.360	0.80 (0.47–1.36)	0.405
On-admission NIHSS score (by 1 point)	0.86 (0.78–0.93)	<0.001	0.86 (0.79–0.94)	<0.001
TICI grade 2b-3 (vs. 0-2a)	4.12 (1.44–13.3)	0.008	3.85 (1.29–11.5)	0.011
Collaterals ≥50% as unaffected side (vs. no)	4.81 (1.53–17.6)	0.007	4.81 (1.43–16.1)	0.007
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.27 (0.07–0.92)	0.036	0.27 (0.07–0.97)	0.035
Pre-index stroke statin use	5.77 (1.64–24.2)	0.005	4.55 (1.24–16.7)	0.015
Post-index stroke statin use	0.29 (0.11–0.75)	0.010	0.31 (0.12–0.81)	0.013
Age (by 10 yr)	0.69 (0.49–0.94)	0.020	0.72 (0.52–0.99)	0.037
Model fit statistics (LL, AIC, BIC)	−73.084, 170.17, 206.69		−70.405, 170.81, 216.46	
Reduced B: no interactions, with CT findings§				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.40 (0.98–2.06)	0.059	1.31(0.96–1.80)	0.079
Rate of BP <80% of reference (by 1/10 min)	0.81 (0.57–1.11)	0.190	0.88 (0.66–1.18)	0.387
Reference BP (by 10 mm Hg)	1.56 (1.01–2.60)	0.042	1.61 (0.87–2.99)	0.111
Procedure mean BP (by 10 mm Hg)†	0.83 (0.52–1.24)	0.363	0.80 (0.44–1.44)	0.443
On-admission NIHSS score (by 1 point)	0.87 (0.79–0.95)	0.002	0.88 (0.81–0.96)	0.004
TICI grade 2b-3 (vs. 0-2a)	3.02 (0.95–10.6)	0.061	2.78 (0.86–8.97)	0.080
Collaterals ≥50% as unaffected side (vs. no)	3.12 (0.91–12.2)	0.071	3.27 (0.90–11.9)	0.061
Ischemic lesion volume (by 2.718-fold)	0.62 (0.46–0.80)	<0.001	0.62 (0.47–0.82)	<0.001
Post-procedure visible hemorrhages (vs. no)	1.87 (0.55–6.34)	0.314	1.88 (0.57–6.22)	0.298

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Supplementary Table 5. Continued

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.18 (0.04–0.68)	0.011	0.17 (0.04–0.70)	0.009
Pre-index stroke statin use	3.62 (0.97–15.7)	0.055	3.19 (0.82–12.5)	0.082
Post-index stroke statin use	0.31 (0.11–0.82)	0.018	0.31 (0.11–0.84)	0.017
Age (by 10 yr)	0.62 (0.42–0.87)	0.005	0.72 (0.52–0.99)	0.008
Model fit statistics (LL, AIC, BIC)	−66.213, 160.42, 203.03		−67.075, 162.15, 204.76	
Reduced C: with interaction, no CT findings§				
Default independent variables				
Rate of BP >120% of reference*TICI grade	8.03 (1.19–54.3)	0.033	2.64 (0.98–7.05)	0.053
Rate of BP >120% at TICI 0-2a	0.25 (0.04–1.56)	-	0.62 (0.24–1.59)	-
Rate of BP >120% at TICI 2b-3	1.98 (1.24–3.17)	-	1.64 (1.15–2.33)	-
Rate of BP <80% of reference (by 1/10 min)	0.81 (0.59–1.11)	0.182	0.80 (0.57–1.12)	0.202
Reference BP (by 10 mm Hg)	1.54 (1.00–2.38)	0.048	1.81 (1.01–3.62)	0.046
Procedure mean BP (by 10 mm Hg)†	0.86 (0.59–1.26)	0.447	0.80 (0.45–1.43)	0.458
On-admission NIHSS score (by 1 point)	0.84 (0.76–0.92)	<0.001	0.86 (0.79–0.94)	<0.001
TICI grade 2b-3 (vs. 0-2a)	11.1 (1.84–66.2)	0.008	5.30 (1.49–18.8)	0.010
Collaterals ≥50% as unaffected side (vs. no)	5.07 (1.47–17.5)	0.010	5.78 (1.68–19.9)	0.005
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.28 (0.07–1.12)	0.071	0.27 (0.07–1.07)	0.062
Pre-index stroke statin use	6.26 (1.52–25.7)	0.011	4.48 (1.18–17.1)	0.028
Post-index stroke statin use	0.25 (0.09–0.69)	0.007	0.28 (0.10–0.74)	0.011
Age (by 10 yr)	0.66 (0.47–0.93)	0.018	0.67 (0.45–0.95)	0.025
Model fit statistics (LL, AIC, BIC)	−68.076, 162.15, 201.72		−70.079, 166.16, 205.72	
Reduced D: with interaction and CT findings§				
Default independent variables				
Rate of BP >120% of reference*TICI grade‡	7.55 (0.91–62.3)	0.061	2.51 (0.92–6.81)	0.071
Rate of BP >120% at TICI 0-2a	0.24 (0.03–1.89)	-	0.61 (0.23–1.59)	-
Rate of BP >120% at TICI 2b-3	1.84 (1.13–3.00)	-	1.53 (1.05–2.21)	-
Rate of BP <80% of reference (by 1/10 min)	0.83 (0.59–1.16)	0.272	0.83 (0.57–1.19)	0.312
Reference BP (by 10 mm Hg)	1.52 (0.90–2.53)	0.056	1.71 (0.90–3.73)	0.103
Procedure mean BP (by 10 mm Hg)†	0.86 (0.56–1.30)	0.471	0.79 (0.41–1.52)	0.485
On-admission NIHSS score (by 1 point)	0.86 (0.78–0.96)	0.005	0.88 (0.80–0.97)	0.007
TICI grade 2b-3 (vs. 0-2a)	8.21 (1.07–62.8)	0.042	3.70 (0.95–14.4)	0.059
Collaterals ≥50% as unaffected side (vs. no)	3.33 (0.90–12.3)	0.072	3.88 (1.05–14.3)	0.042
Ischemic lesion volume (by 2.718-fold)	0.63 (0.48–0.83)	0.001	0.63 (0.48–0.84)	0.001
Post-procedure visible hemorrhages (vs. no)	1.75 (0.50–6.15)	0.380	1.63 (0.48–5.54)	0.435
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.19 (0.04–0.91)	0.036	0.17 (0.04–0.77)	0.021
Pre-index stroke statin use	3.91 (0.91–16.8)	0.066	3.18 (0.79–12.9)	0.104
Post-index stroke statin use	0.25 (0.09–0.73)	0.011	0.28 (0.10–0.77)	0.013
Age (by 10 yr)	0.60 (0.41–0.86)	0.006	0.60 (0.41–0.98)	0.009
Model fit statistics (LL, AIC, BIC)	−62.144, 154.29, 199.94		−64.446, 158.89, 204.54	
Final A: no interactions, no CT findings				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.33 (1.01–1.76)	0.038	1.30 (1.01–1.66)	0.029

Supplementary Table 5. Continued

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Rate of BP <80% of reference (by 1/10 min)	0.85 (0.67–1.08)	0.174	0.85 (0.65–1.10)	0.218
Reference BP (by 10 mm Hg)	1.37 (1.06–1.77)	0.013	1.49 (1.06–2.08)	0.016
On-admission NIHSS score (by 1 point)	0.85 (0.78–0.93)	<0.001	0.86 (0.80–0.94)	<0.001
TICI grade 2b-3 (vs. 0-2a)	3.96 (1.34–11.7)	0.009	3.72 (1.26–11.0)	0.013
Collaterals ≥50% as unaffected side (vs. no)	4.62 (1.45–11.2)	0.007	4.71 (1.44–15.4)	0.006
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.25 (0.07–090)	0.026	0.22 (0.06–0.84)	0.018
Pre-index stroke statin use	5.88 (1.55–22.3)	0.005	4.71 (1.27–17.5)	0.013
Post-index stroke statin use	0.32 (0.12–0.82)	0.015	0.34 (0.13–0.87)	0.020
Age (by 10 yr)	0.69 (0.50–0.96)	0.020	0.72 (0.52–0.99)	0.039
Model fit statistics (LL, AIC, BIC)	−73.504, 169.01, 202.48		−73.544, 169.09, 202.56	
Final B: no interactions, with lesion volume				
Default independent variables				
Rate of BP >120% of reference (by 1/10 min)	1.25 (0.95–1.71)	0.114	1.22 (0.95–1.61)	0.115
Rate of BP <80% of reference (by 1/10 min)	0.88 (0.69–1.11)	0.291	0.89 (0.67–1.15)	0.371
Reference BP (by 10 mm Hg)	1.33 (1.02–1.77)	0.034	1.37 (0.97–1.97)	0.071
On-admission NIHSS score (by 1 point)	0.87 (0.79–0.95)	0.002	0.88 (0.81–0.96)	0.003
TICI grade 2b-3 (vs. 0-2a)	2.73 (0.89–9.10)	0.079	2.55 (0.83–8.46)	0.101
Collaterals ≥50% as unaffected side (vs. no)	2.95 (0.88–11.2)	0.080	3.04 (0.91–11.5)	0.071
Ischemic lesion volume (by 2.718-fold)	0.65 (0.50–0.83)	<0.001	0.66 (0.50–0.84)	<0.001
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.19 (0.05–0.69)	0.011	0.16 (0.04–0.62)	0.007
Pre-index stroke statin use	3.94 (1.08–16.8)	0.037	3.48 (0.97–14.8)	0.057
Post-index stroke statin use	0.34 (0.12–0.88)	0.026	0.33 (0.12–0.87)	0.025
Age (by 10 yr)	0.63 (0.43–0.87)	0.005	0.65 (0.45–0.90)	0.010
Model fit statistics (LL, AIC, BIC)	−67.354, 158.71, 195.23		−67.863, 159.73, 196.25	
Final C: with interaction, no CT findings				
Default independent variables				
Rate of BP >120% of reference*TICI grade	8.42 (1.25–56.9)	0.029	2.80 (1.05–7.43)	0.039
Rate of BP >120% at TICI 0-2a	0.22 (0.04–1.35)	-	0.55 (0.23–1.36)	-
Rate of BP >120% at TICI 2b-3	1.84 (1.20–2.82)	-	1.55 (1.12–2.14)	-
TICI grade 2b-3 (vs. 0-2a) at 0 rate	1.01 (0.25–3.97)	-	1.33 (0.35–5.10)	-
TICI grade 2b-3 (vs. 0-2a) at 0.5/10 min	2.92 (0.92–9.27)	-	2.23 (0.71–7.03)	-
TICI grade 2b-3 (vs. 0-2a) at 1.0/min	8.48 (1.69–42.6)	-	3.73 (1.19–11.7)	-
TICI grade 2b-3 (vs. 0-2a) at mean rate	11.1 (1.84–66.2)	0.009	5.37 (1.52–18.9)	0.009
Rate of BP <80% of reference (by 1/10 min)	0.87 (0.69–1.11)	0.257	0.87 (0.67–1.12)	0.285
Reference BP (by 10 mm Hg)	1.36 (1.04–1.78)	0.026	1.50 (1.06–2.12)	0.022
On-admission NIHSS score (by 1 point)	0.84 (0.76–0.92)	<0.001	0.86 (0.78–0.93)	<0.001
Collaterals ≥50% as unaffected side (vs. no)	5.07 (1.47–17.5)	0.010	5.68 (1.67–19.4)	0.009
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.28 (0.07–1.12)	0.072	0.26 (0.06–1.03)	0.054
Pre-index stroke statin use	6.26 (1.52–25.7)	0.011	4.66 (1.22–17.8)	0.025
Post-index stroke statin use	0.25 (0.09–0.69)	0.007	0.29 (0.11–0.78)	0.014
Age (by 10 yr)	0.66 (0.47–0.93)	0.017	0.67 (0.48–0.95)	0.025
Model fit statistics (LL, AIC, BIC)	−68.374, 160.75, 197.27		−70.370, 164.74, 201.26	

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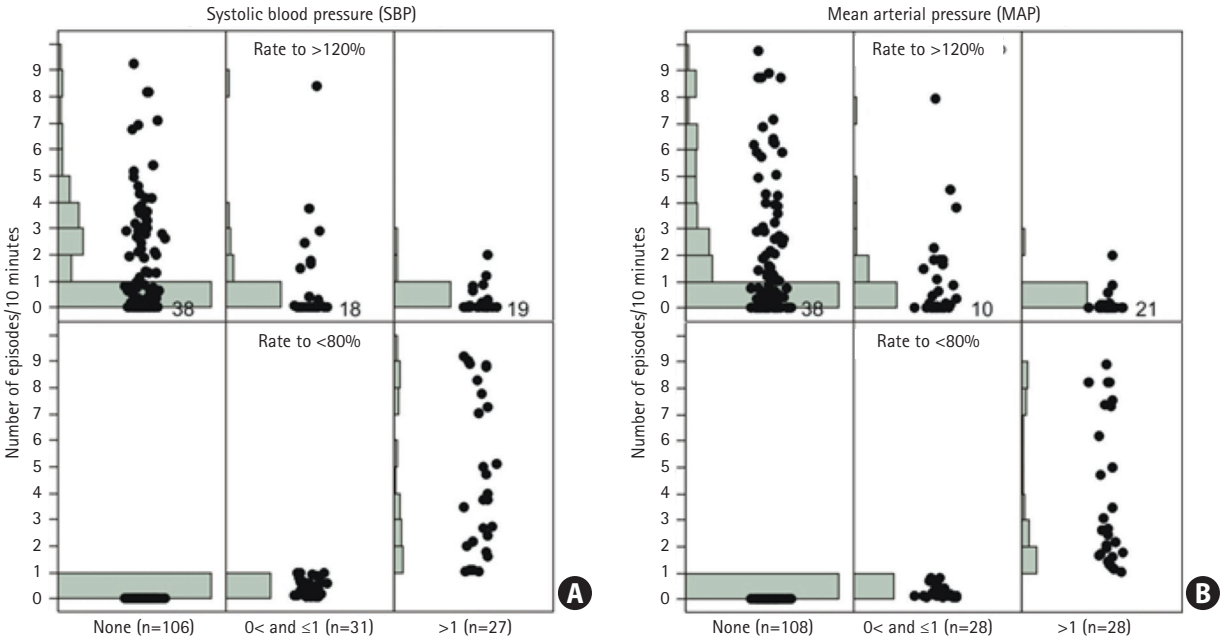
Supplementary Table 5. Continued

Model	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Final D: with interaction, with lesion volume				
Default independent variables				
Rate of BP >120% of reference*TICI grade	7.86 (0.99–62.1)	0.051	2.73 (1.02–7.31)	0.046
Rate of BP >120% at TICI 0-2a	0.21 (0.03–1.55)	-	0.53 (0.21–1.31)	-
Rate of BP >120% at TICI 2b-3	1.67 (1.08–2.60)	-	1.43 (1.03–2.01)	-
TICI grade 2b-3 (vs. 0-2a) at 0 rate	0.77 (0.18–3.20)	-	0.94 (0.23–3.83)	-
TICI grade 2b-3 (vs. 0-2a) at 0.5/10 min	2.16 (0.62–7.56)	-	1.55 (0.46–5.24)	-
TICI grade 2b-3 (vs. 0-2a) at 1.0/min	6.05 (0.99–36.6)	-	2.56 (0.76–8.64)	-
TICI grade 2b-3 (vs. 0-2a) at mean rate	7.21 (1.29–59.1)	0.021	3.64 (0.96–13.8)	0.057
Rate of BP <80% of reference (by 1/10 min)	0.89 (0.69–1.13)	0.341	0.89 (0.68–1.15)	0.389
Reference BP (by 10 mm Hg)	1.33 (1.01–1.79)	0.040	1.39 (0.98–2.02)	0.067
On-admission NIHSS score (by 1 point)	0.86 (0.77–0.95)	0.002	0.88 (0.80–0.96)	0.004
Collaterals ≥50% as unaffected side (vs. no)	3.35 (0.97–13.2)	0.056	3.81 (1.11–14.9)	0.033
Ischemic lesion volume (by 2.718-fold)	0.66 (0.51–0.85)	0.001	0.66 (0.51–0.85)	0.001
Selected independent variables‡				
Cardioembolic/unknown etiology (vs. LAA)	0.22 (0.05–0.85)	0.028	0.19 (0.04–0.85)	0.015
Pre-index stroke statin use	4.28 (1.08–19.6)	0.038	3.44 (0.92–15.1)	0.068
Post-index stroke statin use	0.27 (0.09–0.74)	0.010	0.29 (0.10–0.78)	0.013
Age (by 10 yr)	0.61 (0.41–0.86)	0.004	0.61 (0.41–0.87)	0.005
Model fit statistics (LL, AIC, BIC)	−62.945, 151.89, 191.45		−65.136, 156.27, 195.83	

Three types of models (each separately for systolic and mean arterial pressure) were fitted: "full" (with different interaction terms), "reduced" and "final" (based on biological and statistical plausibility). Intermediate radiological outcomes were introduced to "reduced models". Effects are ORs. ORs for the interaction terms indicate whether the BP excursion effects were conditional on reference BP; or whether BP excursion effects and the effects of reference and procedure mean BP were conditional on the level of reperfusion (TICI grade).

BP, blood pressure; EVT, endovascular thrombectomy; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; LAA, large artery atherosclerosis; LL, logarithmic likelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion; CT, computed tomography.

*The asterisk is a part of the interaction term; †Weighted mean as area under the blood pressure-time curve divided by the time period covered; ‡By stepwise selection procedure (P<0.200 to enter/stay) among: age, sex, comorbidities (hypertension, atrial fibrillation, any form of occlusive arterial disease, diabetes, heart or renal failure), stroke etiology, type of the affected vessel, use of recombinant tissue plasminogen activator, time elapsed since symptom onset till first vessel image, pre- and post-index stroke use of statins, use of sympathomimetics during EVT; §Reduced models excluded interaction terms not indicative of qualitative moderation, use of antihypertensives before EVT (small number of treated patients & highly insignificant), procedure duration and number of BP measurements taken (consistently highly insignificant). Final models further excluded procedure mean BP (highly insignificant, determined by excursion rates, see Supplementary Analysis of Blood Pressure) and presence of post-procedure hemorrhages (consistently highly insignificant).



Supplementary Figure 1. Rates of blood pressure excursions during endovascular procedure to >120% or to <80% of the reference. Patients are classified by the rate of episodes (n/10 minutes) to <80% as those with none, up to 1 and >1 episode/10 minutes, while actual rates are given on the y-axis: rates to >120% of the reference (upper panel) and to <80% of the reference (lower panel). Dots are individual data, shaded bars illustrate frequency of rates and numbers are counts of patients with no excursions to >120% of the reference.

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Supplementary Methods

Data analysis: multivariate model building procedures

Building of all multivariate models was guided by the following general rationale: (a) indicators of in-procedure blood pressure (BP)/BP excursions from the reference value are independent variables of interest. All other potential independent variables serve to improve the control of confounding; (b) the sample size is rather limited, so models can sustain a limited number of independent variables; (c) selection of adjustments needs to follow (i) the nature of the independent variables of interest—they might be affected by procedure duration (i.e., have a "time component"), as well as by the number of measurements taken. BP excursions are defined in respect to reference values; hence, may be influenced by them; (ii) (patho)physiological rationale—certain factors, e.g., stroke severity at presentation (National Institutes of Health Stroke Scale [NIHSS] score), affected vessel(s), existence of leptomeningeal collaterals, use of pharmacological fibrinolysis (recombinant tissue plasminogen activator [rtPA]), the level of achieved reperfusion (Thrombolysis in Cerebral Infarction [TICI] grade [TICI 2b-3=success; TICI 0-2a=failure]) may or are known to reflect on the control computed tomography findings (ischemic lesion volume [ILV], visible hemorrhages) and/or the 3-month functional outcome (modified Rankin Scale [mRS] score 0-2=favorable vs. 3-6=poor); hence, should be accounted for in the analysis of the respective outcomes; (iii) statistical significance—within the sample, some patient characteristics might be a source of confounding although without any obvious biological rationale and should be accounted for simply based on statistical significance; (d) consequently, all models need to include some adjustments by default, while others may be selected based on statistical significance; (e) some interactions need to be evaluated: is the potential effect of BP excursions from the reference value conditional on the reference value?; is it conditional on the level of reperfusion (TICI grade)?; is the potential effect of the reference or in-procedure BP conditional on the level of reperfusion?; (f) there is a risk of overfitting; hence, models should be selected based on biological and statistical plausibility.

The logic and algorithm of model selection is depicted in Figure A. For all outcomes, i.e., imaging (intermediate) (ILV, post-procedure hemorrhages) and the primary clinical endpoint (mRS score 0-2), the procedure started by fitting "full" models including a range of default and selected variables. The initial model contained only main effects and further models sequentially tested interactions of interest. In the next step, models were "reduced" to keep independent variables of interest and biologically and statistically plausible covariates required to demonstrate hypothesized independent associations or lack of such associations. Imaging outcomes were considered as independent variables in the analysis of the 3-month mRS, but were not included in the full models; they were introduced to "reduced" models. Hence, model selection in the analysis of the primary clinical endpoint included a further step of selecting the "final" models.

All full models included the following same "base" default independent variables: rate of excursions to >120% and to <80% of the reference BP, reference BP, weighted mean in-procedure BP, procedure duration (may also be a "proxy" of a more severe stroke/larger occlusion), number of in-procedure BP measurements, reperfusion success (TICI grade 2b-3 or 0-2a), existence of leptomeningeal collaterals ≥50% as on the unaffected side, on-admission NIHSS score and whether antihypertensive treatment was administered between admission and endovascular thrombectomy (EVT). Since data on the initial infarct volume were not available, we considered that on-admission NIHSS could be reasonably considered an independent that largely included (subsumed) the impact of the initial volume. We included also the use of antihypertensives between admission and EVT based on the following reasoning: decision to administer antihypertensives and subsequent (during EVT) decision to keep BP at lower levels/prevent excursions to higher values might have been guided by a larger (initial) infarct volume in order to prevent hemorrhagic transformation, and hence a spurious association between "better outcomes" (ILV, hemorrhages, 3-month functional outcome) and higher in-procedure BP, or "poorer outcomes" and lower in-procedure BP could be inferred. Therefore, on-admission NIHSS and use of antihypertensives between admission and EVT served as a kind of "proxy" to subsume the initial volume effects. A separate detailed analysis of on-admission BP, use of antihypertensives before EVT, use of sympathomimetics during EVT, weighted mean in-procedure BP and BP excursions was also performed (Supplementary Analysis of Blood Pressure).

In the analysis of the ILV, default adjustments additionally included the type of the affected vessel (middle cerebral artery segment 1 or segment 2, or involvement of internal carotid artery, i.e., tandem occlusion), while in the analysis of the presence of visible hemorrhages this was replaced with the use of rtPA as it seemed more plausible to account for a known risk factor for intracerebral hemorrhage. Only "base" default independent variables were included in the full models analyzing the 3-month functional outcome (probability of mRS 0-2 [vs. 3-6]).

In all full models, considered for inclusion through a stepwise selection procedure (P<0.200 to enter/stay) were: age, sex, comorbidities (hypertension, atrial fibrillation, any form of occlusive arterial disease, diabetes, heart or renal failure), stroke etiology by Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (dichotomized as cardioembolic or unknown vs. large artery atherosclerosis), time elapsed since symptom onset till the first vessel image, type of the affected vessel (if not by default), use of rtPA (if not by default), use of sympathomimetics during EVT and pre-index stroke statin use. In the analysis of ILV and visible hemorrhages considered were also pre-index stroke use of antiplatelets and anticoagulants, while in the analysis of the 3-month functional outcome post-procedure use of statins was considered instead.

Analysis of the 3-month functional outcome indicated a statistically significant interaction between the rate of BP excursions to >120% of the reference and TICI grade achieved (Figure A), suggesting no association between excursions and the outcome in patients with TICI grade 0-2a and a strong association of a higher rate with higher odds of mRS 0-2 in patients with TICI grade 2b-3 (Supplementary Table 5). Conversely, it indicated no association between TICI 2b-3 and mRS 0-2 in patients with no BP excursions to >120% of the reference, and increasingly stronger association with higher odds of mRS 0-2 with the increasing rate of excursions (Supplementary Table 5, Model final C, D). However, since there were only 40 patients with TICI 0-2a, only 10 of whom achieved mRS 0-2, there is some uncertainty about this interaction. Therefore, two types of "final" models were generated (Figure A): not accounting and accounting for this interaction. We consider that models without the interaction generally better describe the data due to the mentioned uncertainty and: (a) lack of indication that systolic blood pressure (SBP)/mean arterial pressure (MAP) excursions in the subset of patients with TICI 0-2a were harmful—similar proportions of those with mRS 0-2 (4/10, 40% for SBP, 20% for MAP) and those with mRS 3-6 (20/30, 33.3% for SBP, 20% for MAP) had zero BP excursion rates to >120% of the reference; (b) higher reference SBP/MAP was consistently associated with higher odds of mRS 0-2, both in patients with TICI 0-2a and with TICI 2b-3 (Supplementary Table 5); (c) at the start of EVT, TICI outcome is unknown. Present data indicate a potential benefit of higher rates of SBP/MAP excursions to >120% and, at worst, no benefit (but no harm); (d) differences in formal statistical indicators of model fits (Bayesian information criterion [BIC]) between the final models without and with the interaction term were minor (Supplementary Table 5, Models final A and B vs. C and D). Finally, each of these models was fitted without and with an account for ILV (Figure A). Namely, higher ILV was consistently associated with lower odds of mRS 0-2 in the "reduced" and "final" models (Supplementary Table 5), but introduction of ILV had another consequence: strength of association between mRS 0-2 and several independent variables (BP excursion rates to >120%, existence of good collaterals, TICI grade, pre-index stroke statin use) was considerably reduced or the association was no more apparent (Supplementary Table 5). This phenomenon is typical for "mediator" variables and a possibility of mediated (via ILV) associations between BP excursion rates, existence of collaterals and TICI grade and 3-month mRS 0-2 appeared plausible: all these variables were also independently associated with

ILV (Supplementary Table 3). Mediation analysis was performed specifically to test the hypothesis of an indirect association between in-procedure BP excursions to >120% of the reference and the 3-month functional outcome *via* ILV (BP excursions → ILV → 3-month mRS) with adjustments included in the "reduced" model analyzing ILV and "final" (without interactions) model analyzing mRS 0-2.

	Intermediate (computed tomography [CT]) outcomes		Primary clinical endpoint
Types of models	**Ischemic lesion volume (ILV)**	**Post-procedure visible hemorrhages**	**mRS at 3 months 0-2 (vs. 3-6)**
FULL **Initial:** default and selected independents, main effects, no interactions **Sequentially testing interactions:** a) rate of BP excursions*reference BP; b) rate of excursions*TICI grade; c) reference BP*TICI, in-procedure mean BP*TICI	• **Default:** rate of BP excursions to >120% of the reference, rate of excursions to <80%, reference BP, in-procedure mean BP, EVT duration, number of BP measurements taken, on-admission NIHSS score, TICI grade, affected vessel, collaterals ≥50% as unaffected side, use of antihypertensives before EVT • **Selected:** sex	• **Default:** rate of BP excursions to >120% of the reference, rate of excursions to <80%, reference BP, in-procedure mean BP, EVT duration, number of BP measurements taken, on-admission NIHSS score, TICI grade, use of antihypertensives before EVT • **Selected:** stroke etiology, history of coronary artery disease	• **Default:** rate of BP excursions to >120% of the reference, rate of excursions to <80%, reference BP, in-procedure mean BP, EVT duration, number of BP measurements taken, on-admission NIHSS score, TICI grade, collaterals ≥50% as unaffected side, use of antihypertensives before EVT • **Selected:** stroke etiology, pre-/post-stroke statin use, age
REDUCED Keep: a) excursion rates (primary interest); b) biologically & statistically plausible other effects (default or selected, interactions)	**Kept effects:** rate of BP excursions to >120%, rate of BP excursions to <80%, reference BP, rate to >120%*reference BP interaction, NIHSS score, TICI grade, collaterals, sex	**Kept effects:** rate of BP excursions to >120%, rate of BP excursions to <80%, reference BP, in-procedure mean BP, NIHSS score, TICI grade, stroke etiology, history of coronary artery disease	**A. Without interaction and CT outcomes** **Kept effects:** rate of BP excursions to >120% rate of BP excursions to <80%, reference BP, in-procedure mean BP, NIHSS score, TICI grade, collaterals, stroke etiology, pre-/post-stroke statin use, age **B. Without interaction, with CT outcomes** As A+ILV and hemorrhages **C. With interaction, without CT outcomes** As A+rate to >120%*TICI interaction **D. With interaction and CT outcomes** As C+ILV and hemorrhages
FINAL Further model reduction by final exclusion of the initial default effects and apparently irrelevant CT findings			**A. Without interaction and CT outcomes** **Kept effects:** rate of BP excursions to >120% rate of BP excursions to <80%, reference BP, NIHSS score, TICI grade, collaterals, stroke etiology, pre-/post-stroke statin use, age **B. Without interaction and CT outcomes** As A+ILV **C. With interaction, Without CT outcomes** As A+rate to >120%*TICI interaction **D. With interaction and CT outcomes** As C+ILV

Figure A. Schematic representation of the model selection strategy. All models were fitted separately for systolic blood pressure and mean arterial pressure. mRS, modified Rankin Scale; BP, blood pressure; TICI, Thrombolysis in Cerebral Infarction; EVT, endovascular thrombectomy; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator.

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Supplementary Analysis of Blood Pressure

Relationship between on-admission blood pressure (BP), BP at the start of endovascular thrombectomy (EVT), use of BP-related treatments between admission and EVT, use of sympathomimetics during EVT, weighted mean BP during EVT and rate of BP oscillations

Most subjects received no BP-related treatment between admission and EVT (n=146), two subjects received sympathomimetics and 16 received BP-lowering treatment (15 received 5 to 75 mg of urapidil intravenously, 1 received 50 mg urapidil+0.075 mg clonidine subcutaneously). The latter subset was characterized by numerically higher on-admission systolic blood pressure (SBP) and mean arterial pressure (MAP) and a greater average within-subject decline in SBP and MAP between admission and EVT (reference BP values appeared comparable across subsets) (Table A). Similar proportions of subjects received sympathomimetics during EVT (Table A).

We undertook the following analyses:

1. Identification of on-admission characteristics associated with the use of antihypertensives between admission and EVT
2. Identification of factors associated with the extent of blood pressure change between admission and start of EVT
3. Relationship between on-admission BP and BP at the start of EVT ("reference BP")
4. Identification of on-admission characteristics and factors occurring between admission and EVT associated with the use of sympathomimetics during EVT
5. Identification of factors associated with weighted mean BP during EVT and BP excursions to >120% or <80% of the reference BP during EVT

1. On-admission characteristics associated with the use of antihypertensives between admission and EVT

The use of antihypertensive treatment between admission and start of EVT was considered a binary dependent variable (the two patients who received sympathomimetics were considered as "not treated with antihypertensives"), and was analyzed in a logistic model. It included three default independent variables: on-admission SBP, on-admission MAP, and clinical stroke severity on admission (National Institutes of Health Stroke Scale [NIHSS] score). Demographics, medical history, comorbidity, type of affected vessel (dichotomized as middle cerebral artery segment 1 vs. other) and whether recombinant tissue plasminogen activator (rtPA) was used along EVT were considered as potential independent variables through a stepwise selection procedure with $P<0.200$ to enter/stay in the model. Results are summarized in Table B. Higher on-admission SBP was associated with higher odds of being administered antihypertensives, while pre-stroke anticoagulant use and middle cerebral artery segment 1 occlusion were associated with lower odds. MAP and stroke severity at presentation did not appear associated with the odds of administration of antihypertensives between admission and EVT.

2. Factors associated with the extent of BP change between admission and start of EVT

The extent of intra-individual BP change between admission and start of EVT (Δ reference – on-admission BP) was considered a dependent variable, separately for SBP and MAP. Two models were fitted—Model 1 did not include on-admission BP value, while Model 2 included this adjustment as well. Model 1 included two default independent variables—age and antihypertensive treatment; Model 2 included three default independent variables—age, use of antihypertensives and on-admission BP value. Other effects were selected through backward elimination ($P<0.200$) from a full model including demographic and medical history data, use of rtPA, time-lag between admission BP and reference BP measurement, affected vessel and on-admission NIHSS score. Results are summarized in Table C. When not accounting for on-admission BP (Table C, Model 1), patients who received antihypertensive treatment between admission and start of EVT experienced a considerably greater reduction in BP (vs. those who did not): by around 26 mm Hg greater reduction in SBP and by around 15 mm Hg greater reduction in MAP. There appeared also a tendency towards a greater BP reduction in older subjects. However, when on-admission BP was taken into consideration (Table C, Model 2), the difference between antihypertensive-treated and not-treated patients was several-fold reduced and appeared minor. The effect of age was also reduced. By 1 mm Hg higher on-admission BP (both SBP and MAP) was associated with by close to 1 mm Hg greater BP reduction.

3. Relationship between on-admission BP and BP at the start of EVT ("reference BP")

To evaluate the relationship between on-admission and reference BP (ln-transformed dependent variable), a model was fitted to data with on-admission NIHSS score, use of antihypertensives between admission and EVT and on-admission BP as independent variables. On-admission values were mean-centered (to avoid collinearity) since the model explored potential linear and quadratic relationship, and also included interaction terms between on-admission BP and use of antihypertensives to assess potential dissimilarities between on-admission and reference BP relationship in patients treated and not treated with antihypertensives. Results are summarized in Table D. Figure B shows scatterplot of individual data and adjusted linear and quadratic regression lines overall and by subsets of patients in respect to antihypertensive treatment between admission and start of EVT (separately for SBP and MAP). Considering both SBP and MAP, there appeared no association between on-admission NIHSS score and reference BP, while differences between patients who received and who did not receive antihypertensives between admission and EVT were minor (Table D).

Regarding SBP, there was a linear association between higher on-admission and higher reference systolic BP ($P=0.024$) and a stronger quadratic association ($P=0.004$) (Table D). Adjusted linear regression lines are depicted in Figure BA. The interaction terms between on-admission BP and antihypertensive treatment were insignificant suggesting a similar relationship between on-admission and reference BP in patients not treated and treated with antihypertensives (Table D). In both subsets, there was a linear and a stronger quadratic association between on-admission and reference BP (Table D). Adjusted regression lines are depicted in Figure BB.

Regarding MAP, graphically (Figure BA), there appeared a linear and a quadratic association between on-admission BP and reference BP, but in this model neither appeared significant (Table D). Interaction terms between antihypertensive treatment and on-admission BP did not indicate substantial differences in on-admission-to-reference BP relationship in subsets of patients treated or not treated with antihypertensives between admission and EVT. Numerically, coefficients were similar (Table D), but a "near-significant" linear ($P=0.055$) and a stronger quadratic ($P=0.019$) relationship was observed only in the larger subset of non-treated patients (Table D). Adjusted regression lines for the two subsets of patients are depicted in Figure BB.

4. Factors between admission and EVT associated with the use of sympathomimetics during EVT

Logistic model was fitted to a binary dependent variable "sympathomimetic use during EVT" with reference BP (systolic, MAP), age, admission NIHSS, use of rtPA, use of antihypertensives between admission and EVT, type of affected vessel and use of antihypertensives type of affected vessel interaction. Results are summarized in Table E.

There appeared no association between the use of sympathomimetics during EVT and reference systolic BP or MAP, stroke severity, use of rtPA, use of antihypertesives before EVT and age. Subjects suffering a middle cerebral artery (MCA) 1 stroke were less likely to receive sympathomimetics during EVT –similarly in patients who received and who did not receive antihpyertensives before EVT.

5. Factors associated with weighted mean BP during EVT and BP excursions to >120% or <80% of the reference BP

General linear models were fitted to weighted mean systolic BP/MAP during EVT. Higher reference BP and higher rate of BP excursions to >120% of the reference during EVT were independently associated with higher mean SBP/MAP (Table F). The coefficient for the interaction term indicated that the "effect" of excursions was higher at higher reference BP (understandably). Higher rate of BP excursions to <80% was independently associated with lower mean SBP/MAP during EVT (Table F). The interaction between the rate of excursions to <80% and reference BP was highly insignificant and was removed. Men tended to have lower mean BP during EVT than women (Table F). No association was observed between age, on-admission NIHSS score, pre-EVT use of antihypertensives, use or rtPA, type of affected vessel, procedure duration, number of BP measurements taken and use of sympathomimetics during EVT and the mean BP during the procedure (Table F).

Poisson regression models were fitted to the rate of SBP/MAP excursions to >120% and to <80% of the reference BP. Higher reference SBP was independently associated with a lower risk of SBP excursions to >120% and a higher risk of excursions to <80% (Table G). The same pattern of associations was observed for reference MAP and MAP excursions during EVT (Table G). For both SBP and MAP, use of sympathomimetics during EVT tended towards association with a higher risk of excursions to >120% and a lower risk of excursions to <80% (Table G). Pre-EVT use of antihypertensives was associated with lower risk of SBP excursions to >120% and tended to a higher risk of excursions to <80% (Table G). For both SBP and MAP, rtPA use tended to association with a higher risk of excursions to >120 mm Hg and a lower risk of excursions to <80% (Table G).

The present analyses indicate: (a) on-admission BP appeared the main driver of a decision to administer antihypertensives before EVT, regardless of the stroke severity, likely in order to achieve recommended BP levels for the reperfusion procedure; (b) the predominant decline in BP between admission and start of EVT was only partly ascribable to administered antihypertensives since it occurred to a similar extent in patients not treated with antihypertensives, likely due to calming/induction of general anesthesia. It did not appear associated with the stroke severity; (c) reference BP appeared the main factor guiding the "tolerance" towards BP excursions during EVT (and, hence, overall weighted mean BP) independently of the means by which it was achieved (i.e., with or without pre-EVT antihypertensive use)—higher reference was strongly associated with a lower risk of excursions to higher values and a higher risk of excursions to lower values (vs. the reference). The rate of oscillations did not appear associated with clinical stroke severity. The use of sympathomimetics during EVT appeared associated with BP excursions just in a way opposite to reference BP. Overall data suggest that BP-related measures (antihypertensives, sympathomimetics, "tolerance" towards excursions) were guided predominantly by the intention to ascertain BP values within the recommended limits for reperfusion procedures, and not by stroke characteristics.

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Table A. Subject characteristics in respect to received blood pressure-related treatment between admission and the start of endovascular thrombectomy

Characteristic	No BP-related treatment between admission and EVT	BP-lowering treatment between admission and EVT	Sympathomimetics between admission and EVT
Number	146	16	2
Age (yr)	74 (20 to 92)	76 (53 to 90)	44 to 79
Male sex	66 (45.2)	7 (43.8)	0
Atrial fibrillation	58 (39.7)	5 (31.3)	1
History of hypertension	95 (65.1)	11 (68.8)	0
Previous stroke	17 (11.6)	0 (0)	1
Peripheral artery disease	11 (7.5)	0 (0)	0
Ischemic heart disease	31 (21.2)	3 (18.8)	1
Carotid stenosis ≥50%	15 (10.3)	2 (12.5)	0
Chronic heart failure	25 (17.5)	1 (6.3)	0
Pre-admission anticoagulants	27 (18.5)	1 (6.3)	1
Middle cerebral artery segment 1	104 (71.2)	8 (50.0)	2
Middle cerebral artery segment 2	12 (8.2)	2 (12.5)	0
Tandem occlusion	30 (20.6)	6 (37.5)	0
Admission SBP (mm Hg)	150 (83 to 220)	178 (120 to 223)	100 to 120
Admission MAP (mm Hg)	107 (56 to 167)	115 (97 to 174)	73 to 95
Admission NIHSS (score)	18 (3 to 32)	19 (9 to 32)	16 to 22
Lag: admission–reference BP (min)	24 (1 to 68)	26 (7 to 45)	25 to 52
Reference SBP (mm Hg)	125 (73 to 203)	121 (95 to 174)	116 to 139
SPB Δ reference–admission (mm Hg)	–22 (–105 to 66)	–42 (–126 to 0)	–4 to 39
Reference MAP (mm Hg)	89 (45 to 136)	84 (63 to 124)	83 to 100
MAP Δ reference–admission (mm Hg)	–16 (–101 to 50)	–29 (–83 to 8)	–12 to 27
Use of rtPA	103 (70.6)	12 (75.0)	1
Sympathomimetics during EVT	67 (45.9)	9 (56.3)	1
EVT weighted mean SBP (mm Hg)	128 (69 to 192)	125 (99 to 155)	109 to 127
EVT weighted mean MAP (mm Hg)	92 (43 to 125)	89 (67 to 106)	82 to 96
Rates of BP excursions (n/10 min)			
SBP >120% of reference	1.17 (0 to 9.26)	0.72 (0 to 3.75)	0 to 0.35
MAP >120% of reference	1.18 (0 to 9.74)	1.15 (0 to 4.0)	0 to 2.62
SBP <80% of reference	0.95 (0 to 9.20)	0.83 (0 to 7.79)	0 to 7.03
MAP <80% of reference	0.75 (0 to 8.92)	0.90 (0 to 8.21)	0 to 6.2

Values are presented as median (range), geometric mean (range) for rates of BP excursions, and count (percent). Individual data are shown for two subjects who received sympathomimetics between admission and EVT.
BP, blood pressure; EVT, endovascular thrombectomy; SBP, systolic blood pressure; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator.

Table B. Summary of multivariate analysis of the outcome "antihypertensive treatment between admission and endovascular thrombectomy"

Variable	OR (95% CI)	*P*
Default independent variables		
On-admission SBP (by 10 mm Hg)	1.47 (1.01–2.22)	0.045
On-admission mean arterial pressure (by 10 mm Hg)	0.95 (0.54–1.63)	0.858
On-admission NIHSS score (by 1 score point)	1.04 (0.95–1.15)	0.405
Selected independent variables		
Pre-stroke anticoagulant use (vs. none)	0.15 (0.01–0.97)	0.045
Affected is middle cerebral artery segment 1 (vs. other)	0.35 (0.11–1.10)	0.072

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale.

Table C. Summary of multivariate analysis of the outcome "change in BP between admission and start of endovascular thrombectomy"

Variable	Change in SBP		Change in MAP	
	Δ Change (95% CI)	*P*	Δ Change (95% CI)	*P*
Model 1 (not accounting for admission BP)				
Received antihypertensive treatment (vs. no)	−25.6 (−41.6 to −9.6)	0.002	−14.5 (−25.9 to −3.0)	0.014
Age (by 10 yr)	−2.6 (−6.0 to 0.7)	0.127	−2.3 (−4.7 to 0.1)	0.065
Model 2 (accounting for admission BP)				
Default independent variables				
Received antihypertensive treatment (vs. no)	−6.1 (−18.2 to 5.9)	0.315	−2.7 (−11.3 to −5.8)	0.529
Age (by 10 yr)	−1.3 (−3.9 to 1.2)	0.300	−0.4 (−2.2 to 1.4)	0.678
On-admission BP (by 1 mm Hg)	−0.9 (−1.0 to −0.7)	<0.001	−0.9 (−1.0 to −0.7)	<0.001
Selected independent variables				
Men (vs. women)	-	-	−4.1 (−9.2 to 0.9)	0.105
Pre-existing hypertension (vs. no)	-	-	−3.8 (−9.0 to 1.5)	0.161

BP, blood pressure; SBP, systolic blood pressure; MAP, mean arterial pressure; CI, confidence interval.

Table D. Summary of multivariate analysis of "reference BP" (separately for systolic and mean arterial pressure)

Variable	Systolic blood pressure		Mean arterial pressure	
	β (95% CI)	*P*	β (95% CI)	*P*
On-admission NIHSS score (by 5 points)	0.013 (−0.009 to 0.036)	0.234	0.001 (−0.024 to 0.025)	0.920
Received antihypertensives (vs. no)	0.024 (−0.096 to 0.144)	0.697	−0.041 (−0.149 to 0.068)	0.461
On-admission BP (by 10 mm Hg)	0.026 (0.003 to 0.049)	0.024	0.021 (−0.028 to 0.070)	0.398
On-admission BP^2 (by 100 mm Hg)	−0.007 (−0.012 to −0.002)	0.004	−0.005 (−0.014 to 0.004)	0.280
On-admission BP*antihypertensives	0.024 (−0.021 to 0.069)	0.287	0.008 (−0.089 to 0.104)	0.870
On-admission BP^2*antihypertensives	−0.006 (−0.016 to 0.004)	0.208	0.002 (−0.017 to 0.021)	0.825
BP when no antihypertensive treatment	0.014 (0.003 to 0.025)	0.013	0.017 (0.000 to 0.034)	0.055
BP when antihypertensive treatment	0.038 (−0.006 to 0.082)	0.086	0.025 (−0.070 to 0.012)	0.607
BP^2 when no antihypertensive treat.	−0.004 (−0.007 to −0.001)	0.007	−0.006 (−0.011 to −0.001)	0.019
BP^2 when antihypertensive treatment	−0.011 (−0.020 to −0.001)	0.029	−0.004 (−0.022 to 0.014)	0.654

Models are fitted to ln-transformed reference BP values.
BP, blood pressure; CI, confidence interval; BP^2, blood pressure by 100 mm Hg; NIHSS, National Institutes of Stroke Scale.

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Table E. Summary of multivariate analysis of the outcome "sympathomimetic use during EVT"

	OR (95% CI)	*P*
Systolic BP at start of EVT (by 10 mm Hg)	1.12 (0.83–1.53)	0.449
Mean arterial pressure at start of EVT (by 10 mm Hg)	0.83 (0.54–1.25)	0.376
Age (by 10 yr)	1.00 (0.78–1.28)	0.999
On-admission NIHSS (by 5 points)	1.14 (0.85–1.53)	0.393
Use of rtPA (vs. no)	0.72 (0.35–1.47)	0.373
Use of antihypertensive before EVT (vs. no)	1.18 (0.66–2.18)	0.577
Middle cerebral artery segment 1 (vs. other)	0.56 (0.30–0.97)	0.041
Antihypertensive use*affected vessel	0.73 (0.38–1.30)	0.293
Use of antihypertensives at MCA1	0.74 (0.14–3.34)	-
Use of antihypertensives at "other vessel"	2.59 (0.59–20.1)	-
MCA1 vs. "other" at antihypertensives use	0.17 (0.01–1.41)	-
MCA1 vs. "other" at no antihypertensive use	0.58 (0.27–1.23)	-

EVT, endovascular thrombectomy; OR, odds ratio; CI, confidence interval; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; MCA, middle cerebral artery.

Table F. Summary of multivariate analyses of weighted mean SBP and MAP during EVT

Variable	Weighted mean SBP		Weighted mean MAP	
	β (95% CI)	*P*	β (95% CI)	*P*
Reference BP (mm Hg)	0.76 (0.66 to 0.86)	<0.001	0.80 (0.71 to 0.89)	<0.001
Rate: BP >120% reference (n/10 min)	5.11 (3.99 to 6.24)	<0.001	3.58 (2.87 to 4.29)	<0.001
Reference BP*rate >120%	0.08 (0.02 to 0.15)	0.008	0.07 (0.03 to 0.10)	<0.001
Rate: BP <80% reference (n/10 min)	−4.96 (−5.91 to −4.02)	<0.001	−3.48 (−4.16 to −2.80)	<0.001
Age (by 10 yr)	0.21 (−1.01 to 1.42)	0.738	−0.21 (−1.01 to 0.59)	0.605
Men (vs. women)	−3.41 (−6.63 to −0.18)	0.039	−1.82 (−3.97 to −0.32)	0.095
On-admission NIHSS score	0.02 (−0.27 to 0.31)	0.894	0.10 (−0.09 to 0.29)	0.293
MCA1 (vs. "other" vessel)	−1.50 (−5.05 to 2.06)	0.407	−1.80 (−4.13 to 0.55)	0.133
rtPA use (vs. no)	−1.87 (−5.47 to 1.74)	0.308	−0.98 (−3.40 to 1.44)	0.425
Pre-EVT antihypertensives (vs. no)	1.57 (−3.83 to 6.98)	0.566	1.44 (−2.11 to 5.01)	0.424
Sympathomimetics during EVT (vs. no)	0.31 (−2.91 to 3.53)	0.850	0.17 (−1.98 to 2.32)	0.877
EVT duration (min)	−0.01 (−0.05 to 0.03)	0.541	−0.00 (−0.03 to 0.02)	0.787
BP measurements during EVT (n)	−0.01 (−0.05 to 0.04)	0.813	−0.01 (−0.04 to 0.03)	0.734

SBP, systolic blood pressure; MAP, mean arterial pressure; EVT, endovascular thrombectomy; CI, confidence interval; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; rtPA, recombinant tissue plasminogen activator.

Table G. Summary of multivariate analyses of the "rate (n/10 min) of BP excursions to >120% of the reference BP during EVT" and "rate of BP excursions to <80% of the reference BP during EVT"

Variable	Rate to >120%		Rate to <80%	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Model of SBP/SBP excursions				
Reference BP (by 10 mm Hg)	0.66 (0.61–0.72)	<0.001	1.63 (1.52–1.76)	<0.001
Sympathomimetics during EVT (vs. no)	1.21 (0.89–1.62)	0.220	0.67 (0.45–0.98)	0.040
Pre-EVT use of antihypertensives (vs. no)	0.57 (0.31–0.98)	0.040	1.54 (0.82–2.76)	0.175
rtPA used (vs. no)	1.46 (1.04–2.08)	0.029	0.81 (0.52–1.26)	0.338
Age (by 10 yr)	1.10 (0.98–1.24)	0.095	0.86 (0.75–0.99)	0.036
Men (vs. women)	1.09 (0.81–1.46)	0.576	1.21 (0.81–1.81)	0.340
On-admission NIHSS (by 10 points)	0.99 (0.76–1.29)	0.965	0.77 (0.54–1.10)	0.150
MCA1 (vs. "other" vessel)	0.73 (0.53–1.03)	0.072	0.76 (0.51–1.12)	0.163
EVT duration (by 10 min)	0.95 (0.81–1.02)	0.267	0.96 (0.74–1.03)	0.433
BP measurements during EVT (by 10)	1.05 (0.97–1.25)	0.270	1.10 (0.93–1.43)	0.232
Model for MAP/MAP excursions				
Reference BP (by 10 mm Hg)	0.60 (0.54–0.67)	<0.001	1.97 (1.75–2.23)	<0.001
Sympathomimetics during EVT (vs. no)	1.36 (1.03–1.79)	0.030	0.85 (0.56–1.28)	0.444
Pre-EVT use of antihypertensives (vs. no)	0.70 (0.40–1.14)	0.156	0.97 (0.48–1.83)	0.930
rtPA used (vs. no)	1.38 (1.02–1.90)	0.035	0.61 (0.38–0.98)	0.042
Age (by 10 yr)	1.07 (0.96–1.20)	0.199	0.93 (0.81–1.09)	0.359
Men (vs. women)	1.10 (0.84–1.44)	0.501	1.36 (0.87–2.14)	0.181
On-admission NIHSS (by 10 points)	0.92 (0.72–1.18)	0.514	1.13 (0.76–1.68)	0.551
MCA1 (vs. "other" vessel)	1.00 (0.75–1.37)	0.975	0.66 (0.43–1.01)	0.058
EVT duration (by 10 min)	0.95 (0.84–1.02)	0.232	0.95 (0.73–1.01)	0.130
BP measurements during EVT (by 10)	1.05 (0.97–1.20)	0.266	1.09 (0.93–1.41)	0.211

Four separate models were fitted: one for each rate, separately for SBP and MAP.
BP, blood pressure; EVT, endovascular thrombectomy; RR, relative risk; CI, confidence interval; SBP, systolic blood pressure; rtPA, recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; MAP, mean arterial pressure.

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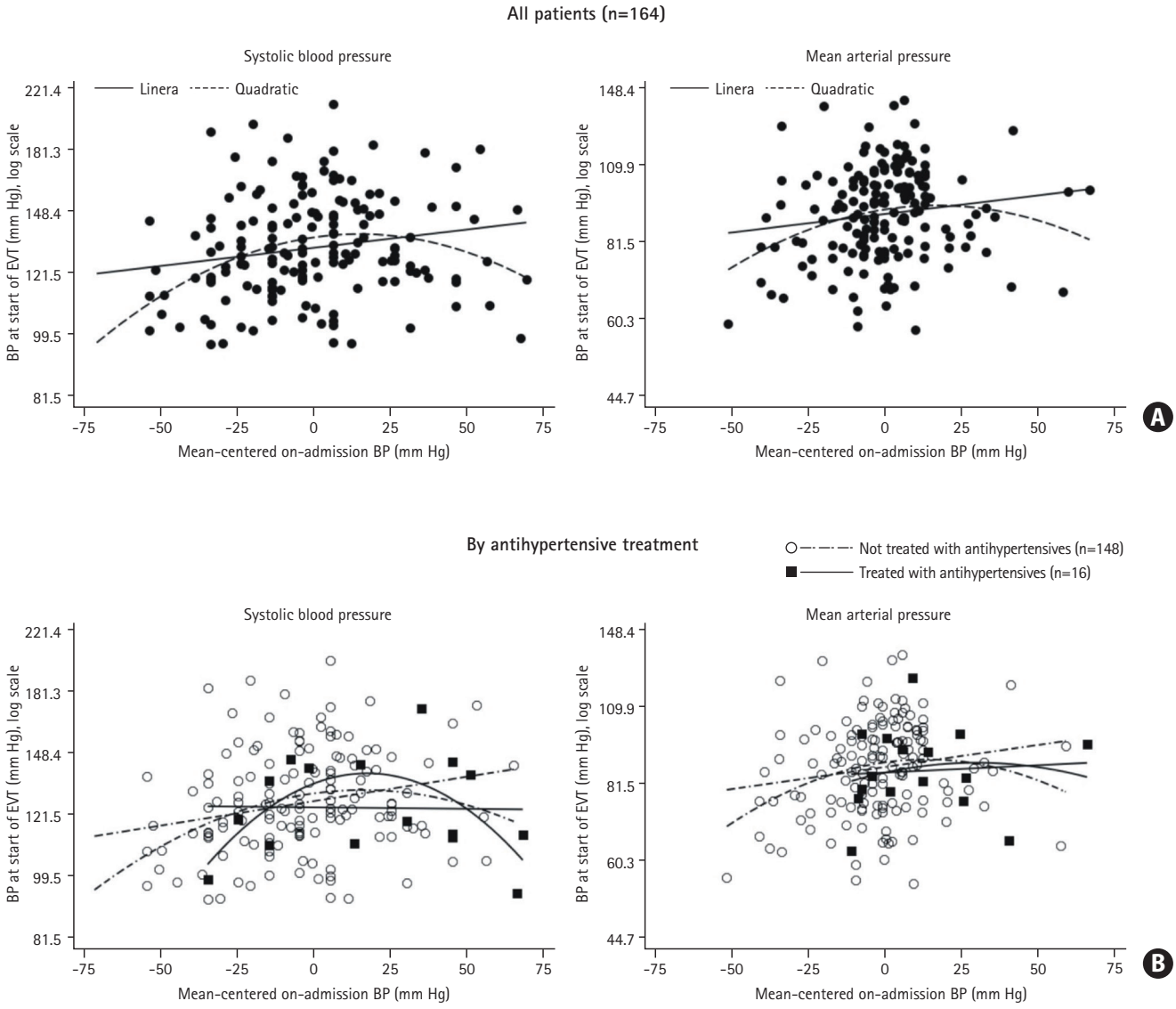

Figure B. Relationship between on-admission blood pressure (BP) and BP at the start of endovascular thrombectomy (EVT) (reference BP: mean of 3–5 values at anesthesia induction). (A) Overall (all patients). Closed circles are observed individual data, lines are adjusted regression lines. (B) By subset of patients in respect to administered antihypertensive treatment between admission and EVT. Symbols are observed individual data, lines are adjusted regression lines (both linear and quadratic). Since quadratic relationship was indicated by the initial analysis, mean-centered on-admission values were used (to avoid collinearity between linear and quadratic terms) in the main analysis. BP values at the beginning of EVT were ln-transformed; hence, log scale is used at the y-axis. The model is depicted in Table D.

Supplementary Analysis of Post-Procedure Hemorrhages

Analysis of the relationship between blood pressure (BP)/BP excursions during endovascular thrombectomy (EVT) to values >120% or <80% of the reference value and finding of visible hemorrhages on the post-procedure computed tomography scans (Supplementary Table 4) demonstrated a consistent lack of association between in-procedure BP excursions and the outcome (across a range of models). However, it disclosed an apparently counterintuitive finding: higher reference systolic blood pressure (SBP)/mean arterial pressure (MAP) consistently tended towards or was associated with higher odds of hemorrhages, whereas higher in-procedure mean BP was consistently associated lower odds of hemorrhages (Supplementary Table 4). Two observations indicated that the relationship between reference BP, in-procedure mean BP and hemorrhages could be a complex one:

1. Strength of association between reference BP and hemorrhages and strength of association between in-procedure mean BP and hemorrhages appeared almost identical (but in an opposite direction). In the "reduced" model in Supplementary Table 4, odds ratio (OR) for the reference SBP was 1.48 and its inverse value (0.67) is almost identical to the OR for the procedure mean SBP (OR=0.65). The same applies for reference MAP (OR=1.86; inverse value=0.53) and in-procedure mean MAP (OR=0.52).
2. Supplemental analysis of BP (Table F) demonstrated that in-procedure mean BP was greatly determined by the reference BP.

We undertook the following analyses:

(a) We re-fitted the "reduced" model in Supplementary Table 4 with (i) inclusion of an interaction term between reference BP and in-procedure mean BP; (ii) with exclusion of the in-procedure mean BP, while reference BP was retained; (iii) with exclusion of reference BP, while in-procedure mean BP was retained.

(b) We performed mediation analysis in which reference BP was considered a predictor, in-procedure mean was considered a mediator, presence of post-procedure hemorrhages was an outcome, while other effects from the "reduced" model in Supplementary Table 4 were covariates. All associations in the model, direct (predictor-mediator; mediator-outcome; predictor-outcome) and indirect (predictor-outcome, via mediator) were adjusted for all other effects; hence, all were independent.

1. Re-fitted "reduced" model from Supplementary Table 4

Table H summarizes results of re-fitting the "reduced" model from Supplementary Table 4. Only data for the reference BP and in-procedure mean BP are shown. All other effects (excursion rates, Thrombolysis in Cerebral Infarction [TICI] grade, stroke etiology, history of coronary artery disease) were consistently virtually identical as in Supplementary Table 4.

The interaction term between reference SBP/MAP and in-procedure mean SBP/MAP (mean-centered) was highly insignificant; however, in this model estimated effects of the reference BP on the odds of post-procedure hemorrhages were considerably changed as they became highly imprecise and statistically insignificant, whereas the effect of in-procedure mean BP remained closely similar as in the starting "reduced" model.

When in-procedure mean BP was removed from the model, reference BP was no longer associated with the odds of post-procedure hemorrhages. When reference BP was removed from the model, in-procedure mean BP was no longer associated with the odds of post-procedure hemorrhages.

2. Mediation analysis

Results are summarized in Table I. The results were consistent in the model for SBP and the model for MAP. Higher reference BP (predictor) was directly associated with higher in-procedure mean BP (mediator). This is in line with the results of the Supplementary Analysis of Blood Pressure (Table F). Higher in-procedure mean BP was directly associated with lower odds of post-procedure hemorrhages (with the adjustment for reference BP and other effects). This is line with the results of the "reduced" model in Supplementary Table 4. Higher reference BP (predictor) tended towards direct association with higher odds of post-procedure hemorrhages (outcome), but this association did not attain statistical significance. This is in line with the results of the "reduced" model in Supplementary Table 4. Namely, when a predictor and a mediator are simultaneously included in a "common" regression model (as is the "reduced" model in Supplementary Table 4), their individual direct associations with the outcome are quantified. Mediation analysis, using a set of consecutive regressions, partials-out direct and indirect associations (through a mediator) between the predictor and the outcome. As depicted in Table I, in both models (SBP/MAP), higher reference BP tended to be associated with lower odds of post-procedure hemorrhages, indirectly via its association with higher in-procedure mean BP, thus illustrating a phenomenon of "inconsistent mediation" (the direct and mediated effects are in an opposite direction). Consequently, in both models (SBP, MAP), the total effect (combined direct and indirect) of the reference BP (predictor) on the outcome was close to zero (direct and indirect effects mutually cancelled-out). This is in line with the results of the re-fitted "reduced" model that did not include in-procedure mean BP (Table H): in a "common" regression model that does not include the mediator, effect of a predictor on the outcome corresponds to a total effect from the mediation analysis (i.e., the direct effect is not partialed-out).

Overall, the present analysis suggests that the observed opposite associations of the reference BP and of in-procedure mean BP with the probability of post-procedure hemorrhages in the "reduced" model in Supplementary Table 4, although apparently counterintuitive, can be explained by their mutual relationship. In terms of their practical meaning, the results of the "reduced" model in Supplementary Table 4 require cautious interpretation in which several facts need to be considered. Firstly, regarding the temporal sequence of events, reference BP precedes the in-procedure BP. Next, the two BP indices are driven by different factors. As shown in the Supplementary Analysis of Blood Pressure, reference BP results from (is defined by) on-admission BP and, in part, from measures undertaken in order to drive it into the limits recommended for the reperfusion procedure (Table D, Figure A). In-procedure mean BP, on the other hand, is largely determined by the reference BP in several ways: (a) higher reference BP is associated with higher in-procedure mean BP (Supplementary Analysis of Blood Pressure, Table F). This appears reasonable within the context of EVT: the procedure starts only after BP (reference BP) has been driven within the recommended boundaries, and BP is then maintained around this (preferred) value. Hence, higher the reference (within the recommendations)—higher the procedure mean BP; (b) in-procedure mean BP is also largely determined by the rate of BP excursions—higher the rate of excursions to >120% of the reference, higher the in-procedure mean; higher the rate of excursions to <80%, lower the in-procedure mean (Supplementary Analysis of Blood Pressure, Table F). Reference BP influences the in-procedure mean BP also by "driving" the rate of BP excursions: higher the reference BP, lower the risk of BP excursions to >120% of the reference and higher the risk of excursions to <80% of the reference (Supplementary Analysis of Blood Pressure, Table G). Therefore, in the context of EVT, with defined recommended pre-EVT BP values, reference BP is a milestone that defines the subsequent (during EVT) BP management, i.e., tolerance towards the oscillations, measures to reduce/control them. In this respect, the relationship between reference BP and post-procedure hemorrhages should preferably (as this is in line with the sequence of events) be viewed "through" the in-procedure mean BP. Hence, the main observation arising from the "reduced" model in Supplementary Table 4 is the association between higher in-procedure BP and lower odds of hemorrhages. Whatever effect reference BP "in itself"

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might have on the risk of post-procedure hemorrhages, this is cancelled-out by the subsequent in procedure BP: this is supported by the lack of a total effect of the reference BP in the mediation analysis due to opposing direct and mediated effects, and a lack of the effect of the reference BP in a "common" regression model when in-procedure mean is not accounted for (i.e., when the direct effect is not partialed-out from the total effect, i.e., when it is not separated from the indirect effect). This reasoning might be objected in the light of the fact that under similar conditions (re-fitted "reduced" model without an account for reference BP), in-procedure mean BP was also not associated with the odds of hemorrhages (Table H). In this respect, one should have in mind the specific temporal (reference BP precedes the in-procedure BP) and causal (reference BP determines in-procedure mean BP, and not *vice versa*) relationship between the reference and in-procedure BP. In this re-fitted model, one actually observes a "total" effect of in-procedure mean BP, i.e., this is a situation in which its specific direct effect on the risk of hemorrhages is not partialed-out from the total effect that it carries. Since it is cardinally determined by the reference BP, this total effect of the in-procedure mean BP actually largely represents the total effect of the reference BP (which is close to zero). It follows that in "common" regression models that exclude reference BP, one cannot actually identify the effect of in-procedure mean BP on the outcome (due to the strong causal relationship between the two).

Table H. Summary of the re-fitted versions of the "reduced" logistic model from Supplementary Table 4 analyzing association between reference BP and in-procedure weighted mean BP and occurrence of post-procedure hemorrhages

Variable	Systolic blood pressure		Mean arterial pressure	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Reference BP (by 10 mm Hg)	1.48 (0.99–2.28)	0.056	1.86 (1.00–3.47)	0.051
In-procedure mean BP (by 10 mm Hg)	0.65 (0.40–0.96)	0.032	0.52 (0.26–0.95)	0.034
[+]Reference BP*in-procedure mean BP interaction				
Reference BP*in-procedure mean BP interaction	0.99 (0.98–1.00)	0.206	1.00 (0.98–1.01)	0.669
Reference BP (by 10 mm Hg)	3.94 (0.81–19.0)	0.088	2.66 (0.45–15.6)	0.278
In-procedure mean BP (by 10 mm Hg)	0.64 (0.42–0.99)	0.046	0.51 (0.27–0.96)	0.039
In-procedure mean BP excluded				
Reference BP (by 10 mm Hg)	1.05 (0.83–1.32)	0.686	1.06 (0.77–1.46)	0.720
Reference BP excluded				
In-procedure mean BP (by 10 mm Hg)	0.89 (0.71–1.14)	0.379	0.88 (0.65–1.21)	0.441

It is extension of model from Supplementary Table 4. In-procedure mean BP (by 10 mm Hg) is added to models from Supplementary Table 4, that's why there is a plus sign.
BP, blood pressure; OR, odds ratio; CI, confidence interval.

Table I. Summary of the mediation analysis: effects are shown as regression coefficients

Effects	β (95% CI); *P*
Model for SBP	
Predictor (reference BP) → mediator (in-procedure mean BP)	0.82 (0.73 to 0.91); <0.001
Mediator → outcome (odds of post-procedure hemorrhages)	−0.0059 (−0.0116 to −0.0002); 0.043
Direct effect predictor → outcome	0.0056 (−0.0001 to 0.0113); 0.056
Indirect effect predictor → outcome via mediator	−0.0048 (−0.0094 to 0.0015); 0.078
Total effect (direct+indirect) predictor → outcome	0.0007 (−0.0026 to 0.0040); 0.661
Model for MAP	
Predictor (reference BP) → mediator (in-procedure mean BP)	0.86 (0.78–0.94); <0.001
Mediator → outcome (odds of post-procedure hemorrhages)	−0.0084 (−0.0168 to −0.0000); 0.050
Direct effect predictor → outcome	0.0082 (−0.0005 to 0.0169); 0.060
Indirect effect predictor → outcome via mediator	−0.0073 (−0.0150 to 0.0020); 0.099
Total effect (direct+indirect) predictor → outcome	0.0010 (−0.0035 to 0.0055); 0.678

CI, confidence interval; SBP, systolic blood pressure; BP, blood pressure; MAP, mean arterial pressure.