EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Blood Pressure Management in Early Ischemic Stroke

Jeffrey L. Saver, MD

Elevated blood pressure is common at the time of presentation among patients with ischemic stroke, occurring in two-thirds to three-quarters of cases.[1,2] 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]

Related article page 479

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 moderation should reduce cerebral edema, deter 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 colleagues[7] 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 2033 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 a substantially greater initial difference 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-

Copyright 2014 American Medical Association. All rights reserved.

dered outcome assessments vulnerable to rater bias. A nonstandard approach to ischemic stroke subtyping was used. The entry stroke severity was relatively mild, with a median National Institutes of Health Stroke Scale score of 4. This degree of severity parallels the average severity of ischemic stroke in clinical practice but is substantially less than typically targeted in clinical trials because of the high rate of good outcomes expected with mild deficits at presentation. As a result, fully two-thirds of enrolled patients in the control group achieved the primary outcome (alive and not disabled), reducing opportunities for the intervention to demonstrate benefit. Patients with known large-artery cervicocerebral disease were excluded from the trial, limiting generalizability to this common stroke population. Most importantly, the median time to randomization was approximately 15 hours, firmly in the subacute period, rather than in the acute first 1 to 10 hours after ischemic stroke onset when there still is substantial vulnerable ischemic penumbra in most patients.

In addition, the CATIS trial reflects the population and clinical practice of China and may not be fully generalizable to other populations. For example, enrolled patients were substantially younger, smoked more often, and received concomitant acute anticoagulation therapy more often than typical Western stroke cohorts. Enrolled patients also likely differed in ways not directly measured in the trial but well known from epidemiologic studies, including having intracranial large- and small-artery atherosclerosis more often, and cervical atherosclerosis less often, as ischemic stroke mechanisms and having a greater predilection to intracerebral hemorrhage.[8]

Nonetheless, CATIS provides evidence to support the view that how blood pressure is managed in the subacute period from 12 hours to 2 weeks after ischemic stroke does not matter much. When blood pressure remained untreated during the first 2 weeks, the frequency of composite recurrent vascular events (vascular death, nonfatal stroke, nonfatal myocardial infarction, rehospitalization for angina, congestive heart failure, or peripheral arterial disease) was low, approximately 3.0%, affording little opportunity for active blood pressure lowering to improve outcome. Conversely, when blood pressure was actively treated in the subacute time frame, there apparently was little risk of infarct extension due to failure of collateral circulation. It is likely that the fate of the threatened penumbra has largely been determined by 10 hours after onset.[9]

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[10] 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. Forthcoming 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

Author Affiliations: Comprehensive Stroke Center and Department of Neurology, University of California, Los Angeles; Associate Editor, *JAMA*.

Corresponding Author: Jeffrey L. Saver, MD, Comprehensive Stroke Center, University of California, Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095 (jsaver@mednet.ucla.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no personal disclosures. In acute stroke, Dr Saver's employer, the University of California, receives funds for his services as a scientific consultant regarding trial design and conduct to Covidien, CoAxia, Grifols, Brainsgate, Lundbeck, and Stryker and holds a patent on retriever devices for stroke.

REFERENCES

1. Alqadri SL, Sreenivasan V, Qureshi AI. Acute hypertensive response management in patients with acute stroke. *Curr Cardiol Rep*. 2013;15(12):426.

2. Sare GM, Geeganage C, Bath PMW. High blood pressure in acute ischaemic stroke. *Cerebrovasc Dis*. 2009;27(suppl 1):156-161.

3. Oliveira-Filho J, Silva SC, Trabuco CC, et al. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. *Neurology*. 2003;61(8):1047-1051.

4. Geeganage C, Bath PM. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev*. 2008;(4):CD000039.

5. Robinson TG, Potter JF, Ford GA, et al; COSSACS Investigators. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS). *Lancet Neurol*. 2010;9(8):767-775.

6. Sandset EC, Bath PM, Boysen G, et al; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST). *Lancet*. 2011;377(9767):741-750.

7. He J, Zhang Y, Xu T, et al; CATIS Investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA*. doi:10.1001/jama.2013.282543.

8. Tsai C-F, Thomas B, Sudlow CLM. Epidemiology of stroke and its subtypes in Chinese vs white populations. *Neurology*. 2013;81(3):264-272.

9. Saver JL. Time is brain-quantified. *Stroke*. 2006;37(1):263-266.

10. Ankolekar S, Fuller M, Cross I, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke. *Stroke*. 2013;44(11):3120-3128.

11. Anderson C. Enhanced control of hypertension and thrombolysis stroke study (ENCHANTED). ClinicalTrials.gov website. http://clinicaltrials.gov/show/NCT01422616. Accessed December 1,2013.

12. ENOS Trial Investigators. Glyceryl trinitrate vs. control, and continuing vs. stopping temporarily prior antihypertensive therapy, in acute stroke. *Int J Stroke*. 2006;1(4):245-249.

13. FAST-MAG Investigators. Field Administration of Stroke Therapy–Magnesium (FAST-MAG) phase 3 trial. ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show/NCT00059332. Accessed August 1, 2013.

Copyright 2014 American Medical Association. All rights reserved.