Management of Hypertension in Stroke

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Elevated blood pressure is present in more than 60% of patients with acute stroke. Moderate to severe hypertension affects stroke outcomes, yet the optimal management has been a gray area in the care of such patients. Although new data are changing the approach, particularly for hemorrhagic events, significant questions remain. This article presents the latest evidence on hypertension in the setting of ischemic and hemorrhagic stroke and highlights management considerations that are relevant to emergency medicine. [Ann Emerg Med. 2014;64:248-255.]

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INTRODUCTION

Acute stroke, be it ischemic or hemorrhagic, remains a significant public health burden, with approximately 800,000 new cases each year in the United States.[1] Although emergency physicians play a significant role in the diagnosis and early management of such patients, emergency department (ED) interventions that can improve neurologic outcomes are limited to thrombolytic therapy for those with an acute, ischemic cause. Only 1 in 20 patients are eligible to receive such therapy,[2] and it is unclear what, if anything, can be done in the ED to modify outcomes for the remaining 95% of patients and especially those with hemorrhagic causes.[3]

Hemodynamic perturbations are common in acute stroke, and management of blood pressure, particularly the acute hypertensive response that accompanies most stroke presentations, is commonly seen as a target for early intervention.[4] Although current resources to guide emergency physicians on the optimal approach to elevated blood pressure in acute stroke are limited,[5] data are evolving and interest in blood pressure management to improve outcomes remains high. Accordingly, the objective of this article is to summarize the latest evidence and raise treatment considerations about the ED management of hypertension in stroke.

We review the relevant literature on blood pressure control for both ischemic and hemorrhagic causes, with particular attention directed toward recent clinical trials that are relevant to the ED. Throughout, we focus on the physiologic implications of hypertension within the context of cerebral autoregulation and emphasize an emerging understanding of the dilemma in blood pressure management: when it is too high, hemorrhagic or cardiovascular complications are more likely; when too low, cerebral perfusion may be compromised.

HYPERTENSION IN THE SETTING OF ACUTE STROKE

Greater than 60% of patients with ischemic or hemorrhagic stroke present to the ED with elevated blood pressure, and 15% of all stroke patients have an initial systolic blood pressure greater than 184 mm Hg.[6] Hypertension in hemorrhagic stroke is on average greater in magnitude than in ischemic stroke, and patients with intracerebral hemorrhage more frequently have a presenting systolic blood pressure greater than 220 mm Hg.[6] In subarachnoid hemorrhage, high blood pressure occurs nearly universally, with approximately 40% of patients having systolic blood pressure greater than or equal to 185 mm Hg.[6]

More than 70% of patients with ischemic or hemorrhagic stroke have a history of hypertension, nearly half of whom can be expected to have poor blood pressure control at baseline.[7-9] Elevation above such premorbid values or new-onset hypertension is termed the *acute hypertensive response* and is a physiologic response to the locus of brain injury. Recent studies indicate that the prefrontal and insular cortices are common sites affected by acute stroke, leading to disruption of normal autonomic control and hence an exaggerated sympathetic response.[10,11] The increased sympathetic outflow, coupled with impairment of parasympathetic activity, leads to elevated endogenous catecholamines, vasoconstriction, and increased systemic vascular resistance. The hypertensive response typically decreases gradually after symptom onset, with a decrease in systolic blood pressure of 10 mm Hg during 24 hours and 20 mm Hg during the first 10 days.[12,13]

It can be difficult to determine the presence and magnitude of the acute hypertensive response in the setting of chronic, uncontrolled hypertension without access to premorbid blood pressure values. Clues may include systolic blood pressure elevation above 180 mm Hg and the presence of subarachnoid hemorrhage. There is limited evidence to guide emergency physicians in this distinction, and guidelines do not directly factor this distinction into management recommendations.[5,14]

Whether high blood pressure reflects a hypertensive response or is consistent with premorbid values, uncontrolled hypertension, it carries prognostic significance.[15-17] Marked hypertension magnifies the risk of adverse cardiovascular events,

renal injury, and encephalopathy. It may also promote hemorrhage propagation in hemorrhagic stroke and increase the likelihood of hemorrhagic transformation in ischemic tissue.[16] Approximately 19% of ischemic stroke patients have cardiovascular events during hospitalization, including acute myocardial infarction, decompensated heart failure, and sudden cardiac death.[17] Observational ischemic stroke data indicate that marked hypertension in the ED is associated with up to a 5-fold increase in the rate of clinical deterioration and poor neurologic outcome, particularly when systolic blood pressure exceeds 180 mm Hg.[18] In hemorrhagic stroke, systolic blood pressure greater than 180 mm Hg is associated with nearly double the risk of death or dependency compared with that of patients presenting normotensive.[19] Although to our knowledge no specific study has been designed to differentiate prognosis for stroke patients according to the magnitude of their acute hypertensive response, subgroup analyses of large-scale stroke trials suggest that outcomes are the same for those with and without a history of chronic hypertension.[13]

CEREBRAL AUTOREGULATION AND THE IMPLICATIONS OF BLOOD PRESSURE CHANGE

Despite the known risks associated with persistent blood pressure elevation, uncertainty about the influence decreasing it may have on cerebral perfusion remains a primary concern.[20,21] Cerebral autoregulation is the process by which cerebral blood flow remains relatively constant despite increases or decreases in systemic blood pressure. Cerebrovascular resistance adapts to changes in perfusion pressure to maintain constant cerebral blood flow. When blood pressure exceeds the upper limit of autoregulation, there is resultant cerebral edema and blood-brain barrier dysfunction.[22] When blood pressure decreases below the lower autoregulation limit, there can be decreased perfusion, with worsening ischemia and stroke progression.

Although autoregulation classically maintains cerebral perfusion across a mean arterial blood pressure range of approximately 60 to 150 mm Hg, these normal limits become altered because of chronic, uncontrolled hypertension.[23] Hence, patients with chronic, uncontrolled hypertension typically have a right shift in their autoregulatory limits such that they are more tolerant of high and less tolerant of low systemic pressure (Figure).[24] At present, there are no reliable methods to determine the degree of this right shift in autoregulatory limits.

Ischemia may additionally impair cerebral autoregulation.[25-27] Hence, patients without a history of hypertension but with an acute hypertensive response are still at risk of impaired autoregulation. Ischemic-induced impairment is postulated in both cortical and subcortical strokes.[28,29] It may also be present in affected and unaffected hemispheres.[28] The extent of autoregulatory impairment in the earliest hours of stroke is unclear because most studies have looked at patients 24 hours after onset. Nevertheless, the notion that cerebral blood flow may depend on systemic blood pressure remains an important consideration for those managing the acute phase of stroke regardless of whether an individual has long-standing, chronic hypertension or not. Our group is currently working to develop a better understanding of this phenomenon through a prospective observational study of cerebral blood flow in hypertensive patients who present within 12 hours of stroke onset.[30]

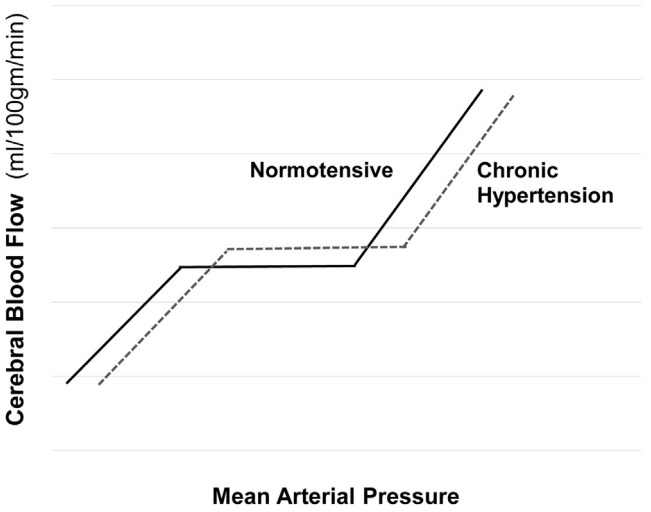

Figure. Right shift of cerebral autoregulation in normotensive versus hypertensive patients.

BLOOD PRESSURE MANAGEMENT IN HEMORRHAGIC STROKE

Intracerebral Hemorrhage

Intracerebral hemorrhage affects approximately 16 of every 100,000 people annually and carries a 30-day mortality that approaches 60%. One key determinant of outcome is the

Table 1. Current guidelines for blood pressure management of stroke subtypes.*

Stroke Subtype	Target SBP	Level of Evidence, Comparative Effectiveness Class
Ischemic stroke[5]		
Lytic candidate (IV or IA)	<185 mm Hg	B, I
Nonlytic patient	<220 mm Hg	C, I
Complicating medical conditions†	15% reduction	C, IIa
Nonaneurysmal hemorrhage[37]		
SBP >180 mm Hg	<160 mm Hg	C, IIb
SBP 150–220 mm Hg	140 mm Hg is safe	B, IIa
Aneurysmal hemorrhage[47]	<160 mm Hg	C, IIa

SBP, Systolic blood pressure; *IV*, intravenous; *IA*, intra-arterial.
*Class I: treatment should be performed, Class IIa: treatment is reasonable to perform, Class IIb: treatment may be considered; Class III no benefit to treatment. Level A: data derived from multiple randomized clinical trials; Level B: data derived from a single randomized trial or nonrandomized studies; Level C: consensus or case studies.
†Active, concomitant medical conditions that may necessitate blood pressure reduction for management, such as acute coronary ischemia, decompensated heart failure, or aortic dissection.

Table 2. Major randomized trials for blood pressure decreasing in ischemic and hemorrhagic stroke.

Trial	Design	Subjects	Time*	Agent	Outcome	Results
Intensive BP reduction in acute ICH (INTERACT)[38]	Randomized open label	404	<6 h	Open-label: target SBP 140 vs 180	Change in hematoma volume	Trend toward lower hematoma growth with intensive arm
Antihypertensive treatment of acute ICH (ATACH)[39]	Prospective, dose escalation	60	<6 h	Nicardipine: target SBP 200 vs 170 vs 140 mm Hg	Feasibility, adverse events and acute neurologic deterioration	Adverse events and neurologic deterioration below prespecified safety thresholds
Rapid BP decreasing in patients with acute ICH (INTERACT2)[9]	Randomized open label with blinded endpoint	2,839	<6 h	Open label: target SBP 140 vs 180 mm Hg	Death or major disability at 90 days	Intensive decreasing of BP did not reduce death or major disability but suggests improved functional outcomes
Low-dose β- blockade in acute stroke (BEST)[67]	Randomized double blind	302	<48 h	Propranolol or atenolol vs placebo	Neurologic recovery within first 8 days and at 1 and 6 mo	Higher death rate in treatment group. Neurologic recovery and functional outcome at 6 mo equivocal.
Effect of intravenous nimodipine on BP and outcome after stroke (INWEST)[51]	Randomized double blind	295	<24 h	Nimodipine 1 or 2 mg IV vs placebo	Neurologic recovery at day 21 and at wk 24	Reduction of diastolic BP (>20%) after high-dose nimodipine associated with death and worse neurologic recovery
Controlling hypertension and hypotension immediately poststroke (CHHIPS)[68]	Randomized double blind	179	<36 h	Labetalol or lisinopril vs placebo	Death or dependency at 2 wk	No difference in death or neurologic recovery at 2 wk. Reduction in mortality at 3 mo with treatment arm.
Candesartan for treatment of acute stroke (SCAST)[13]	Randomized double blind	2,029	<30 h	Candesartan vs placebo	Adverse events and functional outcome at 6 mo	No difference in neurologic recovery or adverse events
CATIS[57]	Randomized double blind	2,038	<48 h	Tiered antihypertensive (10%–25% SBP reduction) vs withhold antihypertensives	Death and functional outcome at 14 days and 3 mo	No difference in death or major disability

BP, Blood pressure; *ICH*, intracerebral hemorrhage.
*Time to initiation of trial intervention from onset of stroke symptoms.

intracerebral hematoma volume.[31,32] Large initial hematoma volume and hematoma expansion are associated with poor outcomes. Approximately one third of patients will have significant hematoma expansion within the first 24 hours of symptom onset, with morbid consequences.[32,33] Although to our knowledge studies have not confirmed a direct link between high blood pressure and hematoma expansion, early high blood pressure in intracerebral hemorrhage is associated with death and dependency, and this link remains plausible.[31,34]

Intense blood pressure reduction is of great clinical interest and appears safe in intracerebral hemorrhage. Despite theoretical concern for an ischemic penumbra surrounding an intracerebral hematoma, which may be sensitive to blood pressure reduction, advanced neuroimaging studies have not identified such.[35] Instead, a hibernation-like state has been postulated in the area surrounding injured tissue where low cerebral blood flow is matched by a low metabolic rate. Computed tomography perfusion studies have confirmed no adverse effect on perihematoma cerebral blood flow with early, aggressive (systolic blood pressure <150 mm Hg) blood pressure reduction.[36]

For intracerebral hemorrhage, current guidelines largely reflect expert consensus opinion,[37] but recent studies are providing important evidence relevant to emergency medicine. For ED patients with a systolic blood pressure greater than 180 mm Hg, guidelines recommend modestly reducing the blood pressure to a target systolic blood pressure of 160 mm Hg with either intermittent or continuous intravenous antihypertensives (Table 1). Guidelines also suggest that a systolic blood pressure target of 140 mm Hg is safe for most patients with presenting systolic blood pressure less than 220 mm Hg. Reflecting residual uncertainty around right-shifted autoregulatory limits, the guidelines do not recommend acutely decreasing severely elevated blood pressures (systolic blood pressure >220 mm Hg) beyond 160 mm Hg. As outlined in the following section, data are emerging that will help guide establishment of more specific blood pressure targets.

Antihypertensive Treatment in Acute Cerebral Hemorrhage trial and Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial. The guideline targets reflect results of 2 pilot trials published within the past 5 years: the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT)[38] and the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial (Table 2).[39] Both trials randomized patients to either more intensive blood pressure decreasing (target systolic blood pressure 140 mm Hg) or modest reduction (target systolic blood pressure 180 mm Hg). ATACH included an additional arm with an even more aggressive blood pressure target (systolic blood pressure 110 to 140 mm Hg). INTERACT used open-label antihypertensives, whereas ATACH exclusively used nicardipine for blood pressure decreasing. Both trials showed safety in the intensive treatment arms, and the INTERACT trial showed lower hematoma volume with intensive treatment.

INTERACT2 Trial. INTERACT led to the design of INTERACT2, the results of which provide the strongest evidence to date to guide blood pressure decreasing in acute intracerebral hemorrhage. INTERACT2 enrolled 2,839 patients with spontaneous intracerebral hemorrhage and acute systolic hypertension within 6 hours of symptom onset.[9] The trial randomized patients to a target systolic blood pressure less than 140 mm Hg versus a target systolic blood pressure less than 180 mm Hg. The choice of antihypertensive agents was left to the discretion of treating physicians. The trial failed to show a reduction in the primary outcome of death or severe disability (defined as a score of 3 to 6 on the modified Rankin Scale). Nevertheless, an ordinal analysis of the modified Rankin scores indicated a favorable shift in the distribution of scores with intensive blood pressure decreasing (pooled odds ratio for shift to higher modified Rankin score 0.87; 95% confidence interval [CI] 0.77 to 1.00). This shift indicates improved functional outcomes at 90 days with targeting a systolic blood pressure less than 140 mm Hg. Furthermore, intensive blood pressure decreasing did not lead to higher rates of early neurologic deterioration or adverse events, demonstrating the safety of targeting a systolic blood pressure less than 140 mm Hg. There was no significant effect modification according to history of hypertension, allaying concern that hypertensive patients with a presumed right shift in autoregulation are prone to cerebral ischemia with intensive blood pressure decreasing. A caveat is that INTERACT2 did not enroll patients presenting with a systolic blood pressure greater than 220 mm Hg, and whether decreasing the systolic blood pressure to 140 mm Hg is safe in such extremes remains unknown.

Notable limitations of the trial included a higher rate of withdrawal of care in the intensive-treatment cohort (5.4% versus 3.3%), variability in open-label antihypertensive agents, and limited generalizability because two thirds of patients were enrolled in China.[40] The higher enrollment in China affected drug selection because their most common antihypertensive was urapidil, an intravenous α-adrenergic antagonist not available in the United States. Last, 84% of patients in the trial had deep, small-volume hemorrhages that may make the results less applicable to a broader scope of ED patients.

ATACH II Trial. Similar to INTERACT, ATACH promoted a follow-up study. The ongoing ATACH II trial will further inform the ED management of intracerebral hemorrhage.[41] This trial targets its intervention at an even earlier point than INTERACT2. ATACH II randomizes within 4.5 hours of symptom onset to a standard treatment group (target systolic blood pressure 160 mm Hg) versus an intensive decreasing arm (target systolic blood pressure 140 mm Hg, lower limit 110 mm Hg). ATACH II also standardizes antihypertensive management with nicardipine. The results of this trial (estimated to come in 2016) will be of great interest to emergency physicians who manage such patients in the most acute phase. In the meantime, the results of INTERACT2 make intensive decreasing of blood pressure toward a target systolic blood pressure of 140 mm Hg a justifiable approach in the ED for the majority of patients presenting with a systolic blood pressure less than 220 mm Hg.

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage accounts for nearly 10% of all strokes, affecting 14.5 per 100,000 people in the United States each year.[42] It has a mortality that exceeds 25%, and up to 20% of survivors go on to have long-term disability.[43] Subarachnoid hemorrhage is typically aneurysmal because of rupture of a saccular aneurysm. A minority of such aneurysms are hereditary; tobacco use and uncontrolled hypertension are significant risk factors for the development of the majority of saccular aneurysms.[44]

Aneurysmal rebleeding, a marker of poor prognosis, typically occurs within the first 12 hours of hemorrhage and is strongly associated with persistent hypertension (systolic blood pressure >160 mm Hg).[45,46] As such, consensus favors early control of blood pressure in patients with subarachnoid hemorrhage, using a titratable agent to prevent rebleeding until the aneurysm is secured.[47] Regardless of presenting blood pressure, it is reasonable to target a systolic blood pressure less than 160 mm Hg, with an understanding that any concern for reduced cerebral perfusion with aggressive treatment is offset by the need to avoid pressure-mediated hemorrhage. Whether even more intensive parameters for the systolic blood pressure target would be beneficial is unknown, and data from recent and ongoing intracerebral hemorrhage studies may be applicable.[9,41] Guidelines introduce one caveat for the systolic blood pressure target. For patients with hydrocephalus on initial imaging, in whom raised intracranial pressure may compromise global cerebral perfusion, blood pressure targets should be individualized in consultation with neurosurgical physicians.

Beyond rebleeding, patients with subarachnoid hemorrhage are at risk of developing delayed cerebral ischemia as a result of arterial vasospasm. This complication most frequently occurs 1 week after subarachnoid hemorrhage and is a major cause of morbidity. Management of vasospasm and delayed cerebral

ischemia currently hinges on maintenance of adequate cerebral perfusion by establishing euvolemia and considering induced hypertension after the aneurysm is secured.[47] The calcium channel blocker nimodipine acts as an adjunct neuroprotective agent, improving outcome in subarachnoid hemorrhage. Despite its cerebral vasodilatory effects, it does not appear that nimodipine prevents vasospasm, and the exact mechanism of benefit is unclear.[48-50] Whether other calcium-channel blockers such as nicardipine are as effective in improving clinical outcomes in subarachnoid hemorrhage is inconclusive.[47] Nimodipine should be started within the first few days of hospitalization in all patients with subarachnoid hemorrhage and does not require emergency administration in the ED.

BLOOD PRESSURE MANAGEMENT IN ISCHEMIC STROKE

As with its hemorrhagic counterpart, there has been significant interest in decreasing blood pressure in acute ischemic stroke (Table 2). This interest reflects the potential to reduce cerebral edema, hemorrhagic transformation, vascular injury, and further cardiovascular events.[16]

As previously discussed, the primary concern with blood pressure reduction is the potential to worsen perfusion to the ischemic penumbra and ultimately enlarge the area of infarction. Long-term blood pressure control clearly reduces recurrent cardiovascular disease, but short-term blood pressure reduction could be harmful. This concern was particularly raised in earlier studies using intravenous nimodipine in acute stroke, in which large decreases in blood pressure were associated with worse clinical outcomes.[51,52] These study authors theorized that decreases in cerebral blood flow accompanied decreases in blood pressure and contributed to worse outcomes.[52] Observational studies have also found an association between decreasing blood pressure in acute stroke and poorer functional recovery.[53-55]

Such data should be approached with caution because intravenous nimodipine produced unpredictable and sometimes precipitous decreases in blood pressure, and larger randomized controlled trials testing blood pressure decreasing with different classes of agents have not consistently shown harm. Moreover, the largest systematic review to date on blood pressure decreasing in acute stroke (37 trials and 9,008 patients) did not demonstrate greater hazard in the treatment arms and showed a trend toward improvement with modest blood pressure reduction.[56]

Two large randomized controlled trials are of particular interest in the discussion of managing blood pressure in ischemic stroke. The first trial is the Scandinavian Candesartan Acute Stroke Trial [SCAST], which sought to evaluate earlier blood pressure reduction, targeting the first 24 hours after presentation.[13] SCAST randomized 2,029 patients with ischemic (85%) or hemorrhagic stroke (14%) and a mean blood pressure of 171/90 mm Hg to candesartan cilexetil or placebo for 7 days. The average time from symptom onset to enrollment was 18 hours. The trial found that decreasing of blood pressure with candesartan did not benefit functional outcome (risk ratio 1.04; 95% CI 0.97 to 1.12). However, on subgroup analysis, there was a signal of benefit for patients who presented to the ED within 6 hours of symptom onset, suggesting a window of opportunity with more immediate blood pressure reduction.

The second trial is the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS), which randomized 2,038 patients with a systolic blood pressure of 140 to 220 mm Hg to a 10% to 25% systolic blood pressure decreasing arm or a control arm (withhold antihypertensives).[57] CATIS found no reduction in death or major disability (odds ratio 0.99; 95% CI 0.86 to 1.15) with antihypertensive treatment. The trial enrolled patients up to 48 hours after symptom onset (mean 15.3 hours [SD 12.9 hours]) and used a tiered combination of intravenous antihypertensive medications: first-line enalapril, second-line calcium channel blockers, and third-line diuretics. Subgroup analysis showed a signal of efficacy opposite of SCAST, with reduced death and disability in patients randomized after 24 hours (odds ratio 0.73; 95% CI 0.55 to 0.97). Limitations of the trial include the exclusive conduct in China, the heterogeneity of antihypertensive agents, and the broad time for enrollment. Neither this trial nor SCAST reported harm in the antihypertensive arm.

Because these trials generally initiate therapy after the most acute phase of stroke, it is difficult to draw firm conclusions on the safety of antihypertensive management in the ED. Concern for impaired cerebral autoregulation is still warranted, and other factors related to the variability of stroke presentation cloud the picture: timing of stroke onset, lesion location, hemodynamic differences such as dehydration or poor cardiac output, chronic antihypertensive use, and associated cardiovascular events. Identification of patients who are at greatest risk for clinical deterioration, as well as those who stand to benefit from acute blood pressure control, might improve the clinical outcomes of these patients. Whether more intensive blood pressure decreasing should be administered post–thrombolytic therapy than current guidelines recommend is an unanswered question. Future clinical trials may determine whether more aggressive systolic blood pressure targets such as 160 mm Hg reduce the risk of hemorrhagic transformation.

Current guidelines (Table 1) recommend a cautious approach for the majority of stroke patients who are not lytic candidates, avoiding treatment unless blood pressure exceeds 220/120 mm Hg, at which point antihypertensives may be administered to gradually decrease the pressure approximately 15% or just below this threshold. The large number of stroke patients with systolic blood pressure in the 160 to 220 mm Hg range should not receive antihypertensive medications in the ED. An exception is when other, active cardiovascular conditions are present (eg, aortic dissection or acute heart failure) that warrant urgent antihypertensive therapy. For managing these conditions in the setting of acute stroke, the goal blood pressure reduction should be as gradual and as modest (15%) as the condition permits. Guidelines do recommend that stroke patients who are candidates for thrombolytic therapy have their blood pressure rapidly reduced to less than or equal to 185/110 mm Hg before

Table 3. Antihypertensive agents for acute stroke.

	Class	CBF Change	Dose	Onset, Minutes	Half-life
Labetalol	Mixed adrenergic antagonist β-blocker	Stable	10–20 mg bolus every 15 min up to 300 mg	5–10	3–6 h
Nicardipine	Calcium-channel blocker	Stable	5 mg/h IV, increase by 2.5 mg/h every 5–10 min	5–10	0.5–4 h
Nitroglycerin	Nitrate	Conflicting data	10–400 μg/min	1–2	3–5 min
Sodium nitroprusside	Nitrate	Increase	0.2–10 μg/kg/min	<1	2–5 min
Clevidipine[69]	Calcium-channel blocker	Unknown	1–2 mg/h and double at 90-s intervals initially and then at 5- to 10-min intervals when approaching goal, up to 16 mg/h	2–4	5–15 min

CBF, Cerebral blood flow.

administration of thrombolytics and that their blood pressure be maintained at less than or equal to 180/105 mm Hg throughout the infusion and during the next 24 hours.[5] Although the risk of decreasing cerebral perfusion with rapid blood pressure decreasing still exists for such patients, the potential to rapidly restore perfusion with lytics takes priority in the guidelines.

THERAPEUTIC OPTIONS

There is currently no consensus about what the best agents for blood pressure decreasing in ischemic or hemorrhagic stroke are. Nevertheless, several principles should be considered in choosing an agent. First, short-acting, titratable antihypertensives are most appropriate in the ED setting. Second, agents that maintain stable cerebral blood flow and are rapidly effective are preferred. These principles are of particular import when lytic candidates and patients with subarachnoid or intracerebral hemorrhage are managed because failure to control blood pressure smoothly and expeditiously can increase the chance of further hemorrhage or eliminate the opportunity to administer thrombolytics.

Because of associated aspiration risk and their slow onset of action, oral agents should be avoided. Transdermal agents have inconsistent absorption and efficacy. Some intravenous agents such as hydralazine or enalapril have been included as treatment options in stroke guidelines[5] but can be difficult to titrate and have unpredictable effects.[58] Enalapril, however, was first-line therapy in the CATIS trial, with no reported increase in adverse events.[57] There is also theoretical concern that nitroglycerin and hydralazine diminish cerebral perfusion through systemic vasodilation.[59] Recent evidence in glyceryl trinitrate, however, indicates stable cerebral perfusion with this nitrate.[60] Intravenous labetalol has long been a first-line ED agent for blood pressure control in ischemic or hemorrhagic stroke. It has a rapid onset of action and is associated with stable cerebral perfusion (Table 3). Intravenous labetalol remains a reasonable choice for hypertension control, particularly when the blood pressure is close to goal.

Intravenous nicardipine is a newer agent that has many ideal characteristics for managing the acute hypertensive response in the ED. It has been shown to decrease blood pressure more smoothly than sodium nitroprusside or labetalol and to be associated with stable brain oxygen tension.[61-63] Data indicate that nicardipine achieves goal blood pressure more reliably and more expeditiously than labetalol.[64,65] In a recent trial of 54 patients with hypertension in acute stroke, 89% of nicardipine-treated patients achieved goal blood pressure within 60 minutes of drug administration compared with 25% of labetalol-treated patients.[64] Nicardipine patients had fewer requirements for rescue antihypertensives and less blood pressure variability than those treated with labetalol. Although data do not show improved patient-centered outcomes with nicardipine use, such properties have led to nicardipine's inclusion in recent guidelines for stroke management.[5]

Clevidipine is another newer, short-acting calcium channel blocker that is titratable and appropriate for ED management of acute hypertension in stroke. Although it has not been as well studied in stroke as nicardipine, it carries similar pharmacokinetic properties and has a much shorter half-life.[66] Clevidipine is thus a feasible alternative to nicardipine and may offer some advantage in terms of rapid drug clearance.

CONCLUSIONS

The emergency management of acute hypertension in stroke remains largely informed by expert opinion. This is particularly true in ischemic stroke, for which randomized trials of blood pressure management in the first 24 hours are lacking. New evidence suggests that more intensive antihypertensive therapy in hemorrhagic stroke is likely safe and potentially more effective. Although data are emerging, it is unlikely that a singular target will be best for all patients, and an individualized approach to blood pressure management for acute stroke will likely be the next frontier.

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REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics 2012 update: a report from the American Heart Association. *Circulation*. 2012;125:188-197.
2. Adeoye O, Hornung R, Khatri P, et al. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. *Stroke*. 2011;42:1952-1955.
3. Sacco S, Marini C, Toni D, et al. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. *Stroke*. 2009;40:394-399.
4. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation*. 2008;118:176-187.
5. Jauch EC, Saver JL, Adams HP Jr, et al. 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*. 2013;44:870-947.
6. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007;25:32-38.
7. Niska RW. Blood pressure measurements at emergency department visits by adults: United States, 2007-2008. *NCHS Data Brief* 2011;(72):1-8.
8. Ishitsuka K, Kamouchi M, Hata J, et al. High blood pressure after acute ischemic stroke is associated with poor clinical outcomes: Fukuoka Stroke Registry. *Hypertension*. 2014;63:54-60.
9. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355-2365.
10. Meyer S, Strittmatter M, Fischer C, et al. Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. *Neuroreport*. 2004;15:357-361.
11. Barron SA, Rogovski Z, Hemli J. Autonomic consequences of cerebral hemisphere infarction. *Stroke*. 1994;25:113-116.
12. Toyoda K, Okada Y, Fujimoto S, et al. Blood pressure changes during the initial week after different subtypes of ischemic stroke. *Stroke*. 2006;37:2637-2639.
13. Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomized, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741-750.
14. Wallace JD, Levy LL. Blood pressure after stroke. *JAMA*. 1981;246: 2177-2180.
15. Rodriguez-Yanez M, Castellanos M, Blanco M, et al. New-onset hypertension and inflammatory response/poor outcome in acute ischemic stroke. *Neurology*. 2006;67:1973-1978.
16. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*. 2004;43:18-24.
17. Prosser J, MacGregor L, Lees KR, et al; VISTA Investigators. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke*. 2007;38:2295-2302.
18. Leonardi-Bee J, Bath PMW, Philips SJ, et al; for the IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315-1320.
19. Zhang Y, Reilly KH, Tong W, et al. Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. *J Hypertens*. 2008;26:1446-1452.
20. Fischer U, Rothwell PM. Blood pressure management in acute stroke: does the Scandinavian Candesartan Acute Stroke Trial (SCAST) resolve all of the unanswered questions? *Stroke*. 2011;42:2995-2998.
21. Kang J, Ko Y, Park JH, et al. Effect of blood pressure on 3-month functional outcome in the subacute stage of ischemic stroke. *Neurology*. 2012;79:2018-2024.
22. Symon L, Held K, Dorsch NW. A study of regional autoregulation in the cerebral circulation to increased perfusion pressure in normocapnia and hypercapnia. *Stroke*. 1973;4:139-147.
23. Olsen TS, Larsen B, Herning M, et al. Blood flow and vascular reactivity in collaterally perfused brain tissue: evidence of an ischemic penumbra in patients with acute stroke. *Stroke*. 1983;14:332-341.
24. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients: the modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. *Circulation*. 1976;53:720-727.
25. Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke. *Am J Hypertens*. 2012;25:946-950.
26. Aries MJ, Elting JW, De Keyser J, et al. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke*. 2010;41: 2697-2704.
27. Wojner-Alexander AW, Garami Z, Chernyshev OY, et al. Heads down: flat positioning improves blood flow velocity in acute ischemic stroke. *Neurology*. 2005;64:1354-1357.
28. Schwarz S, Georgiadis D, Aschoff A, et al. Effects of induced hypertension on intracranial pressure and flow velocities of the middle cerebral arteries in patients with large hemispheric stroke. *Stroke*. 2002;33:998-1004.
29. Gur AY, Gucuyener D, Uzuner N, et al. Cerebral vasomotor reactivity of patients with acute ischemic stroke: cortical versus subcortical infarcts: an Israeli-Turkish collaborative study. *J Neurol Sci*. 2007;257: 121-125.
30. Miller JB; Henry Ford Hospital. *Hemodynamic Effects on Cerebral Autoregulation in Acute Stroke*. Bethesda, MD: National Library of Medicine; 2000. [Cited February 10, 2014.] ClinicalTrials.gov [Internet]. Available at: http://clinicaltrials.gov/ct2/show/NCT02056821. Accessed March 25, 2014.
31. Ohwaki K, Yano E, Nagashima H, et al. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke*. 2004;35: 1364-1367.
32. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5.
33. Davis SM, Broderick J, Hennerici M, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181.
34. Jauch EC, Lindsell CJ, Adeoye O, et al. Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. *Stroke*. 2006;37:2061-2065.
35. Zazulia AR, Diringer MN, Videen TO, et al. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage. *J Cereb Blood Flow Metab*. 2001;21:804-810.
36. Butcher KS, Jeerakathil T, Hill M, et al. The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure trial. *Stroke*. 2013;44:620-626.
37. Morgenstern LB, Hemphill JC 3rd, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2010;41:2108-2129.
38. Anderson CS, Huang Y, Wang JG, et al. Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT): a randomized pilot trial. *Lancet Neurol*. 2008;7:391-399.
39. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Investigators. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med*. 2010;38:637-648.
40. Frontera JA. Blood pressure in intracerebral hemorrhage—how low should we go? *N Engl J Med*. 2013;368:2426-2427.

41. Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. *Neurocrit Care*. 2011;15:559-576.
42. Shea AM, Reed SD, Curtis LH, et al. Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003. *Neurosurgery*. 2007;61:1131-1137.
43. Nieuwkamp DJ, Setz LE, Algra A, et al. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol*. 2009;8:635-642.
44. Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773-2780.
45. Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. *Neurosurgery*. 1983;13:479-481.
46. Naidech AM, Janjua N, Kreiter KT, et al. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. *Arch Neurol*. 2005;62:410-416.
47. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2012;43:1711-1737.
48. Feigin VL, Rinkel GJ, Algra A, et al. Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: a systematic review. *Neurology*. 1998;50:876-883.
49. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2007;(3):CD000277.
50. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm: a controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med*. 1983;308:619-624.
51. Wahlgren NG, MacMahon DG, De Keyser J, et al; for the INWEST Study Group. The Intravenous Nimodipine West European Trial (INWEST) of nimodipine in the treatment of acute ischemic stroke. *Cerebrovasc Dis*. 1994;4:204-210.
52. Ahmed N, Näsman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. *Stroke*. 2000;31:1250-1255.
53. 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;61:1047-1051.
54. Vlcek M, Schillinger M, Lang W, et al. Association between course of blood pressure within the first 24 hours and functional recovery after acute ischemic stroke. *Ann Emerg Med*. 2003;42:619-626.
55. Castillo J, Leira R, García MM, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke*. 2004;35:520-526.
56. Geeganage CM, Bath PM. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension*. 2009;54:775-781.
57. 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*. 2014;311:479-489.
58. Garden A, Davey DA, Dommisse J. Intravenous labetalol and intravenous dihydralazine in severe hypertension in pregnancy. *Clin Exp Hypertens*. 1982;1:371-383.
59. Overgaard J, Skinhoj E. A paradoxical cerebral hemodynamic effect of hydralazine. *Stroke*. 1975;6:402-410.
60. Willmot M, Ghadami A, Whysall B, et al. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension*. 2006;47:1209-1215.
61. Liu-Deryke X, Janisse J, Coplin WM, et al. A comparison of nicardipine and labetalol for acute hypertension management following stroke. *Neurocrit Care*. 2008;9:167-176.
62. Roitberg BZ, Hardman J, Urbaniak K, et al. Prospective randomized comparison of safety and efficacy of nicardipine and nitroprusside drip for control of hypertension in the neurosurgical intensive care unit. *Neurosurgery*. 2008;63:115-121.
63. Narotam PK, Puri V, Roberts JM, et al. Management of hypertensive emergencies in acute brain disease: evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation. *J Neurosurg*. 2008;109:1065-1074.
64. Liu-Deryke X, Levy PD, Parker D Jr, et al. A prospective evaluation of labetalol versus nicardipine for blood pressure management in patients with acute stroke. *Neurocrit Care*. 2013;19:41-47.
65. Peacock WF, Varon J, Baumann BM, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. *Crit Care*. 2011;15:R157.
66. Deeks ED, Keating GM, Keam SJ. Clevidipine: a review of its use in the management of acute hypertension. *Am J Cardiovasc Drugs*. 2009;9:117-134.
67. Barer DH, Cruickshank JM, Ebrahim SB, et al. Low dose beta blockade in acute stroke ("Best" Trial): an evaluation. *BMJ*. 1988;296:737-741.
68. Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48-56.
69. Medicines Company [Internet]. Parsippany (NY): Cleviprex full prescribing information; c2008 [cited 2014 Jan 30]. Available at: http://www.cleviprex.com/clev-pdfs/1%2014_Proposed_PI-S-003%20(clean%20ver).pdf.