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ORIGINAL RESEARCH

Standard Versus Individualized Blood Pressure Targets During Thrombectomy: A Randomized Controlled Pilot Trial

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BACKGROUND: The optimal blood pressure management strategy in patients undergoing endovascular therapy for acute ischemic stroke is unknown. This pilot study aimed to assess the feasibility of a standard versus individualized blood pressure management strategy during endovascular therapy.

METHODS: This randomized controlled pilot trial included adult patients with acute ischemic stroke with large-vessel occlusion in the anterior circulation undergoing endovascular therapy. Patients were randomized to either standard (mean arterial blood pressure [MABP] targeted between 70 and 90 mm Hg) or individualized (MABP targeted ±10% of a baseline value measured in the neurointerventional suite) blood pressure targets until reperfusion or removal of groin sheath. The main outcome was the modified Rankin Scale score at 90 days. Secondary outcomes included feasibility outcomes, 90-day dichotomized modified Rankin Scale score (0–2 versus 3–6), and reperfusion rates.

RESULTS: Between April 2021 and February 2022, 60 patients (median [interquartile range] age, 76 [66–84] years) were randomly assigned to standard (n=30) or individualized (n=30) blood pressure targets. Median (interquartile range) National institutes of Health Stroke Scale score was 15 (10–18). Mean (SD) MABP, mean (SD) systolic blood pressure, and median (interquartile range) cardiac output were significantly higher in the individualized group compared with the standard group (MABP: 94 [9] versus 88 [9] mm Hg; *P*=0.012; systolic blood pressure: 149 [21] versus 139 [17] mm Hg; *P*=0.032; and cardiac output: 5.82 [4.22–7.23] versus 4.35 [3.73–5.1] L/min; *P*=0.02). The odds ratio for improved outcome in the individualized group was 1.37 (95% CI, 0.56–3.36). The relative risk for improved dichotomized outcome in the individualized group was 1.31 (95% CI, 0.87–1.98). Full reperfusion rates were comparable between the standard and individualized groups (90% versus 93%; *P*=0.64). The median percentage of time outside the MABP targets was 54.3% in the standard group versus 61.4% in the individual group (*P*=0.30) and did not meet the feasibility target. Recruitment rate, data completeness, and safety were within feasibility limits.

CONCLUSIONS: The feasibility criteria were not met in this study because of difficulties in achieving the desired blood pressure targets. These findings do not support continuing with a large trial using the current protocol.

Key Words: anesthesia ■ blood pressure ■ ischemic stroke ■ thrombectomy

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There is no consensus about blood pressure management in patients undergoing endovascular therapy (EVT) for acute ischemic stroke.[1] Current standard management of blood pressure during EVT aims to maintain blood pressure above or within predefined fixed targets and is based on retrospective data and expert consensus rather than evidence from randomized trials.[2–5] Patients with acute ischemic stroke often have impeded autoregulatory capacity, and observational studies have shown that both hypotension and hypertension before reperfusion are associated with worse outcomes.[3,4,6] Therefore, an individualized approach maintaining blood pressure within narrow limits could improve outcome.[7–10] This randomized pilot trial aimed to assess whether standard versus individualized blood pressure targeting during the EVT procedure is feasible.

Nonstandard Abbreviations and Acronyms

EVT	endovascular therapy
MABP	mean arterial blood pressure
mRS	modified Rankin Scale
OR	odds ratio
RR	relative risk
SBP	systolic blood pressure

CLINICAL PERSPECTIVE

What Is New?

- This pilot randomized trial provides currently unknown data on the feasibility of a standard versus individualized blood pressure management strategy during thrombectomy.

What Are the Clinical Implications?

- The hemodynamic feasibility criteria were not met in this study. These findings do not support continuing with a large trial using the current protocol.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The trial protocol was registered at ClinicalTrials.gov. The Ethics Committee of the Central Denmark Region approved the trial and accepted a waiver of consent before randomization. Patients or their next of kin were later required to give written informed consent to remain in the trial. We followed the Consolidated Standards of Reporting Trials reporting guideline.

The study was a single-center randomized, controlled pilot trial with blinded end point evaluation. Expanded methods are described in Supplemental Material. Briefly, we screened all adult patients (aged ≥18 years) with acute ischemic stroke and large-vessel occlusion in the anterior circulation who were deemed candidates for EVT. Groin puncture should be performed within 24 hours of symptom onset or last seen well.

Randomization, Anesthesia, and Procedure Blood Pressure Management

Patients were randomized to either standard (mean arterial blood pressure [MABP] targeted to remain within 70–90 mm Hg)[4] or individualized (MABP targeted to remain within ±10% of the baseline value)[7] blood pressure targets until reperfusion or removal of groin sheath (Figure 1). The baseline MABP value was measured just before anesthesia induction. The standard blood pressure range is based on the results from an observational study, which reported that critical MABP thresholds during EVT for poor outcome were an MABP of <70 mm Hg and an MABP of >90 mm Hg.[4]

All patients were intubated and treated under general anesthesia using intravenously administered anesthetics.[11,12] Blood pressure targets were achieved using vasopressor agents (infusions of noradrenaline [10 μg/mL]/phenylephrine [100 μg/mL], bolus doses of ephedrine [10 mg/mL], or both). Extubation was attempted immediately after completion of the procedure, and the patient was temporarily admitted to the postanesthesia care unit.[11]

Invasive blood pressure and cardiac output were continuously monitored and sampled (LIDCOrapid hemodynamic monitor) during the EVT procedure. The hemodynamic monitoring and sampling system allows for precise hemodynamic monitoring with high data sampling frequency (1 Hz).

Post-EVT Blood Pressure Management

In reperfused patients, systolic blood pressure (SBP) was targeted <160 mm Hg in the period from reperfusion until the patient was discharged from the postanesthesia care unit.[12] In nonreperfused patients, SBP was targeted <160 mm Hg in the period from removal of the femoral sheath until the patient was discharged from the postanesthesia care unit.[12] The period from reperfusion/removal of groin sheath until

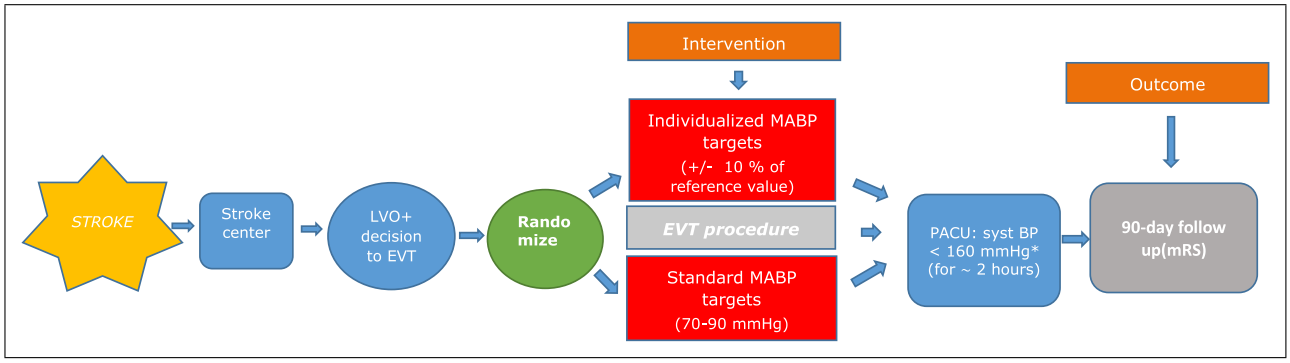

Figure 1. Study flowchart. Patients arrived at the stroke center. Decision to endovascular therapy (EVT) was made. Patients were subsequently randomized to individualized or predefined fixed mean arterial blood pressure (MABP) targets during the EVT procedure. Primary outcome (modified Rankin Scale [mRS] score) was assessed after 90 days. ∗In reperfused patients: post-EVT systolic blood pressure (syst BP) was maintained at <160 mm Hg in the period from reperfusion until the patient was discharged from the postanesthesia care unit (PACU). ∗In nonreperfused patients: post-EVT syst BP was maintained at <160 mm Hg in the period from removal of groin sheath until the patient was discharged from the PACU. LVO indicates large-vessel occlusion.

postanesthesia care unit discharge to Neurology Stroke Ward was ≈2 hours and according to institutional guidelines. In the case of SBP >160 mm Hg, the patient was treated with intravenous labetalol, 5 to 10 mg.

Sample Size and Statistical Analysis

The sample size estimation was based on bootstrapping of respective MABP measurements from a database containing physiological and outcome data from 365 patients included in the sedation vs. intubation for endovascular stroke treatment (SIESTA), anesthesia during stroke (ANSTROKE), and general or local anesthesia in intra-arterial therapy (GOLIATH) studies.[13] The expected odds ratio (OR) of the extracted sample was 0.25 toward improved outcome in the individualized group. With 10% dropout, 60% power, and a significance level of 5%, the estimated sample size was 30 subjects in each arm. The 60% power was selected to have the opportunity of finding a statistically significant effect.

The primary analysis was unadjusted and according to the intention-to-treat principle. Ordinal logistic regression analysis was used to estimate ORs with 95% CIs for the primary outcome. Poisson regression with robust variance estimation was used to estimate the relative risk (RR) with 95% CI for the dichotomized secondary outcome of modified Rankin Scale (mRS) score 0 to 2 versus 3 to 6. OR and RR values >1 indicate improved outcomes in the individual group. Restricted cubic spline curve analysis was used to investigate differences in means for hemodynamic outcomes as a function of time. Remaining secondary outcomes were compared using a 2-sided Fisher exact or Mann-Whitney *U* test, where appropriate. All analyses were conducted in Stata, version 17 (Stata-Corp LLC). $P<0.05$ was considered statistically significant.

Outcomes

The primary outcome was the ordinal score on the mRS at 90 days. Secondary outcomes were 90-day dichotomized mRS score of 0 to 2 versus 3 to 6, 24-hour National Institutes of Health Stroke Scale score, successful reperfusion (modified Trombolysis in Cerebral infarction score 2b–3), safety (symptomatic intracranial hemorrhage), and use of vasopressors. Infarct size is also listed as a secondary outcome on the trial registration website, but these data will not be reported in this publication.

Patient follow-up was performed by an mRS certified study nurse or stroke physician blinded for treatment strategy. Feasibility outcomes and predefined criteria to continue with the current protocol were that the 2 arms were distinguishable on 90-day mRS score with a trend statistically significant $P<0.1$ or all of the following 3 criteria: (1) During the intervention, a cumulated time of maximum 10 minutes outside the MABP targets was allowed.[5] During this period, the additional cumulated time outside the respective MABP targets should on average be <8% of the duration of the intervention (ie, the period from anesthesia induction to reperfusion). (2) Dropout rate is <10%. and (3) The trial data completion rate is >90%.

RESULTS

Between April 2021 and February 2022, EVT was performed on 168 patients who were all screened for possible inclusion. Ultimately, 60 patients (median age, 76 [interquartile range, 66–84] years) were randomly assigned to individual or individualized blood pressure targets (Figure 2). Because of technical issues, hemodynamic measurements were not sampled in 4

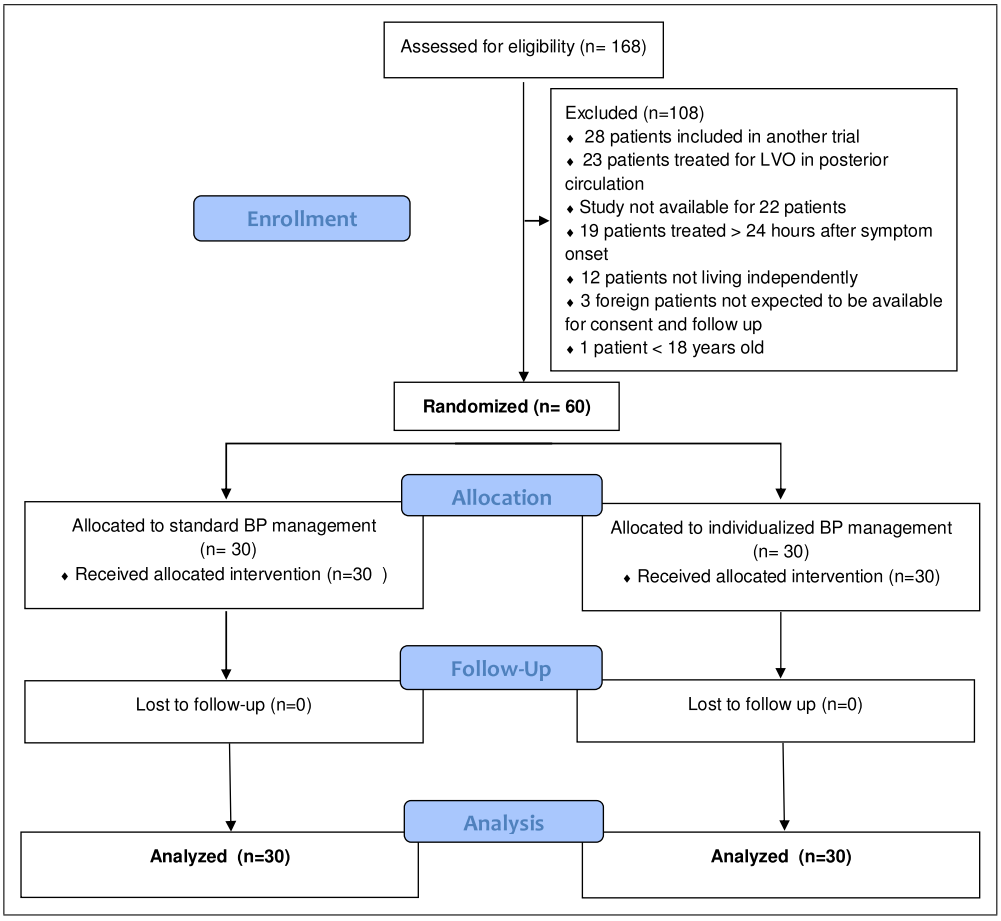

Figure 2. Flowchart of patients screened. The first patient was enrolled on April 10, 2021, and the last patient was enrolled on February 16, 2022. In that period, endovascular therapy was performed on 168 patients who were all screened for possible inclusion. A total of 60 patients were included in the study and received the intended treatment. BP indicates blood pressure; LVO, large-vessel occlusion; and SBP, systolic BP.

patients. Baseline characteristics are shown in Table 1. Patients in the individualized group were younger, but otherwise baseline characteristics were balanced between the groups. The median number of procedure hemodynamic measurements was 1691 (interquartile range, 1084–2500).

Outcomes and Feasibility End Points

Outcomes and feasibility outcomes are shown in Table 2. The OR for improved outcome in the individualized group was 1.37 (95% CI, 0.56–3.36). Median (interquartile range) 90-day mRS score was 2 (1–3) in the standard group and 2 (1–4) in the individualized group.

The RR for improved dichotomized outcome in the individualized group was 1.31 (95% CI, 0.87–1.98). In the individualized group, 1 patient (3.3%) had type 2 parenchymal hematoma hemorrhage without clinical deterioration. The recruitment rate was on average 6 patients per month, and complete data records were present in 92% of the cases in both groups. The percentage of time outside the MABP range was comparable between groups (54.3% in the standard group versus 61.4% in the individual group; P=0.30) (Table 2).

Hemodynamic Measurements

The hemodynamic parameters are shown in Table 3, and a graphical presentation of blood pressures versus time is shown in Figure 3. Procedural MABP, SBP, cardiac output postprocedure heart rate, and the dosage of noradrenaline were significantly higher in the individualized group. Postprocedure labetalol was not administered in any patients.

DISCUSSION

There was no significant difference in functional outcome between the groups. The median percentage of time outside the MABP range was 54% in the

Table 1. Baseline Characteristics

Characteristic	Standard care (n=30)	Individualized care (n=30)	*P* value
Demographic characteristics			
Age, median (IQR), y	78 (73–85)	71 (59–80)	0.006*
Female sex, n (%)	10 (33)	16 (53)	0.12†
Vascular risk factors, n (%)			
Hypertension	20 (67)	13 (43)	0.12†
Atrial fibrillation	11 (37)	12 (41)	0.79†
Diabetes	3 (10)	8 (27)	0.18†
Smoking	7 (23)	9 (30)	0.77†
Scores on admission			
Premorbid mRS score, n (%)			0.28‡
0	24 (80)	22 (73)	
1	1 (3)	5 (17)	
2	4 (13)	3 (10)	
>2	1 (3)	0	
NIHSS score on admission, median (IQR)	15 (10–18)	15.5 (10–18)	0.83*
NIHSS score 24 h after EVT, median (IQR)	7 (4–10)	6 (3–15)	0.57*
Localization of occlusion, n (%)			
Single ICA (neck)	7 (25)	5 (19)	0.56†
Single ICA-T[4]	1 (4)	0	0.32†
Single MCA			
M1	19 (68)	13 (48)	0.14†
M2	6 (21)	13 (48)	0.04†
ACA	0	3 (11)	0.07†
ICA+ICA-T§	0	0	–
ICA+M1	0	0	–
ICA+M2	0	0	–
No thrombus‖	3 (11)	0	0.08†
Reperfusion treatments, n (%)			
Premechanical thrombectomy intravenous tPA	18 (60)	17 (57)	1.00†
Thrombectomy approach, n (%)			
Aspiration	12 (43)	8 (30)	0.24‡
Mechanical device (stent retriever)	3 (11)	8 (30)	
Both	8 (29)	9 (33)	
No aspiration or device	5 (18)	2 (7)	
Time-related parameters, median (IQR), min			
Symptom onset–to–groin puncture time	310 (179–633)	285 (177–667)	0.93*
Symptom onset–to–reperfusion time	362 (199–626)	328 (206–696)	0.90*
Door–to–groin puncture time	47 (26–64)	53 (30–72)	0.62*
Door-to-reperfusion time	78 (57–101)	75 (46–119)	0.91*
Groin puncture–to–reperfusion time	33 (16–40)	18 (15–30)	0.24*
Anesthesia induction–to–extubation time	77 (42–90)	57 (46–75)	0.36*

ACA indicates anterior cerebral artery; EVT, endovascular therapy; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ICA-T, T-type occlusion defined by occlusion of the carotid artery, middle- and the anterior cerebral artery; and tPA, tissue-type plasminogen activator.

*Test for differences in ranks by Wilcoxon rank-sum test.

†Test for differences in proportions.

‡Test for differences in frequency distribution by Fisher exact test.

‖A thrombus was detected on the preinterventional magnetic resonance imaging sequence, and the patients were scheduled for EVT. In these patients, thrombolysis was administered before the EVT procedure, and the lack of thrombus is most likely attributable to spontaneous recanalization.

Table 2. Outcomes

Primary and secondary outcomes	Standard care (n=30)	Individualized care (n=30)	*P* value
90-d mRS score, median (IQR)	2 (1–3)	2 (1–4)	0.5
90-d mRS score of 0–2, n (%)	16 (53)	21 (70)	0.19
NIHSS score in 24 h, median (IQR)	7 (4–10)	6 (3–15)	0.57
Successful reperfusion (mTICI score 2b–3), n (%)	27 (90)	28 (93)	0.64
Feasibility outcomes			
Time outside MABP range, median (IQR), %	54 (29–69)	61 (35–83)	0.30
Time outside MABP range after subtraction of the acceptable cumulated 10 min outside the MABP range, median (IQR), %*	17 (0–36)	31 (0–51)	0.33
Time above MABP range, median (IQR), %	31 (19–58)	1 (0–12)	<0.001
Time below MABP range, median (IQR), %	6 (0–20)	48 (19–81)	<0.001
Safety (sICH), n	0	0	
Data completeness, %	93	90	
Recruitment rate	On average, 6 patients per month		

IQR indicates interquartile range; MABP, mean arterial blood pressure; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Score; and sICH, symptomatic intracranial hemorrhage.

∗During the intervention (ie, the time period from anesthesia induction to reperfusion), a cumulated time of maximum 10 minutes outside the MABP targets was allowed. This feasibility criterion was defined according to the findings in Rasmussen et al.[4]

Table 3. Comparison of Hemodynamic Variables Stratified According to Randomization

Hemodynamic variables	Standard care (n=30)	Individualized care (n=30)	*P* value
Baseline values			
Baseline MABP, mean (SD), mm Hg	111 (20)	108 (14)	0.73
Baseline SBP, mean (SD), mm Hg	162 (49)	163 (44)	0.99
Baseline CO, median (IQR), L/min	4.9 (4.4–6.0)	6.7 (4.1–8.5)	0.14
Procedural variables			
MABP during procedure, mean (SD), mm Hg	88 (9)	94 (9)	0.012
SBP during procedure, mean (SD), mm Hg	139 (17)	149 (21)	0.032
CO during procedure, median (IQR), L/min	4.35 (3.73–5.1)	5.82 (4.22–7.23)	0.020
Minimum MABP during procedure, mean (SD), mm Hg	59 (12)	62 (12)	0.61
Maximum MABP during procedure, mean (SD), mm Hg	130 (23)	131 (17)	0.50
Minimum SBP during procedure, mean (SD), mm Hg	90 (23)	95 (24)	0.96
Maximum SBP during procedure, mean (SD), mm Hg	200 (35)	201 (34)	0.51
Difference in MABP from baseline to reperfusion, mean (SD), mm Hg	−27 (23)	−13 (14)	0.012
Difference in SBP from baseline to reperfusion, mean (SD), mm Hg	−30 (51)	−9 (38)	0.086
Decreased by >20% in MABP, n (%)	27 (96)	25 (89)	0.30
Decreased by >20% in SBP, n (%)	25 (89)	24 (89)	1.00
Postprocedure variables			
Postprocedure MABP, median (IQR), mm Hg	90 (79–99)	87 (80–93)	0.32
Postprocedure SBP, median (IQR), mm Hg	137 (125–134)	134 (127–146)	0.51
Postprocedure heart rate, median (IQR)	62 (55–76)	76 (68–82)	0.001
Use of vasopressor agents during procedure			
Vasopressor used, n (%)	30 (100)	28 (93)	0.15
Noradrenaline, median (IQR), mg	0.17 (0.11–0.28)	0.28 (0.19–0.39)	0.042
Ephedrine, median (IQR), mg	10 (10–10)	10 (10–15)	0.87
Phenylephrine, median (IQR), mg/patient	0.8 (0.47–2.2)	0	

CO indicates cardiac output; IQR, interquartile range, MABP, mean arterial blood pressure; and SBP, systolic blood pressure.

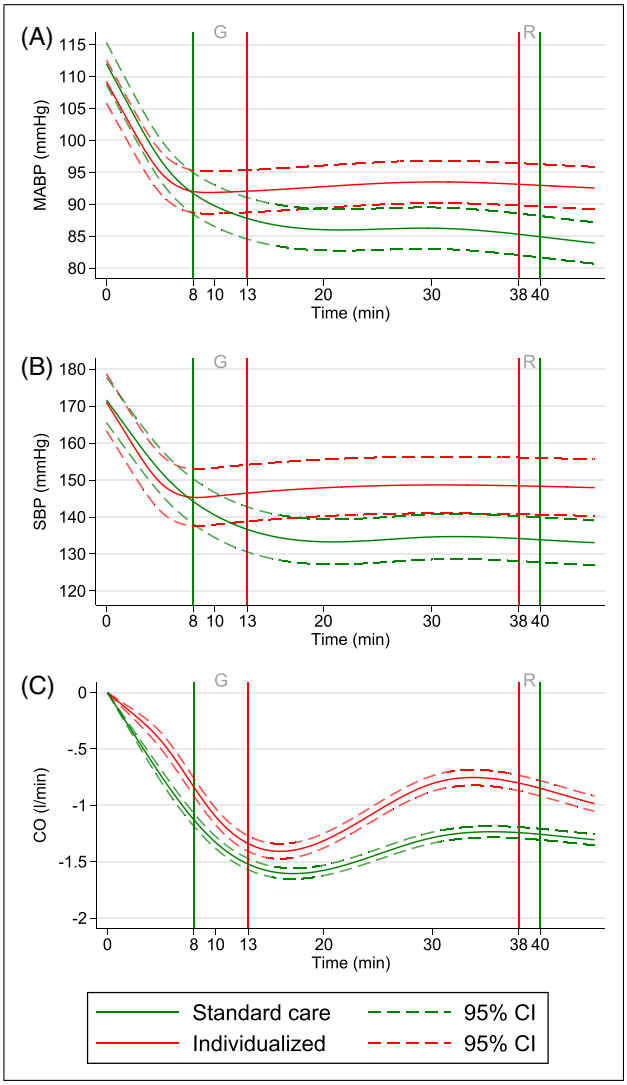

Figure 3. Hemodynamics.Hemodynamic spline curves of mean procedural changes in mean arterial blood pressure (MABP) (**A**), systolic blood pressure (SBP) (**B**), and cardiac output CO (**C**), stratified by blood pressure management strategy in 56 patients undergoing endovascular therapy. Time 0 is baseline values measured just before induction of anesthesia. Changes in CO are calculated as procedure values minus baseline value. G indicates groin puncture; and R, reperfusion.

standard group and 61% in the individualized group. During the intervention, a cumulated time of maximum 10 minutes outside the MABP targets was allowed.[4] Taking this criterion into account, the median percentage of time outside the MABP targets was 17% and 31% in the standard and individualized groups, respectively. Despite acceptable safety, dropout, recruitment, and data completion rates, the hemodynamic feasibility criteria were not obtained. Thus, the findings from this study do not support conducting a large randomized trial with a similar protocol. Currently, there are no randomized data available on the use of individualized blood pressure management during the EVT procedure. A randomized trial ("Individuate Trial") comparing standard versus individualized SBP targets will soon be published and will provide additional evidence on whether an individualized blood pressure management approach is preferable.[14]

The substantial percentage of time outside the MABP range indicates the difficulty to comply with the narrow blood pressure targets and that a higher blood pressure was often required in the individualized group to maintain MABP within the targets. The percentage of time outside the MABP ranges in both groups should be considered in the context that the studies were conducted by specialist neuroanesthesia personnel aiming to provide meticulous blood pressure management and included patients with a high degree of comorbidity.

This study has limitations. All patients in the study received general anesthesia, and this may limit the generalizability of the study because local anesthesia and conscious sedation are preferred at many centers. Patients in the standard group were younger, and this difference may have impacted the outcome assessments. The baseline blood pressure was measured in the neurointerventional suite before anesthesia induction. This is a potential limitation as some patients may have received antihypertensive treatment before arrival to neurointervention. The "standard" blood pressure range was selected on the basis of retrospective data. However, currently, there is no consensus on "fixed" blood pressure targets during EVT or whether to target MABP or SBP targets. Different MABP or SBP targets for the standard group may have provided different results.

In conclusion, the feasibility criteria were not met in this study because of difficulties in achieving the desired blood pressure targets. These findings do not support continuing with a large trial using the current protocol. Additional research is needed to identify whether an individualized blood pressure management strategy is feasible and whether to apply MABP or SBP targets. Here, studies based on artificial intelligence and machine learning algorithms may have the potential to identify blood pressure patterns associated with improved functional outcome.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Expanded Materials & Methods

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