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Blood Pressure Management After Endovascular Therapy: An Ongoing Debate

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The etiology, significance and management of elevated blood pressure (BP) after acute ischemic stroke (AIS) are complex issues, dependent upon various factors such as the site of vessel occlusion, extent of cerebral ischemia, and patient comorbidities.[1] Since multiple positive clinical trials of endovascular therapy (EVT) were published in 2015, and subsequent wide utilization of EVT, BP lowering treatment has attracted attention for its potential in mitigating reperfusion injury.[1] Although observational studies are consistent in demonstrating a strong link between elevated BP after reperfusion and poor outcome,[2, 3] further reinforced in meta-analysis,[4] the benefits of altering BP after AIS has yet to be proven. Post-AIS hypertension may simply be a marker of neurological severity, underlying chronic hypertension, or other co-morbid factors related to poor outcome,[5] further reinforced by the neutral results of randomized trials in AIS to date. [67]

The 2019 American Heart Association / American Stroke Association (AHA/ASA) guidelines recommended a BP goal of 180/105 after EVT, as a reasonable extrapolation from the intravenous thrombolysis literature.[8] However, this may not be appropriate for AIS patients receiving EVT, as evident by the variable adoption of these recommendations by providers in the US;[9] and emphasizing the need for more randomized controlled trials to assess the efficacy and safety of intensive BP lowering (or enhancement) in this important patient group.

The Blood Pressure Target in Acute stroke to Reduce hemorrhaGe after Endovascular Therapy (BP TARGET), is the first such multicenter clinical trial conducted in France, which has a prospective randomized open blinded endpoint design to evaluate the impact of

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intensive SBP reduction on outcomes after successful post-EVT reperfusion (modified treatment of cerebral ischemia [mTICI] 2b-3).[10] Eligible adult patients with AIS from proximal vessel occlusion of the anterior circulation (intracranial carotid or proximal middle [M1] cerebral arteries, or both) with SBP ≥130 mmHg after successful reperfusion at the end of EVT were randomly assigned to standard (130–185 mmHg) or intensive (100–129 mmHg) SBP targets, to be achieved within 1 hour. The study enrolled 324 patients (162 in each arm), including 236 (74%) with isolated middle cerebral artery occlusion and 172 (54%) achieving complete reperfusion (mTICI 3) at the end of procedure.

BP TARGET achieved only a modest between-group difference in average SBP over 24 hours (128±11 versus 138±17 mmHg in the intensive and standard groups, respectively), and the times spent at SBP targets was only 61% and 66.6% in the intensive and standard groups. As expected, more patients in the intensive group received at least one antihypertensive medication at 24 hours than the standard group (83% vs. 20%), with calcium channel blockers being the most commonly used agent. In the intention-to-treat analysis, there was no difference in the primary outcome, any intraparenchymal hemorrhage at 24–36 hours (42% versus 43%; adjusted odds ratio [OR] 0.96, 95% confidence interval [CI] 0.60–1.51) between the groups. Moreover, there were no differences in favorable outcome (adjusted OR 0.93; 95% CI 0.58–1.48) or excellent outcome (adjusted OR 1.20; 95% CI 0.72–1.97) on the modified Rankin scale, but there were also no differences in any of the safety outcomes (symptomatic intracerebral hemorrhage, parenchymal intracerebral hematoma type 2, all-cause mortality, and hypotensive events). The lack of a treatment effect was consistent across pre-planned subgroups based on age, location of occlusion, and use of intravenous thrombolysis.

The neutral results of BP TARGET are somewhat surprising, given the abundance of observational evidence to support a benefit from SBP reduction.[9,11] However, this could largely be explained by the challenges in achieving the BP lowering protocol parameters. In particular, the SBP goal of 100–129 mmHg was only achieved at 3–4 hours post-randomization in the intensive arm, with patients being outside of this BP target more than 30% of the time. The modest SBP difference was therefore potentially insufficient to detect a potential treatment effect.

A similar modest SBP difference was observed in the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED),[12] reflecting both a natural decrease in BP after AIS,[13] and especially post-EVT,[14] but also the challenges investigators face in achieving different BP targets. Furthermore, there are uncertainties regarding the clinical relevance of the primary outcome of the BP TARGET trial, since reperfusion with EVT has not been shown to increase hemorrhagic complications, and radiographic hemorrhage may not be a reliable indicator of reperfusion injury.[15] The lack of an effect on functional outcomes is difficult to interpret given the small sample size. Because the effect size of intensive SBP reduction after EVT may be modest compared to that of EVT itself, an adequately powered trial may require considerably more patients. Moreover, the trial did not provide data regarding other important and clinically relevant safety outcomes, such as cardiac and renal adverse events, which is of special concern in patients treated with EVT due to contrast exposure. Finally, the trial was not able to test the effect of intensive BP

reduction on infarct extension, an important biomarker outcome, especially in patients with incomplete recanalization. In summary, the BP TARGET trial provided reassurance regarding the safety of BP lowering treatment after EVT but failed to demonstrate a clear benefit from the intervention.

While BP TARGET trial provides useful data on BP management post-EVT, several questions remain unanswered. There is persistent uncertainty as to whether reperfusion status modifies the effect of intensive BP treatment. It is possible that patients with complete reperfusion, who constituted nearly half of the BP TARGET trial cohort, respond more favorably to BP lowering than others. Furthermore, it remains unclear if the effect of BP lowering treatment is modified by collateral status. It is possible that BP lowering treatment could have detrimental effect in patients with poor collateral circulation, especially in the setting of incomplete reperfusion. Finally, the effect of vasoactive and anesthetic agents administered pre- or peri-procedurally on post-EVT BP trajectories and overall outcome is still not fully understood and future trials need to take these factors into consideration.

Three ongoing randomized controlled trials evaluating different BP targets (Table) will provide more guidance on the optimal BP management after EVT. Unlike BP TARGET, the primary outcomes of the ongoing trials are functional recovery, and effort has gone into the use of standardized BP management protocols in the hope of achieving faster and more sustained BP lowering. Similar to BP TARGET, however, these new trials are using fixed BP cutoffs and do not take into account patient-specific hemodynamic physiology. Emerging evidence suggest the feasibility and potential benefit of individualized BP measurements based on autoregulation indices. [16] However, there are practical considerations such as how to efficiently measure autoregulation indices across clinical sites of varying expertise, will prevent a truly personalized approach to post-EVT BP management for the near future.

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Abbreviations:

AIS	acute ischemic stroke
BP	blood pressure
EVT	endovascular therapy
SBP	systolic blood pressure

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Table

Ongoing trials comparing blood pressure management protocols after successful reperfusion with endovascular therapy

Name	Identifier*	Location	SBP target (mmHg) by group		Primary outcomes	Estimated year of completion
			Experimental	Control		
Second Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED2)	NCT04140110	China	<120 **	140–180	shift in mRS scores at 90 days	2023
Outcome in Patients Treated With Intraarterial Thrombectomy - optiMAL Blood Pressure Control (OPTIMAL-BP)	NCT04205305	South Korea	<140 **	<180	-mRS 0–2 at 90 days -symptomatic intracerebral hemorrhage -death at 90 days	2024
Blood Pressure After Endovascular Stroke Therapy-II (BEST-II)	NCT04116112	USA	−<160 ** −<140 **	<180	Final infarct volume Utility-weighted mRS at 90 days	2023

mRS denotes modified Rankin scale, SBP systolic blood pressure

* ClinicalTrials.gov

** To be achieved within 60 minutes of randomization