Blood pressure goals after mechanical thrombectomy: a moving target

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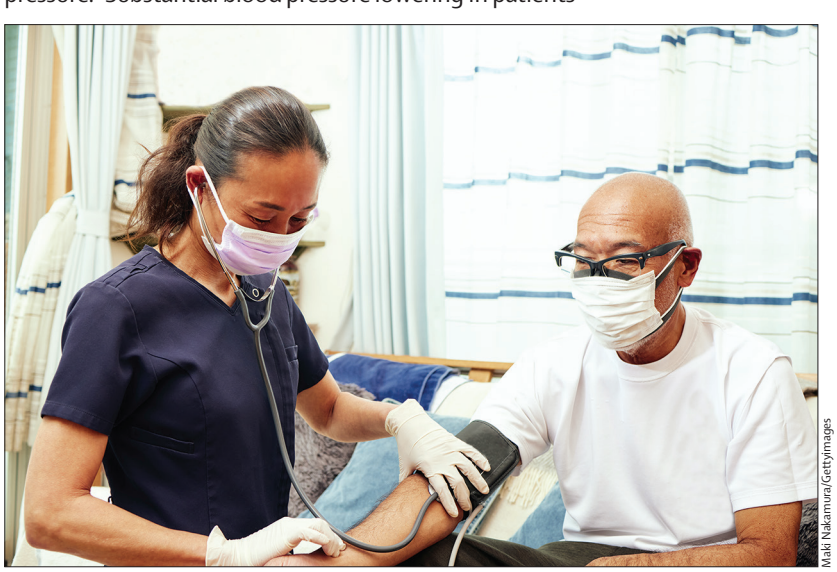
Mechanical thrombectomy markedly improves the outcomes of patients with stroke due to large-vessel occlusion. Despite preventing disability in 12·5–50% of patients, about half of patients treated with mechanical thrombectomy have disability or die after the procedure.[1] Blood pressure management after mechanical thrombectomy is a proposed strategy to improve outcomes of patients based on observational studies reporting worse functional outcomes with higher post-mechanical thrombectomy blood pressure.[2,3] A previous randomised trial showed no improvement in the incidence of intracerebral haemorrhage after mechanical thrombectomy when a lower systolic blood pressure target was used;[4] however, the trial was underpowered to test superiority of this target for the improvement of functional outcomes.

In *The Lancet*, Pengfei Yang and colleagues[5] report the findings of a pragmatic, open-label, multicentre, blinded-endpoint randomised controlled trial (ENCHANTED-2), in which more intensive treatment (systolic blood pressure target <120 mmHg) after successful mechanical thrombectomy (defined as an expanded treatment in cerebral infarction score of 2b, 2c, or 3) was compared with less intensive treatment (systolic blood pressure target 140–180 mmHg). The trial was stopped early by the Data Safety Monitoring Board after 821 of 2257 patients had been enrolled at 44 centres across China. There were 816 patients included in the intention-to-treat analysis: 407 participants (mean age 68 years [SD 12]) were assigned to the more intensive treatment group and 409 participants (mean age 67 years [12]) were assigned to the less intensive treatment group. The primary outcome was functional recovery assessed according to the distribution in scores on the modified Rankin scale (mRS; range 0 [no symptoms] to 6 [death]) at 90 days. The proportion of patients with a poor functional outcome was higher in the more intensive treatment group than the less intensive treatment group (common odds ratio [OR] 1·37 [95% CI 1·07–1·76]). Secondary outcomes of early neurological deterioration or death at 7 days and major disability (defined by an mRS score of 3–5 among survivors) at 90 days were also worse in the more intensive treatment group than the less intensive treatment group (common OR 1·53 [95% CI 1·18–1·97] for early neurological deterioration or death; 2·07 [1·47–2·93] for major disability). Insufficient data were available to identify a difference in the haemorrhagic outcomes between groups, but the proportion of participants who required dialysis was higher in the more intensive treatment group than the less intensive group (seven [2%] of 405 patients *vs* one [<1%] of 405 patients) and the proportion of patients who required assisted feeding was also higher in the more intensive treatment group than the less intensive group (256 [63%] of 405 patients *vs* 200 [49%] of 405 patients). Population and study-design-related reasons could explain why the findings of ENCHANTED-2 differed from observational safety and efficacy findings from previous trials of lower systolic blood pressure targets after mechanical thrombectomy.

Consistent with stroke epidemiology in China,[6] the majority of enrolled patients (421 [52%] of 816) had large artery atherosclerosis. In contrast, cardioembolic and embolic stroke of unknown source are more common causes of large-vessel occlusion in high-income countries.[7] Chronic hypertension, a major contributor to large artery atherosclerosis, is associated with a right shift in cerebral autoregulation whereby cerebral perfusion is dependent on higher systemic blood pressure.[7] Substantial blood pressure lowering in patients



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with chronic hypertension can compromise cerebral blood flow and worsen outcomes.[8] However, this is difficult to ascertain without infarct volume data. In ENCHANTED-2, patients with incomplete recanalisation had less favourable outcomes with more intensive treatment than did those who had less intensive treatment; however, this subgroup was underpowered to draw firm conclusions.

The lower systolic blood pressure target chosen in ENCHANTED-2 is controversial. Some retrospective studies have reported positive outcomes with lower systolic blood pressure,[9] whereas others have shown that moderate systolic blood pressure levels (<140 mmHg and <160 mmHg) are better than targets of less than 180 mmHg.[10] However, in these observational studies,[9,10] the lower systolic blood pressure observed after thrombectomy might be a physiological response to better reperfusion and cerebral autoregulation without a causal association with outcomes. Although the results of ENCHANTED-2 are applicable to regions in which intensive blood pressure lowering is used after thrombectomy, they have limited applicability within the USA. A national clinical practice survey within the USA showed that only 5% of institutions preferred a systolic blood pressure target lower than 120 mmHg after a successful mechanical thrombectomy.[11] Incomplete adherence to the lower blood pressure target in ENCHANTED-2 further limits applicability; the mean systolic blood pressure remained higher than the target for several hours in the more intensive treatment group, and was 125 mmHg (SD 18) at 1 h and 121 mmHg (13) at 24 h.

In ENCHANTED-2, the blood pressure target was achieved using locally available antihypertensives and maintained for 72 h. Urapidil, a sympatholytic drug that is a $5HT_{1a}$ receptor activator and α-1-receptor antagonist, was used in 439 (76%) of 577 participants. Although urapidil is available and relatively common in Germany and the European Union, licensing varies by country. In the French BP-TARGET trial of blood pressure after endovascular thrombectomy, central agonists such as urapidil were used in fewer than 2% of patients.[4] Calcium-channel blockers and β blockers are more commonly used in high-income countries. Differential effects of antihypertensive drugs on blood pressure variability and rebound hypertension, associated with patient outcomes,[12] should be considered when applying the findings of ENCHANTED-2 in clinical practice. However, data regarding blood pressure variability with urapidil after stroke are limited.

ENCHANTED-2 shows that aiming to lower blood pressure to less than 120 mmHg after thrombectomy in a population with large-vessel occlusion stroke predominantly due to large artery atherosclerosis is unsafe. It is important to understand that these results do not imply that patients with naturally occurring low systolic blood pressure after thrombectomy should have their systolic blood pressure elevated above 120 mmHg. Several questions about post-mechanical thrombectomy blood pressure management remain. First, are moderate goals of 140 mmHg or 160 mmHg safe and efficacious? Second, should post-mechanical thrombectomy blood pressure management be individualised according to the cause of stroke, recanalisation status, and baseline blood pressure control? Third, are outcomes influenced by the type of antihypertensive medication used? Fourth, is blood pressure autoregulation after mechanical thrombectomy better than iatrogenic lowering? In addition to the results of ENCHANTED-2, ongoing studies (NCT04205305, NCT04116112, NCT04775147) are expected to advance this knowledge. Until these results are available, patients should expect their clinical team to take an individualised approach to blood pressure management after endovascular thrombectomy.

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