Blood Pressure Management in Early Ischemic Stroke

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Elevated blood pressure is common at the time of presentation among patients with ischemic stroke, occurring in two-thirds to three-quarters of cases.1-3 The early hypertension that follows ischemic stroke often reflects undiagnosed or undertreated chronic hypertension. However, in the great preponderance of patients, an early hypertensive response to brain ischemia is an important contributing factor, partially explained by neuroendocrine response to physiologic stress. This initial hypertensive response is self-limiting, most marked in the first few hours following the onset of cerebral ischemia and resolving over several days. Within the first 24 hours after stroke, blood pressure spontaneously declines by about one-quarter in most patients.3

One of the major unresolved management issues in stroke care is how to manage this early elevation of blood pressure in patients with cerebral ischemia. Plausible physiologic arguments can be advanced both for aggressively lowering blood pressure and for completely refraining from early blood pressure intervention (ie, permissive hypertension). On one hand, blood pressure modulation should reduce cerebral edema, decrease hemorrhagic transformation of the cerebral infarct, help prevent concurrent myocardial injury, and hasten the transition to long-term antihypertensive therapy. On the other hand, early blood pressure reduction might diminish collateral flow through arteries that have lost autoregulatory function because of ischemia and increase the size of the cerebral infarct.

Accordingly, large-scale clinical trials are needed to delineate optimum blood pressure management regimens in early ischemic stroke. Prior trials have provided only incomplete guidance. A systematic review through 2008 identified 12 small randomized trials, which included a total of only 1153 patients with stroke, and concluded there was insufficient evidence to evaluate the effect of altering blood pressure on functional outcome or death.4 In the intervening years, 2 large trials provided further useful data but included both mixed ischemic and hemorrhagic stroke, rather than ischemic stroke alone.

The COSSACS trial randomized 763 patients with primarily ischemic stroke (5% primary intracerebral hemorrhage) to strategies of continuing or temporarily halting prestroke antihypertensive drugs for the first 2 weeks after stroke.5 Although the “continue” vs “stop” strategies produced a substantial difference (13 mm Hg) in systolic blood pressure at 2 weeks, there was no difference in the primary end point of death or dependency. The SCAST trial randomized 2029 patients with subacute stroke (approximately 85% ischemic, 15% hemorrhagic) to receive an angiotensin receptor blocker (ARB) or placebo for 7 days.6 Concomitant therapy with open-label antihypertensive agents was permitted at physician discretion and received by more than one-quarter of enrolled patients. A modest blood pressure–lowering effect was achieved, with systolic blood pressure 5 points lower in the ARB group at day 7. Disparate effects on the coprimary end points were observed, with no significant difference in death, myocardial infarction, or recurrent stroke at 6 months but a mild harmful effect of ARB therapy on the main functional outcome, frequency of death or major disability, at 6 months.

Against this background, the CATIS trial by He and colleagues7 in this issue of JAMA is a welcome addition to the literature on management of blood pressure in patients with acute ischemic stroke. The trial had several important design features. The CATIS trial was large (2038 patients assigned to the intervention group and 2037 to the control group), indeed by far the largest single trial to date of blood pressure lowering in subacute ischemic stroke, and enrolled only patients with cerebral ischemia, rather than also patients with primary intracerebral hemorrhage, a fundamentally different pathophysiologic entity. Unlike SCAST, CATIS analyzed blood pressure lowering in an unconfounded manner, not allowing blood pressure treatment in the control group except in circumstances of either extreme blood pressure elevation to hypertensive encephalopathy range or active end-organ injury that hypertension might further complicate. Unlike COSSACS, CATIS compared withholding antihypertensive agents, not with simply continuing the variable regimens patients may have been receiving prior to experiencing stroke, but with an aggressive, treat-to-target, blood pressure–lowering intervention.

The CATIS trialists succeeded in lowering blood pressure faster and more substantially in the intervention group than in the control group, in which a natural decline was observed. The early absolute difference in systolic blood pressure between the 2 groups at 24 hours after randomization (8.2 mm Hg) was substantially greater than in SCAST (3.3 mm Hg). The final absolute difference in systolic blood pressure at 2 weeks (8.5 mm Hg) was pronounced, although less than that achieved in COSSACS (13 mm Hg). The achieved blood pressure reduction was certainly sufficient to have expected to see an effect on clinical outcomes if blood pressure modulation in the subacute period plays an important role in determining recurrent events and final disability. However, no such effect was seen. The intervention in CATIS failed to alter the primary outcome of death or major disability at 2 weeks (683 events [33.6%] in the intervention group and 681 events [33.6%] in the control group) and failed to alter the leading secondary outcome of death or major disability at 3 months (500 events [25.2%] in the intervention group and 502 [25.3%] in the control group).

Several caveats must be considered before deciding on the importance of these results. The CATIS design and implementation had some limitations. The open-label intervention ren-
The urgent remaining unanswered question in blood pressure management in early ischemic stroke involves the acute period, within the first few hours after stroke onset, when there is still substantial penumbral, at-risk tissue. Physiologic reasoning suggests that an optimal strategy for management of blood pressure might be to avoid blood pressure-lowering agents during the first 12 hours after stroke onset, when collateral circulation compromise is still a substantial concern in most patients, and then to implement blood pressure lowering beginning in the 12- to 36-hour period if there has not been any early neurologic worsening, to help avert secondary injury and ensure that the patient will be transitioned to long-term antihypertensive therapy for secondary prevention. This time-indexed approach would be based on knowing when the actual stroke began, not when the patient presented for medical care. The CATIS time-to-randomization subgroup analysis provides a tantalizing hint that this approach might be advantageous, with a suggestion of better 6-month outcomes if blood pressure lowering was withheld in the first 12 hours and if it was started beyond 24 hours. However, a recent phase 2 trial of nitroglycerin given hyperacutely (median of 55 minutes after onset) suggested the opposite: a potential beneficial signal was observed with hyperacute blood pressure lowering but perhaps was conveyed by neuroprotective rather than hypotensive effects. Forcoming trials, including ENCHANTED,11 ENOS,12 and FAST-MAG,13 may help to resolve this remaining issue. Although results from these trials are pending, the CATIS results suggest that blood pressure lowering may safely be initiated in the subacute period following ischemic stroke and need not be delayed until 2 weeks after stroke onset.

ARTICLE INFORMATION

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REFERENCES


