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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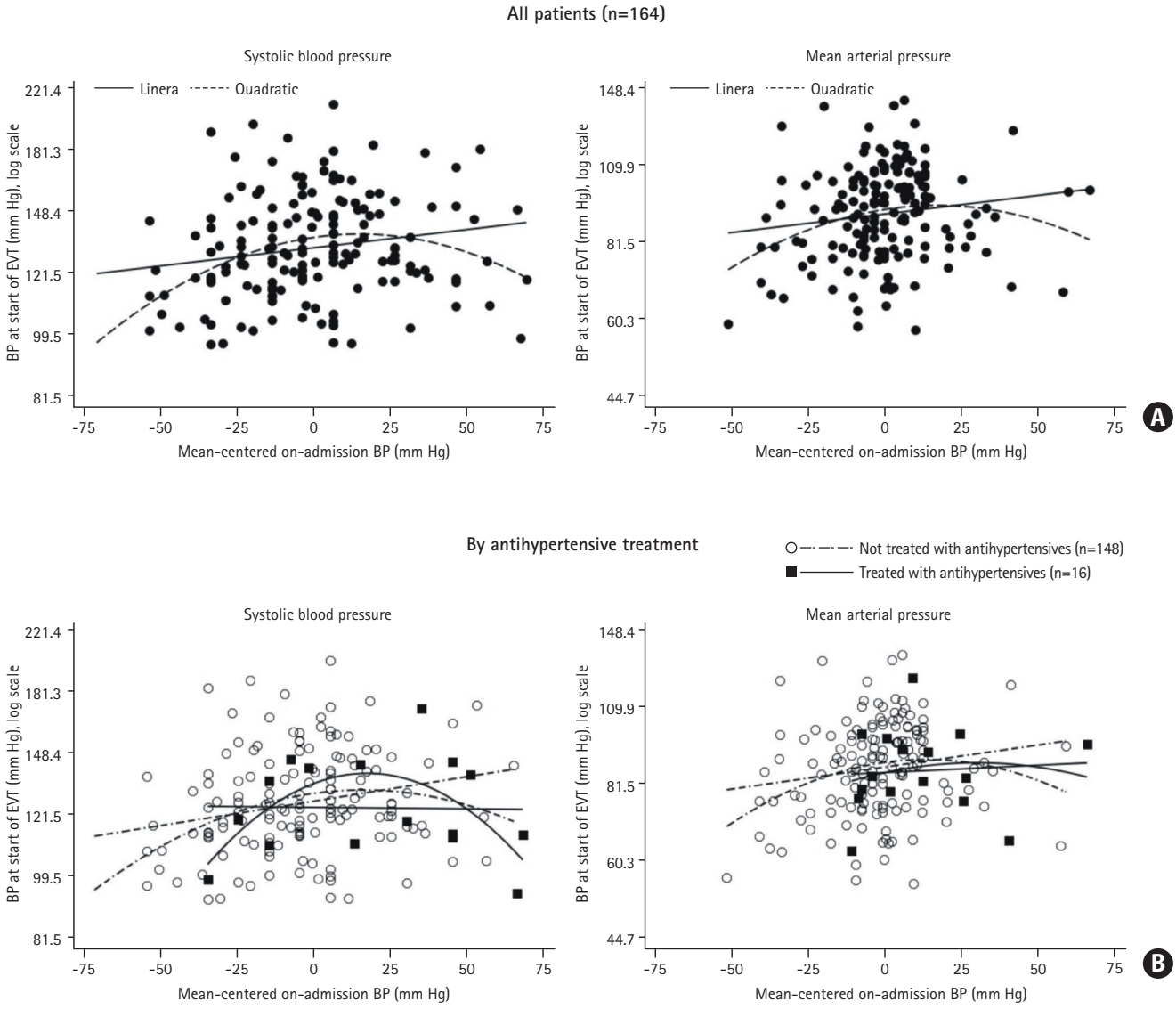

Figure B. Relationship between on-admission blood pressure (BP) and BP at the start of endovascular thrombectomy (EVT) (reference BP: mean of 3–5 values at anesthesia induction). (A) Overall (all patients). Closed circles are observed individual data, lines are adjusted regression lines. (B) By subset 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.