Comparative effects of intensive-blood pressure versus standard-blood pressure-lowering treatment in patients with severe ischemic stroke in the ENCHANTED trial

Jatinder S. Minhas, Xia Wang, Richard I. Lindley, Candice Delcourt, Lili Song, Mark Woodward, Tsong-Hai Lee, Joseph P. Broderick, Octavio M. Pontes-Neto, Jong S. Kim, Stefano Ricci, Pablo M. Lavados, Philip M. Bath, Alice C. Durham, Ji-Guang Wang, Vijay K. Sharma, Andrew M. Demchuk, Sheila O. Martins, John Chalmers, Craig S. Anderson, Thompson G. Robinson, on behalf of the ENCHANTED Investigators

Objective: Limited data exist on the optimum level of SBP in thrombolysed patients with acute ischemic stroke (AIS). We aimed to determine the effects of intensive blood pressure (BP) lowering, specifically in patients with severe AIS who participated in the international, Enhanced Control of Hypertension and Thrombolysis Stroke Study.

Methods: Prespecified subgroup analyzes of the BP arm of Enhanced Control of Hypertension and Thrombolysis Stroke Study, a multicenter, partial–factorial, open, blinded outcome assessed trial, in which 2227 thrombolysis-eligible and treated AIS patients with elevated SBP (>150 mmHg) were randomized to intensive (target 130–140 mmHg) or guideline-recommended (<180 mmHg) BP management. Severe stroke was defined by computed tomography or magnetic resonance angiogram confirmation of large-vessel occlusion, receipt of endovascular therapy, final diagnosis of large artery atheromatous disease, or high (>10) baseline neurological scores on the National Institutes of Health Stroke Scale. The primary efficacy outcome was death or any disability (modified Rankin scale scores 2–6). The key safety outcome was intracranial hemorrhage (ICH). Treatment effects estimated in logistic regression models are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: There were 1311 patients (mean age 67 years; 37% female; median baseline National Institutes of Health Stroke Scale of 11 [range 6.0–15.0]) with severe AIS. Overall, there was no significant difference in the primary outcome of death or disability. However, intensive BP lowering significantly increased mortality (OR 1.52, 95% CI 1.09–2.13; \( P = 0.014 \)) compared with guideline BP lowering, despite significantly lowering clinician-reported ICH (OR 0.63, 95% CI 0.43–0.92; \( P = 0.016 \)).

Conclusion: Intensive BP lowering is associated with increased mortality in patients with severe AIS despite lowering the risk of ICH. Further randomized trials are required to provide reliable evidence over the optimum SBP target in the most serious type of AIS.

Trial registration: ClinicalTrials.gov Identifier: NCT01422616.

Keywords: hypertension, ischemic stroke, large vessel occlusion, recanalization, thrombolysis, trial

Abbreviations: AIS, acute ischemic stroke; BP, blood pressure; CI, confidence interval; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; ICH, intracranial hemorrhage; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale
INTRODUCTION

Guidelines have understandably extrapolated the conventionally recommended conservative level of blood pressure (BP) control (<180 AND <105 mmHg) in patients with acute ischemic stroke (AIS) eligible for reperfusion therapy with intravenous thrombolysis to those patients with large vessel occlusion, the most serious type of AIS [1]. However, as there is limited direct randomized evidence, wide ranging opinions exist as to the most appropriate level of SBP control before, during and after, endovascular thrombectomy for large vessel occlusion AIS [2]. The situation appears complex, with poor functional outcome associated with high pre-endovascular thrombectomy SBP (>140 mmHg) [3], low intraprocedural SBP (<140 mmHg) with general anesthesia [4], and high SBP immediately postendovascular thrombectomy (>160 mmHg) [5]. Moreover, post-hoc analyses of the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands trial suggest J-shaped or U-shaped correlations of baseline SBP and adverse outcome [3]. All these data suggest that ‘moderate’ levels of SBP control could provide the optimal outcome from endovascular thrombectomy, but there are ongoing concerns that BP-lowering treatment may increase the risk of harms in large vessel occlusion AIS [6], particularly where the AIS lesion is large [7].

Recently, the BP arm of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) showed no overall benefit of intensive BP reduction (SBP target 130–140 mmHg) compared with guideline BP control (<180 mmHg) in thrombolysis-eligible AIS patients [8,9], despite a significant reduction in intracranial hemorrhage (ICH). However, only a modest 5 mmHg SBP separation was achieved between the randomized groups, most AIS patients had mild-moderate neurological severity [median National Institutes of Health Stroke Scale (NIHSS) score 7], and few had endovascular thrombectomy which was being introduced into routine clinical practice during the course of the trial. Although there was no significant heterogeneity of the treatment effect by neurological severity and across other prespecified subgroups, we wished to undertake more detailed investigation of the effects of intensive versus guideline SBP lowering in patients with severe AIS.

MATERIALS AND METHODS

Study design

These are post-hoc analyzes of ENCHANTED, an international, 2 × 2 factorial, multicenter, prospective, randomized, open-label, blinded-endpoint trial, as outlined elsewhere [8,9]. In brief, the study included adult patients (age ≥18 years) with a clinical diagnosis of AIS confirmed by brain imaging who fulfilled standard criteria for thrombolysis treatment, including having a SBP of 185 mmHg or less. The BP arm recruited 2227 participants with elevated SBP (≥150 mmHg), where the treating clinician was uncertain of the balance of benefits and risks of different intensities of BP control over 72 h (or hospital discharge (or death), if earlier) postthrombolysis, between 3 March 2012 and 30 April 2018. Participants were randomly assigned to a strategy of intensive BP lowering (target SBP 130–140 mmHg <60 min) or guideline-recommended BP lowering (target SBP <180 mmHg) within 6 h of intravenous alteplase.

Definition of severe stroke

For these analyzes, we pragmatically defined severe stroke as having at least one of the following characteristics: large vessel occlusion confirmed either on computed tomography (CT) or magnetic resonance (MR) angiogram (n = 84) or use of endovascular thrombectomy (n = 42), or clinician-reported final diagnosis of large artery atheromatous disease (due to significant intracranial or extracranial atheroma) (n = 952); and all patients with a high baseline score (>10) on the NIHSS (n = 701).

Procedures

Sociodemographic and clinical details were obtained at the time of randomization. BP-lowering treatment was undertaken according to standardized protocols based upon the use of locally available intravenous (bolus and infusion), oral and/or topical antihypertensive patients. All patients were managed in an acute stroke unit, or alternative environment with appropriate staffing and monitoring, and received active care with best practice management according to guidelines. Noninvasive BP monitoring was undertaken using an automated device applied to the nonhemiparetic arm (or right arm in situations of coma or tetraparesis) with the patient resting supine for at least 3 min according to a standard protocol. BP measurements were recorded every 15 min for 1 h, and 6-hourly from 1 to 24 h, postthrombolysis, and then twice daily for 7 days (or hospital discharge or death, if earlier). Neurological status, according to the NIHSS and Glasgow Coma Scale scores, was assessed at baseline, and at 24 and 72 h, and 7 days. Brain imaging (computed and/or MRI) was conducted at baseline, and at 24 h, and additionally if clinically indicated; analyzes were undertaken centrally for diagnoses of categories of ICH by trained readers blind to clinical details and treatment allocation. Clinical outcome data were collected at 24 and 72 h, 7 days (or at hospital discharge if earlier), and 28 and 90 days.

Outcomes

The primary efficacy outcome was death or any disability, defined as scores 2–6 on the modified Rankin scale (mRS). Secondary outcomes included death or major disability (mRS scores 3–6), all-cause specific mortality, and death or neurological deterioration (≥4 points decline in NIHSS) within 24 and 72 h. The key secondary safety outcome was any ICH reported by investigators with or without central adjudication of relevant brain imaging within 7 days post-randomization. Other safety outcomes included the topography of ICH identified on centrally adjudicated brain images in relation to a patient’s symptoms: that is, symptomatic ICH, whereby an ICH leads to significant neurological deterioration and/or death, as defined by several criteria used in other studies [8].
Statistical analysis

Dichotomous logistic regression analyzes were used to assess the treatment effect. Data were presented as odds ratios (ORs) and 95% confidence intervals (CIs). A priori [9], the primary analysis for the effect of intensive versus guideline-recommended BP lowering was unadjusted. Sensitivity analyzes were performed on the subgroup of high baseline NIHSS (>10) and final diagnosis of large artery atheromatous disease to confirm the consistency of any association. All tests were two-sided and the significance level was set at 5%. SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina, USA) was used for analyzes.

RESULTS

There were 1311 patients (mean age 67 ± 12 years; 37% female; median baseline NIHSS of 11 (range 6.0–15.0) with severe AIS included in these analyzes (Fig. I in the Supplementary Files, http://links.lww.com/HJH/B451). CT or MR angiographic imaging was performed in 84 patients (6.4%), with large vessel occlusion identified in 56 (4.3%) and endovascular thrombectomy performed in 42 (3.2%) patients. In our severe stroke group there were no significant differences in the baseline characteristics or management over 7 days between the guideline and intensive BP-lowering groups (Table I in Supplementary Files, http://links.lww.com/HJH/B451). There were 938 (72%) patients with a history of hypertension, and 576 (44%) were on prior antihypertensive therapy. In keeping with the randomized allocation, patients in the intensive BP-lowering group were more likely to have received BP-lowering therapy, in particular intravenous agents within 24h and all types of therapy from 24h to Day 7 (Table 1 in Supplementary Files, http://links.lww.com/HJH/B451); with significant between-group SBP differences postrandomization (Fig. 1).

Overall, there was no significant difference in the primary outcome of death or disability (mRS scores 2–6), between the guideline and intensive BP lowering in patients with severe AIS (Table 2 and Fig. 2). However, there was a significant reduction in clinician-reported ICH with intensive BP lowering (OR 0.63, 95% CI 0.43–0.92; P = 0.016), but this was NS for the key safety outcome of any ICH (P = 0.065). There were no significant treatment differences in symptomatic ICH across a range of definitions but there was a significant increase in deaths (OR 1.52, 95% CI 1.09–2.13; P = 0.014) in the intensive BP-lowering group, compared with guideline BP lowering (Table 2).

Sensitivity analyzes demonstrated a significant association between high baseline NIHSS (>10) and death within 90 days (OR 1.57, 95% CI 1.08–2.28; P = 0.018) and death or neurological deterioration in 7 days (OR 1.57, 95% CI 1.07–2.31; P = 0.021) (Table I in Supplementary Files, http://links.lww.com/HJH/B451).

DISCUSSION

In these posthoc secondary analyzes of the ENCHANTED study, we have shown that in the subgroup of severe AIS patients, there were diverging effects of increased death and reduced ICH from intensive BP lowering, but without any influence on the overall odds of good functional outcome.

TABLE 1. Baseline characteristics in patients with severe acute ischemic stroke

| BP-lowering group | Guideline, n = 669 | Intensive, n = 642 | P value |
|-------------------|-------------------|-------------------|---------|
| Time from onset to randomization (h) | 3.3 (2.6–4.0) | 3.3 (2.5–4.1) | 0.961 |
| Age (year) | 67.4 (11.8) | 67.1 (12.4) | 0.852 |
| Female | 255 (38.1) | 225 (35.0) | 0.249 |
| Asian | 549 (82.1) | 507 (79.0) | 0.158 |
| SBP (mmHg) | 165 (9) | 165 (9) | 0.972 |
| DBP (mmHg) | 91 (11) | 91 (12) | 0.824 |
| Heart rate (bpm) | 79 (15) | 79 (15) | 0.832 |
| Alteplase dose (mg) | 0.8 (0.1) | 0.8 (0.1) | 0.702 |
| Glasgow coma score | 14 (13–15) | 14 (12–15) | 0.381 |
| NIHSS | 11 (6–15) | 11 (6–15) | 0.647 |
| History of hypertension | 478 (71.4) | 460 (71.8) | 0.900 |
| Antihypertensive agent(s) use | 286 (42.8) | 290 (45.2) | 0.364 |
| History of stroke | 137 (20.5) | 138 (21.5) | 0.651 |
| History of coronary artery disease | 105 (15.7) | 116 (18.1) | 0.246 |
| History of other heart disease | 35 (5.2) | 28 (4.4) | 0.465 |
| History of diabetes mellitus | 156 (23.3) | 139 (21.7) | 0.479 |
| History of hypercholesterolemia | 62 (9.3) | 63 (9.8) | 0.730 |
| Cigarette smoker | 145 (21.7) | 128 (20.0) | 0.456 |
| Premorbid function | | | |
| mRS score 0 | 577 (86.2) | 545 (85.0) | 0.527 |
| mRS score 1 | 92 (13.8) | 96 (15.0) | |
| Antiplaque use | 108 (16.1) | 91 (14.2) | 0.326 |
| Anticoagulant use | 10 (1.5) | 9 (1.4) | 0.891 |
| Glucose-lowering therapy | 91 (13.6) | 77 (12.0) | 0.390 |
| Lipid lowering therapy | 81 (12.1) | 80 (12.5) | 0.837 |

Values are n (%), mean (SD) or median (iqr). BP, blood pressure; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.
A widely accepted hypothesis is that any potential benefits of intensive BP lowering in reducing the risk of reperfusion ICH are offset by worsening functional outcome from exacerbating the ischemic penumbra [10,11]. However, previous meta-analyses have not clearly shown that early BP-lowering treatment adversely affects the likelihood of death, dependency, stroke recurrence, and other vascular outcomes [7]. Overall, the BP arm of ENCHANTED showed that BP-lowering treatment is safe, and appears to reduce the likelihood of ICH. However, as there was no influence on functional outcome, it is possible that these benefits on ICH risk were independent of the ischemic lesion, although the SBP differences over time between randomized groups were small.

Our finding of increased mortality from intensive BP lowering has physiological rationale from a cerebral hemodynamic perspective: moderate–severe AIS is associated with greater cerebral blood flow velocity asymmetries between unaffected and affected hemispheres, worsened cerebral autoregulation ipsilateral to the infarct, and bilateral neurovascular coupling impairment [12]. It is accepted that in ambulatory individuals with mild and moderate hypertension, the brain is able to quickly adapt the cerebral vasculature to protect against hypoperfusion when antihypertensive therapy is commenced [13]. However, in those with chronic hypertension, akin to over 70% of patients within this study, the autoregulatory curve is presumed to have shifted to right, although individual variability exists as

TABLE 2. Efficacy and safety outcomes at 90 days in patients with severe acute ischemic stroke

| BP-lowering group | Guideline, n/N (%) | Intensive, n/N (%) | Odds ratio (95% CI) | P value |
|-------------------|--------------------|--------------------|---------------------|---------|
| Death or disability at 90 days (mRS scores 2–6) | 378/667 (56.7) | 368/638 (57.7) | 1.04 (0.84–1.3) | 0.713 |
| Death or major disability at 90 days (mRS scores 3–6) | 283/667 (42.4) | 283/638 (44.4) | 1.08 (0.87–1.35) | 0.482 |
| Death within 90 days | 67/669 (10.0) | 93/642 (14.5) | 1.52 (1.09–2.13) | 0.014 |
| Death or neurological deterioration in 24 h | 78/669 (11.7) | 86/642 (13.4) | 1.17 (0.84–1.63) | 0.342 |
| Death or neurological deterioration in 7 days | 106/669 (15.8) | 124/642 (19.3) | 1.27 (0.96–1.69) | 0.099 |
| Symptomatic intracerebral hemorrhage | | | |
| SITS-MOST criteria | 16/669 (2.4) | 11/642 (1.7) | 0.71 (0.33–1.55) | 0.390 |
| NINDS criteria | 67/669 (10.0) | 61/642 (9.5) | 0.94 (0.65–1.36) | 0.754 |
| ECASS2 criteria | 43/669 (6.4) | 41/642 (6.4) | 0.99 (0.64–1.55) | 0.976 |
| ECASS3 criteria | 20/669 (3.0) | 18/642 (2.8) | 0.94 (0.49–1.79) | 0.841 |
| IST-3 criteria | 25/669 (3.7) | 21/642 (3.3) | 0.87 (0.48–1.57) | 0.647 |
| Clinician-reported | 75/669 (11.2) | 47/642 (7.3) | 0.63 (0.43–0.92) | 0.016 |
| Fatal (<7 days) | 10/669 (1.5) | 4/642 (0.6) | 0.41 (0.13–1.32) | 0.137 |
| Any adjudicated intracerebral hemorrhage | 142/669 (21.2) | 118/642 (18.4) | 0.84 (0.64–1.1) | 0.197 |
| Any intracranial hemorrhage | 164/669 (24.5) | 130/642 (20.2) | 0.78 (0.6–1.01) | 0.065 |

BP, blood pressure; CI, confidence interval; ECASS, European Co-operative Acute Stroke Study; IST, International Stroke Trial; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study.
to the magnitude of such a shift, or indeed its timing [14]. On the contrary, this shift may potentiate an increased likelihood of harm as the lower limit of autoregulation and acute hypoperfusion in the presence of large vessel occlusion may explain why intensive BP lowering has adverse outcome. However, in hypertensive patients without acute cerebrovascular disease, as included in the randomized trial of intensive versus standard BP control (SPRINT) trial, the intensive (<120 mmHg) BP target was associated with lower incidence of stroke and overall lower all-cause mortality. Our study does not support patients with acute (or acute on chronic) hypertension and AIS being treated with a similar intensive strategy [15].

Nonetheless, intensively lowering BP was associated with less ICH. Previously, very limited small retrospective analyzes have examined clinical outcome in those receiving BP-lowering prethrombolysis. This showed no relationship to higher rates of ICH or poor outcome [10]. Our results suggest that as ICH occurrence was lower in the intensively managed group; ICH occurrence alone does not explain the increased risk of death in the intensively lowered group at day 90.

ENCHANTED was first randomized clinical trial to examine the effects of intensive BP lowering in thrombolized patients, and herein we have attempted to explore the effects of such treatment in those with severe AIS. Prior data from subgroup analyzes of the AT1 blocker candesartan for treatment of acute stroke (SCAST) trial demonstrated no association with composite vascular endpoint or functional outcome in those receiving blood pressuring lowering and thrombolysis for AIS [16]. The large sample of a broad range of AIS patients who had systematic outcome assessments are strengths of the ENCHANTED trial. However, a clear limitation is the inability to systematically confirm the presence of large vessel occlusion angiographically, although there is clear correlation between NIHSS scores and large vessel occlusion on arteriogram. An additional consideration is the generalizability of the findings with reference to 90-day outcome, particularly if the hypothesis of BP lowering in the presence of impaired autoregulation associated with severe AIS is to be considered [14]. Concerns over generalizability may also be raised by the majority of the cohort being Asian but it could be argued that this ethnic group may be at high risk of risks of hypoperfusion and worsening ischemia from their a high prevalence of intracranial atheromatous disease and cerebral small vessel disease. In addition, without data on carotid status, we are unable to infer whether this contributed to potential risks of hypoperfusion and subsequent mortality [11]. Lastly, we did not assess whether recanalization occurred, or the extent to which BP varied, within the first 24 h post-AIS, which is relevant to SBP variability and outcomes [17].

In summary, our study has shown that in patients suffering severe AIS, intensive BP-lowering treatment showed benefits of reduced ICH and increased odds of death, without this translating into any overall change in functional recovery. Given the increasing use of endovascular thrombectomy in severe AIS, there is urgent need to establish the most appropriate level of BP control that provides the optimal balance of potential benefits and harms.

ACKNOWLEDGEMENTS

The current work falls under the portfolio of research conducted within the NIHR Leicester Biomedical Research Centre.

C.S.A. and L.S. report receiving grants (paid to their institution) and speaker fees and travel reimbursement from Takeda China. J.C. reports research grants from Servier and from NHMRC, paid to his institution. M.W. is a consultant to Amgen and Kirin. O.M.P.N. received speaker fees from Boehringer-Ingelheim, Pfizer, Medtronic, Penumbra and Bayer. P.M.B. reports honoraria for Advisory Boards from DiaMedica, Molec, Nestlé, Phagenesis, and Sanofi. J.G.W. reports having received grants from Bayer and MSD and lecture and consulting fees from Novartis, Servier, and Takeda. A.M.D. is a shareholder has a granted patent with Circle NVI for stroke imaging software. S.O.M. received speaker fees from Boehringer-Ingelheim, Pfizer, Medtronic, Penumbra.
Ethical approval: The trial protocol was approved by appropriate regulatory and ethical authorities at participating centres. Written consent was obtained from each participant or from their approved surrogate for patients who were too unwell to comprehend the information.

J.S.M. is a National Institute for Health Research (NIHR) Clinical Lecturer in Older People and Complex Health Needs. T.G.R. is an NIHR Senior Investigator. P.M.B. is Stroke Association Professor of Stroke Medicine and an Emeritus NIHR Senior Investigator. C.S.A. holds a Senior Investigator Fellowship of the National Health and Medical Council of Australia. The funders stated above did not have any involvement in the design, conduct, reporting, or decision to submit for publication.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018; 49:e166–e1100.

2. Mistry EA, Mayer SA, Khatri P. Blood pressure management after mechanical thrombectomy for acute ischemic stroke: a survey of the StrokeNet sites. J Stroke Cerebrovasc Dis 2018; 27:2474–2478.

3. Mulder MJHL, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PSS, Beumer D, et al. Baseline blood pressure effect on the benefit and safety of intra-arterial treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands). Stroke 2017; 48:1869–1876.

4. Schonenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: a randomized clinical trial. JAMA 2016; 315:1986–1996.

5. Goyal N, Tsvigoulis G, Pandhi A, Chang JJ, Dillard K, Ishfaq MF, et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. Neurology 2017; 89:540–547.

6. Petersen NH, Ortega-Gutierrez S, Wang A, Lopez GV, Strander S, Kodali S, et al. Decreases in blood pressure during thrombectomy are associated with larger infarct volumes and worse functional outcome. Stroke 2019; 50:1797–1804.

7. Lee M, Ovbiagele B, Hong KS, Wu YL, Lee JE, Rao NM, et al. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. Stroke 2015; 46:1885–1889.

8. Anderson CS, Huang Y, Lindley RJ, Chen X, Arima H, Chen G, et al. Intensive blood pressure reduction with intravenous thrombolysis for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet 2019; 393:877–888.

9. Anderson CS, Woodward M, Arima H, Chen X, Lindley RJ, Wang X, et al. Statistical analysis plan for evaluating different intensities of blood pressure control in the ENHanced Control of Hypertension And Thrombolysis stroke E stuDy. Int J Stroke 2018; 14:555–558.

10. Martin-Schild S, Halleli H, Albright KC, Khaja AM, Barreto AD, Gonzales NR, et al. Aggressive blood pressure-lowering treatment before intravenous tissue plasminogen activator therapy in acute ischemic stroke. Arch Neurol 2008; 65:1174–1178.

11. Jusufovic M, Sandset EC, Bath PM, Karbon BW, BERGE E, SCANDINAVIAN Candesartan Acute Stroke Trial Study Group. Effects of blood pressure lowering in patients with acute ischemic stroke and carotid artery stenosis. Int J Stroke 2015; 10:554–559.

12. Salinet AS, Silva NC, Caldas J, de Azevedo DS, de-Lima-Oliveira M, Nogueira RC, et al. Impaired cerebral autoregulation and neurovascular coupling in middle cerebral artery stroke: influence of severity? J Cereb Blood Flow Metab 2018; 39:2277–2285.

13. Zhang R, Witkowski S, Yu Q, Claassen JA, Levine BD. Cerebral hemodynamics after short- and long-term reduction in blood pressure in mild and moderate hypertension. Hypertension 2007; 49:1149–1155.

14. Ruland S, Aiyagari V. Cerebral autoregulation and blood pressure lowering. Hypertension 2007; 49:977–978.

15. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al., SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control [published correction appears in 2017 Dec 21;377(25):2506]. N Engl J Med 2015; 373:2103–2116.

16. Sandset EC, Bath PM, Boysen G, Jatuzis D, Køvraa K, Lüders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 2011; 377:741–750.

17. Goyal N, Tsvigoulis G, Pandhi A, Dillard K, Alsbrook D, Chang JJ, et al. Blood pressure levels post mechanical thrombectomy and outcomes in nonrecanalized large vessel occlusion patients. J Neurointerv Surg 2018; 10:925–931.