Acute hypertensive response is the elevation of blood pressure (BP) above normal and premorbid values that initially occurs within the first 24 hours of symptom onset in patients with stroke. This phenomenon was reported in >60% of patients presenting with stroke in a nationally representative study from the United States. With ~980,000 patients admitted with stroke each year in the United States, the estimated annual prevalence of acute hypertensive response is more than half a million patients. With ~15 million patients experiencing stroke worldwide each year, the acute hypertensive response may be expected in ~10 million patients per year. The acute hypertensive response in stroke patients is managed by a diverse group of physicians, including emergency physicians, intensivists, internists, primary care physicians, neurologists, neurosurgeons, and cardiologists. Previous audits suggest that antihypertensive agents and management strategies vary considerably and are not always consistent with recommended guidelines.

Data from 11,81 acute ischemic stroke patients enrolled in the Project for Improvement of Stroke Care Management suggested that administration of antihypertensive medication within 24 hours in 56% of the patients was inconsistent with guidelines provided by the American Stroke Association (ASA). The present review article summarizes the current concepts pertaining to treatment of the acute hypertensive response derived from recent guidelines provided by professional organizations and “best available” evidence derived from experimental and clinical studies and discusses incorporation of these concepts into clinical practice. Randomized trials, nonrandomized controlled studies, and selected observational studies were identified with multiple searches on Medline from 1980 to 2007 by cross-referencing the key words of stroke, acute hypertension, antihypertensive agents, acute stroke, and hypertension. Pertinent articles identified from bibliographies of selected articles were also reviewed. Treatment targets and strategies were identified by review of existing guidelines from professional organizations.

Definition of Acute Hypertensive Response
The 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) define hypertension on the basis of the presence of consistent BP ≥140/90 mm Hg (multiple readings on separate days). This definition of hypertension is a threshold for the use of long-term antihypertensive treatment that is supported by evidence derived from randomized trials and clinical or population-based data that demonstrate reduction in cardiovascular events with this threshold for treatment. The same definition cannot be applied in the case of acute hypertensive response, because the above-mentioned ascertainment criteria and rationale are not valid. The executive summary of the ISH statement on management of BP in acute stroke stated that high BP (>140/90 mm Hg) is very common early after ischemic stroke (occurring in 75% of cases) and intracerebral hemorrhage (ICH; >80%) and is independently associated with a poor functional outcome. To maintain consistency with the ISH statement, acute hypertensive response is defined as "systolic BP ≥140 mm Hg or diastolic BP of ≥90 mm Hg demonstrated on 2 recordings taken 5 minutes apart within 24 hours of symptom onset.” This definition predominantly serves to provide a uniform standard for measuring prevalence and not for setting treatment thresholds for antihypertensive treatment, which may vary depending on stroke subtype and other considerations.

Prevalence of Acute Hypertensive Response
The reported prevalence of the acute hypertensive response depends on patient selection, study design, referral patterns, and the definition used. In a systematic review of 18 studies, 52% of patients with stroke were reported to have an acute hypertensive response at the time of admission. The criteria used to define high BP varied considerably: Systolic BP criteria ranged from 150 to 200 mm Hg and diastolic BP criteria from 90 to 115 mm Hg. In one of the largest studies in the United States using the National Hospital Ambulatory Medical Care Survey, systolic BP ≥140 mm Hg was observed in 63% of the 563,704 adult stroke patients, diastolic BP ≥90 mm Hg in 28%, and mean arterial pressure (MAP) ≥107 mm Hg in 38%. In the International Stroke Trial, 17,398 patients were randomized within 48 hours of stroke onset (median time 20 hours) from 467 hospitals in 36 countries. Mean systolic BP at enrollment was 160.1 mm Hg, and 82% of patients had high BP based on the WHO definition of hypertension (systolic BP >140 mm Hg).
Characteristics of Acute Hypertensive Response
The acute hypertensive response in stroke is characterized by its high prevalence, self-limiting nature, and prognostic significance. With the definition of hypertension provided by the WHO6 and JNC 7,7 the age-, sex-, and ethnicity-adjusted rates were 61% among stroke patients and 14% in the US population in 1999 to 2000.1,11 New-onset high BP in patients without a previous history of hypertension has been observed in 20% of patients with stroke12 and 8% of the general population.11 A crude comparison suggests that these proportions are higher than expected on the basis of premorbid hypertension among stroke patients. There is also spontaneous reduction of BP (by an average of 20/10 mm Hg) within 10 days after the acute event without any specific antihypertensive therapy.13 Among the 1455 patients from the Glycine Antagonist in Neuroprotection International Trial14 evaluated within 6 hours of symptom onset, MAP declined gradually over the next 60 hours regardless of initial MAP value, with a prominent reduction observed within 10 hours of the first measurement. The prognostic significance is highlighted in a systematic review of 18 studies9 that demonstrated that patients with stroke and high initial BP were at a 1.5- to 5.0-fold increased risk of death or dependency and clinical deterioration.

Underlying Causes of Acute Hypertensive Response
In at least a portion of these patients, the acute hypertensive response is merely a reflection of inadequately treated or undetected chronic hypertension15; however, spontaneous reduction in the initial BP over the next few days in most patients13,14 supports the role of other transient and stroke-specific mechanisms. Spontaneous reduction of BP after vessel recanalization in patients with ischemic stroke also implies stroke-specific mechanisms.16 Stroke involves transient or permanent damage to the areas involved in the brain regulation of cardiovascular functioning, including BP. The parasympathetic and sympathetic nervous systems are laterialized to the left and right cerebral hemispheres, respectively.17 Prefrontal18 and insular19 cortices provide inhibitory and excitatory input, respectively, through pathways that connect to the nuclei in the brainstem, particularly in nucleus tractus solitarius and ventrolateral medulla.20 Further modulation is provided by cingulated cortex, amygdala, and hypothalamus. Because of the widespread distribution of these areas, most stroke lesions involve these areas to a varied extent.

Increased sympathoadrenal tone21 with subsequent release of renin and vasoconstriction of arterioles results from (1) direct injury to inhibitory or modulatory brain regions or (2) indirect effects of reduced parasympathetic activity,22 which leads to impaired cardiac baroreceptor sensitivity in patients with stroke.23 Although direct injury is the most likely explanation, an indirect effect of muscle paralysis24 or the release of neurotransmitters such as nitric oxide25 during ischemia may be contributing factors to altered activity of these nuclei. Other stress responses to hospitalization, headache, urinary retention, or concomitant infection26 may lead to abnormal autonomic activity and raised levels of circulating catecholamines27 and inflammatory cytokines12 and subsequently may contribute to the hypertensive response. Presumably, these abnormal autonomic responses normalize over a few hours owing to spontaneous or therapeutic recanalization and resolution of the ischemia and perhaps because of other neural compensatory mechanisms.28 An increase in systemic BP associated with increased intracranial pressure (ICP), particularly in the presence of brainstem compression,29–31 has particular relevance for patients with intracerebral and subarachnoid hemorrhages. Elevated ICP can result in a systemic BP increase52; however, the elevation in systemic BP does not appear to demonstrate a clear relationship to the presence of cerebral ischemia,23,33 ICP values, transtentorial herniation,32,33 or response to hypervolemic treatment.32,33 This suggests that the primary cause of the acute hypertensive response is damage or compression of specific regions in the brain that mediate autonomic control. Hypertensive responses to other factors mentioned above are exaggerated and additive because of impaired parasympathetic activity and baroreceptor sensitivity.

Cerebrovascular Physiology and Implications for Treatment
Under normal circumstances, changes in precapillary arteriolar diameter (<400 μm) maintain constant cerebral blood flow in the capillary bed between MAPs of 60 and 150 mm Hg.34 A fast dynamic response to changes in pressure pulsations is followed by a slow static response that restores cerebral blood flow after the initial dynamic response has settled35 by myogenic (mechanogenic) and metabolic (chemogenic) mechanisms.36 With decreasing BP, there is vasodilation of arterioles until maximal vasodilation occurs, and subsequently, there is reduction of blood flow. With increasing BP, there is progressive vasoconstriction of arterioles until the BP exceeds the upper limit of autoregulation, followed by breakthrough vasodilation, increase in cerebral blood flow,36 blood-brain barrier dysfunction, and cerebral edema.

In chronic hypertension, the lower end of the autoregulation curve is shifted toward high pressure,37 presumably because vessel wall thickening and luminal narrowing limit the capacity of the resistance vessels for dilation. In acute stroke, autoregulation may be impaired in regions surrounding an acute lesion and even in the hemisphere contralateral to the lesion because of dilation of cerebral resistance vessels in an attempt to increase blood flow in response to tissue ischemia and acidosis.38 More recently, it has been shown that autoregulation is impaired for rapid changes (dynamic autoregulation) in systemic BP even when it is preserved for controlled changes.39 Other conditions, such as cerebral vasospasm in subarachnoid hemorrhage,40 also cause arteriolar constriction, which shifts the autoregulatory range toward higher values.

In the presence of elevated ICP, MAPs >60 mm Hg may not be adequate to maintain constant cerebral blood flow in the capillary bed. Ascertainment of the difference between MAP and ICP is recommended as an index of cerebral perfusion pressure. The standard, global measure of cerebral perfusion pressure can underestimate the localized pressure...
and perfusion changes in focal stroke lesions but is still useful in the absence of another, more sensitive measure. The Brain Trauma Foundation recommends maintenance of a cerebral perfusion pressure >70 mm Hg to enhance perfusion to ischemic regions of the brain after severe traumatic injury. In stroke, such treatment thresholds have been extrapolated from global cerebral perfusion data derived from traumatic brain injury patients in the absence of any other pertinent data.

**Management of Acute Hypertensive Response in Stroke Subtypes**

Despite the high prevalence of acute hypertensive responses observed in all stroke subtypes, differences in underlying pathophysiology mandate different management strategies (Figure). BP responses can be categorized as (1) spontaneous decline without medication; (2) no clear decline, or even an elevation, despite administration of antihypertensive medication; (3) modest decline with antihypertensive medication (~10% to 15% from baseline value); and (4) intense decline with antihypertensive medication (~20% from baseline value). The studies presented below are confounded by overlap of the 4 categories of responses in varying proportions and require interpretation with this understanding. Another important issue in management is the identification of intravascular volume depletion (dehydration) in these patients, which may result in a natural hypertensive or hypotensive response or an exaggerated hypotensive response to antihypertensive medication. Early identification and appropriate fluid repletion before pharmacological intervention ensures a controlled response to treatment.

**Patients With Acute Ischemic Stroke**

Ischemic stroke results from occlusion of an artery with subsequent reduction in regional cerebral blood flow, demarcated into regions of severe reduction (core) and moderate reduction (penumbra). The penumbra remains viable for hours because some degree of blood flow is sustained through collateral supply; however, it is theoretically vulnerable to further ischemic injury with systemic BP reduction because of impaired regional autoregulation, particularly during rapid BP reduction. Conversely, in an experimental model of focal cerebral ischemia and reperfusion, BP reduction reduced infarct size and deficits. Therefore, a period of vulnerability to progression of ischemic deficits may exist after which there may be benefit from BP reduction. A higher rate of death or dependency was observed in patients with initially high or low systolic BP (U-shaped relationship) among 17,398 ischemic stroke patients randomized in the International Stroke Trial. The relationship appeared to be mediated in part by increased rates of early recurrence and death that resulted from presumed cerebral edema in patients with high BP and increased coronary heart disease events in
those with low BP. Recent data suggest that wide fluctuations (not initial values) of BP in the first few hours in patients with acute ischemic stroke may be associated with an increased risk of death at 90 days.14,54

The Low Dose Beta Blockade in Acute Stroke (BEST) study65 (Table 142–47,55–60) revealed greater mortality among patients in whom β-blocker therapy was begun within 48 hours of symptom onset. An analysis of data from the Intravenous Nimodipine West European Stroke Trial (INWEST) found a significant correlation between diastolic BP reduction with nimodipine and worsening of neurological status (within 24 hours of symptom onset).61 Patients with a diastolic BP reduction ≥20% or a diastolic BP drop to ≤60 mm Hg had a significantly higher risk of death or dependency at 21 days. A subsequent meta-analysis88 evaluating the use of oral or intravenous calcium channel blockers initiated at 6 hours to 5 days after symptom onset in acute ischemic stroke patients found that intravenous administration, higher doses, and administration within 12 hours of symptom onset were associated with an increased risk of poor outcomes. The effect may be mediated in part by alterations of regional cerebral blood flow.62 This susceptibility varies with stroke subtype and evolution stage, showing higher tolerance to BP lowering in patients with total anterior circulation infarction63 and in those treated after 12 hours of symptom onset.58

New data suggest that the increased risk of poor outcomes is probably limited to patients treated very aggressively or to specific antihypertensive agents (Table 1). The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS)47 trial initiated treatment with either the angiotensin receptor antagonist candesartan or placebo in patients with ischemic stroke and a BP measurement ≥200/100 mm Hg 6 to 24 hours after admission or ≥180/105 mm Hg at 24 to 36 hours. The target reduction in BP was 10% to 15% within 24 hours. If patients in the candesartan group displayed a hypertensive profile on day 7 (mean daytime BP >135/85 mm Hg), candesartan was increased or an additional antihypertensive drug was added. In placebo-treated patients with a hypertensive profile on day 7, candesartan was begun. Both the cumulative 12-month mortality rate (2.9% versus 7.2%) and the incidence of vascular events (9.8% versus 18.7%) were lower in the candesartan-treated group; however, the primary outcome of disability measured by Barthel index at 3 months was not different between the 2 treatment groups.

A post hoc analysis of hypertensive patients in the National Institutes of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen (rtPA) trial42 who received antihypertensive therapy (intravenous labetalol and/or nitroprusside in selected patients) but no rtPA therapy within 24 hours of randomization showed no difference in rates of deterioration or death at 24 hours or in rates of favorable outcome at 3 months compared with hypertensive patients who received neither antihypertensive medication nor rtPA. The results from various studies suggest somewhat contradictory consequences of antihypertensive treatment in acute ischemic stroke: INWEST showed a detrimental effect; ACCESS, a favorable effect; and post hoc analysis of NINDS rtPA study showed no effect. The mean systolic BP in the ACCESS trial was higher than in INWEST (196 versus 162 mm Hg), and the mean value during the first 2 days was also higher (>150 versus <145 mm Hg). The average maximum MAP in the NINDS placebo group (those not given rtPA) who received antihypertensive medication (133 mm Hg) and the average lowest value during the first 24 hours (>110 mm Hg) also appear higher than those observed in INWEST. The difference in aggressiveness of BP reduction between the studies was also evident from the 60% incidence of diastolic BP values of ≤60 mm Hg during nimodipine treatment in INWEST. These differences stress the importance of BP thresholds and treatment targets in determining tolerability of antihypertensive treatment in acute ischemic stroke.

Another aspect that requires further consideration is the potential for differential benefit or harm between classes of antihypertensive medication. The differences in results between trials such as the BEST, INWEST, ACCESS, and NINDS rtPA studies may be related to the properties of the antihypertensive medication used. A systematic review64 of 7 randomized, controlled trials involving patients with prior stroke or transient ischemic attack demonstrated heterogeneity in outcomes that were related in part to the class of antihypertensive drugs used. Angiotensin-converting enzyme inhibitors and diuretics, separately and in combination, but not β-blockers, reduced vascular events. Another estimate of stroke reduction with different antihypertensive medications (angiotensin-converting enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, and diuretics or β-blockers) using data from 29 randomized trials65 directed toward primary prevention suggested that the greatest reduction was observed with angiotensin receptor blockers, with small (borderline significance) differences between the other different classes of antihypertensive medication. Conclusive evidence for differential effects of different antihypertensive medications in the acute period is not available.

The management of high BP in acute ischemic stroke is highly controversial because of a lack of reliable evidence from randomized, controlled trials. The current recommendations regarding BP management in acute ischemic stroke46 are based on 2 observations. BP reduction is associated with an increased risk of neurological deterioration and worse outcome in patients with ischemic stroke in some studies,59,66 although a causal relationship has not been demonstrated conclusively. The benefit of acute BP lowering (unlike chronic treatment) in patients with ischemic stroke remains unclear.46 There may be a reduction of cardiovascular events with early institution of angiotensin receptor antagonists; however, the benefit is not conclusively related to BP reduction.47 Therefore, in the absence of definitive benefit, both the ASA and the European Stroke Initiative are consistent in not recommending routine lowering of BP unless it is repeatedly exceeds 200 to 220 mm Hg systolic or 120 mm Hg diastolic in the acute period.46,67,68 However, with the anticipated completion of several large clinical trials42,47,55–60 in the next 5 years (Table 1), these recommendations may be modified.
### Table 1. Summary of Completed and Ongoing Prospective Clinical Trials That Evaluated or Are Evaluating Various Aspects of Antihypertensive Treatment in the Acute Period of Stroke

<table>
<thead>
<tr>
<th>Trial(s) Description</th>
<th>Design</th>
<th>Patients Included</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>No. of Patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions for deliberately altering BP in acute stroke</td>
<td>Meta-analysis (5 trials)</td>
<td>Any stroke within 2 wk of symptom onset</td>
<td>Nimodipine (n=66), nicardipine (n=5), captopril (n=3), clonidine (n=2), nitroglycerin (n=16), perindopril (n=14), and placebo/control (n=92)</td>
<td>BP reduction and case fatality</td>
<td>218</td>
<td>Oral calcium channel blockers reduced SBP (weighted mean difference 10.9 mm Hg) at 48 h; ACEI reduced SBP (weighted mean difference 15.0 mm Hg) at 24 h; Nitroglycerin showed a nonsignificant reduction in BP at 24 h;</td>
</tr>
<tr>
<td>Low Dose Beta Blockade in Acute Stroke (BEST)</td>
<td>Randomized trial</td>
<td>Hemispheric stroke presenting within 48 h of symptom onset</td>
<td>Atenolol (50 mg/d), slow-release propranolol (80 mg/d), or matching placebo capsules for 3 wk or until discharge</td>
<td>Neurological assessment at entry, day 8, and 1 and 6 mo</td>
<td>302</td>
<td>Deaths more common among patients taking β-blockers. Neurological recovery and functional outcome at 6 mo did not differ</td>
</tr>
<tr>
<td>Acute Candesartan Cil synergists in Stroke Survivors (ACCESS)</td>
<td>Double-blind, randomized multicenter trial</td>
<td>Initial BP &gt;200/110 mm Hg, acute cerebral ischemia and motor paresis</td>
<td>Candesartan or placebo for 7 d initiated over a mean period of 30 h after symptom onset</td>
<td>Functional status assessed by mRS and Barthel Index and mortality rates after 3 mo</td>
<td>339</td>
<td>Total mortality, cerebral complications, and cardiovascular complications reduced by 47.5% with candesartan initiated within 24 h of admission; No clear effect on end-of-treatment death, combined death or deterioration, or end-of-trial death, combined death, or dependency</td>
</tr>
<tr>
<td>Nitroglycerin for acute stroke</td>
<td>Meta-analysis (2 studies)</td>
<td>Any stroke within 4 d of symptom onset</td>
<td>Nitroglycerin (5–10 mg/d) by transdermal patch</td>
<td>BP change on day 1</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists for acute ischemic stroke</td>
<td>Meta-analysis (28 trials)</td>
<td>Any stroke 6 h to 5 d after symptom onset (ischemic stroke only in 23 trials)</td>
<td>IV isradipine (1 trial); oral nimodipine (16 trials); IV flunarizine (3 trials); oral PY108-608 (1 trial); and IV and oral nimodipine (2 trials)</td>
<td>Poor outcome, defined as death or dependency in activities of daily living</td>
<td>7521</td>
<td>No overall effect on outcome at the end of follow-up. IV administration, higher doses, and administration within 12 h of symptom onset were associated with an increased rate of poor outcome</td>
</tr>
<tr>
<td>NINDS rt-PA Stroke Trial</td>
<td>Post hoc analysis of randomized trial</td>
<td>Ischemic stroke within 3 h of symptom onset and BP &gt;180/105 mm Hg after receiving IV rt-PA or placebo</td>
<td>IV labetalol or nitropusside infusion if DBP &gt;140 mm Hg or inadequate response to labetalol; treatment for 24 h; 80/195 placebo-treated patients and 65/177 rtPA-treated patients received antihypertensive treatment</td>
<td>Neurological deterioration, ICH, and good outcome (multiple scales at 3 mo)</td>
<td>372</td>
<td>All outcome measures similar for those patients who received postrandomization antihypertensive therapy and those who did not among placebo-treated patients; among rtPA patients, those who received antihypertensive therapy had worse outcomes than those who did not</td>
</tr>
<tr>
<td>Controlling Hypertension and Hypotension Immediately Post-Stroke Trial (CHHIPS)</td>
<td>Prospective, multicenter, randomized, double-blind, titrated-dose trial</td>
<td>(1) Hypotensive (SBP &lt;140 mm Hg) nonhemorrhagic stroke patients treated within 12 h of symptom onset; (2) Hypertensive (SBP &gt;160 mm Hg), nonhypertensive within 36 h of stroke onset; (3) Hypertensive, dyhypertensive within 36 h of stroke onset</td>
<td>(1) IV phenylephrine at 80 μg/min titrated to target SBP 150 mm Hg or 15 mm Hg increase above baseline; (2) oral lisinopril 5 mg or labetalol 50 mg to target SBP 150 mm Hg or 15 mm Hg reduction from baseline; (3) sublingual isosorbid 5 mg and/or IV labetalol 50 mg to target SBP 150 mm Hg or 15 mm Hg reduction from baseline</td>
<td>Death or dependency (mRS &gt;3) at 14 d</td>
<td>2050</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Trial(s) Design Patients Included Intervention Primary Outcome</th>
<th>No. of Patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy of Nitric Oxide in Stroke Trial (ENOS)</strong></td>
<td>Any stroke treated within 48 h</td>
<td>Transdermal nitroglycerin or placebo for 7 d. Patients taking antihypertensive drugs will be randomized to continue or discontinue their medication for 7 d</td>
</tr>
<tr>
<td><strong>Scandinavian Candesartan Acute Stroke Trial (SCAST)</strong></td>
<td>Acute stroke within 30 h and SBP $\geq$140 mm Hg</td>
<td>Candesartan (dose increasing from 4 to 16 mg/d) or placebo for 7 d</td>
</tr>
<tr>
<td><strong>Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)</strong></td>
<td>Any stroke within 24 h of symptom onset</td>
<td>Patients will receive antihypertensive therapy for a 2-wk period</td>
</tr>
<tr>
<td><strong>Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH)</strong></td>
<td>Supratentorial ICH within 6 h of symptom onset and SBP $\geq$200 mm Hg</td>
<td>Stepwise, interventional design to test 3 tiers of SBP reduction: 170–200 mm Hg, 140–170 mm Hg and 110–140 mm Hg with IV nicardipine</td>
</tr>
<tr>
<td><strong>Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage – (INTERACT) Pilot Study</strong></td>
<td>ICH within 6 h of symptom onset and SBP $\geq$150 mm Hg and $\leq$200 mm Hg</td>
<td>Intensive SBP lowering; control group receives ASA guideline-based BP management</td>
</tr>
<tr>
<td><strong>Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT)</strong></td>
<td>Primary ICH and SBP $\geq$150 mm Hg</td>
<td>IV labetalol to reduce SBP to $&lt;$$150$ mm Hg within 1 h of treatment; control group receives ASA guideline-based BP management</td>
</tr>
<tr>
<td><strong>Nicardipine for the Treatment of Hypertension in Patients with Ischemic Stroke, Intracerebral Hemorrhage or Subarachnoid Hemorrhage (CARING)</strong></td>
<td>Ischemic stroke, ICH, or SAH patients who require BP control</td>
<td>25 Patients will receive double-concentrate dose; 25 will receive triple-concentrate dose</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; ACEI, ACE inhibitor; mRS, modified Rankin scale; DBP, diastolic BP; ASA, American Stroke Association; rCBF, regional cerebral blood flow; and SAH, subarachnoid hemorrhage.
Patients With Acute Ischemic Stroke Receiving Thrombolysis

The acute hypertensive response among patients with ischemic stroke receiving thrombolysis is frequently transient and resolves after recanalization; however, elevated BP before receipt of thrombolysis has been associated with an increased risk of ICH. In the Australian Streptokinase Trial, baseline systolic BP >165 mm Hg resulted in a 25% increased risk of major ICHs among patients with ischemic stroke treated with streptokinase. In a multicenter retrospective and prospective investigation of individual data from 1205 patients treated in routine clinical practice with intravenous rtPA within 3 hours of stroke symptom onset, elevated pretreatment MAP was associated with an increased rate of ICH. In a large audit of practices and outcomes in 29 hospitals in the Cleveland, Ohio, area, BP parameters recommended by the NINDS rtPA trial were not followed in 52% of the 70 patients treated with intravenous thrombolysis. The result was a 16% rate of symptomatic ICHs. A quality-improvement program in 9 of these hospitals decreased the rate of noncompliance to BP recommendations to 6% in 47 patients subsequently treated with rtPA. The rate of symptomatic ICH dropped to 6%, which indirectly supports the beneficial value of BP control in reducing rtPA-related ICHs.

Both the ASA and European Stroke Initiative guidelines recommend the reduction of BP according to the eligibility thresholds for inclusion in the NINDS rtPA efficacy trial before thrombolytics are administered. In the NINDS rtPA efficacy trial, patients were not eligible if they required aggressive antihypertensive therapy, defined as use of intravenous nitroprusside or repeated intravenous infusions of other medications. A post hoc analysis reported the frequency, course, and treatment of hypertension (>185/110 mm Hg before randomization or >180/105 mm Hg within the first 24 hours after randomization). Antihypertensive treatment before and after treatment with rtPA was used in 9% and 24%, respectively, of the patients treated with rtPA. Prethrombolyis use of antihypertensive treatment did not adversely affect the rate of favorable outcomes at 3 months. Postthrombolysis hypertension and use of antihypertensive treatment correlated with a lower rate of favorable outcome at 3 months. It remains unclear whether this adverse effect was related to more severe ischemic injury, persistent vascular occlusion, or pronounced reduction in BP. Patients treated with thrombolytics and antihypertensive therapy were more likely to have an abrupt decline in BP than those who were not treated. The higher susceptibility to hypotension associated with antihypertensive treatment after thrombolytic use (not seen in the placebo group) may be related to recanalization or reperfusion; however, the rate of ICH among patients with acute hypertension with appropriate control was similar to that observed in nonhypertensive patients. Another study reported that postthrombolytic acute hypertension occurred predominantly within 6 hours of receipt of thrombolysis, and if treated adequately, is not associated with an increased risk of ICH. Therefore, early BP reduction with rapidly acting antihypertensive treatment appears paramount for safe and beneficial thrombolysis among patients with acute ischemic stroke. Frequent BP monitoring and titration with short-acting intravenous agents are preferable to avoid uncontrolled decline in BP. The data about treating the acute hypertensive response after thrombolytic use are limited, because most studies excluded patients with difficult-to-control BP and did not use some of the newer antihypertensive agents. With the increasing use of thrombolysis and other endovascular treatment in acute ischemic stroke, new studies are required to address these issues.

Patients With ICH

One third of subjects presenting with ICH continue to demonstrate hematoma expansion (with subsequent deterioration and death) in the first few hours after onset. An initial systolic BP ≥200 mm Hg is associated with hematoma expansion and increased mortality among patients with ICH. Persistently higher systolic BP is also associated with perihematoma brain edema formation. Reducing BP may reduce the rate of hematoma expansion, although conclusive evidence of this is not available. Recent studies suggest that reduction of BP may be tolerated because of reduced metabolism (hibernation) and preserved autoregulation in the perihematoma region.

A multicenter prospective observational study reported the use of intravenous labetalol, hydralazine, and/or nitroprusside for maintaining BP <160/90 mm Hg within 24 hours of symptom onset among patients with ICH. Low rates of neurological deterioration and hematoma expansion were observed in treated patients. Patients treated within 6 hours of symptom onset were more likely to be functionally independent at 1 month than patients who were treated between 6 and 24 hours. Another study evaluated the tolerability and safety of intravenous nicardipine infusion within 24 hours of symptom onset to reduce and maintain MAP <130 mm Hg, consistent with previous ASA guidelines. The primary outcome of tolerability was achieved in 86% of the patients. Low rates of neurological deterioration and hematoma expansion were observed among treated patients. Indirect comparisons suggest that intermittent intravenous bolus regimens of antihypertensive agents have greater variability in BP control than continuous infusion regimens.

The current ASA and European Stroke Initiative guidelines recommend lowering BP in patients with an ICH to maintain systolic BP below 180 mm Hg. Both guidelines acknowledge that there may be a subset of patients who can tolerate more aggressive BP reduction, such as those with good neurological status or those without chronic hypertension. A recent observational study suggested that more aggressive BP reduction may have greater benefit in reducing the rate of hematoma expansion. One study assessed the results of lowering systolic BP below targets of 140, 150, or 160 mm Hg. The rate of hematoma expansion was 9% in patients with systolic BP <150 mm Hg and 30% among patients treated to maintain systolic BP <160 mm Hg or a higher threshold. Several ongoing trials (Table 1) are prospectively evaluating whether more aggressive BP lowering is safe and reduces the rate of hematoma expansion. The NINDS-funded Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial is presently determining...
the exact threshold of BP lowering (systolic BP <140 mm Hg, <170 mm Hg, or <200 mm Hg) for patients with ICH within 6 hours of symptom onset. Another pilot randomized study, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT), is comparing clinical outcomes in patients treated with intensive BP lowering (systolic BP <140 mm Hg) versus those treated according to ASA guidelines within 6 hours of symptom onset. Both trials recently reported preliminary results that suggested that aggressive BP reduction to a target of <140 mm Hg probably decreases the rate of substantial hematoma enlargement without increasing adverse events.

A new consideration is the combination of intravenous hemostatic treatment and aggressive BP control. In an exploratory analysis from a study of recombinant activated factor VII in ICH, initial systolic BP <170 mm Hg was associated with a trend toward lower hematoma expansion rates. In another study, a total of 188 patients admitted within 24 hours of symptom onset were treated with a combination of rapidly administered antifibrinolytic agents and systolic BP maintained <150 mm Hg. Hematoma enlargement was observed in only 4.3% of patients, which supports further evaluation of this approach.

Antihypertensive Agents and Regimens
The agents that are recommended by the ASA for acute hypertensive response are either intravenous or transdermal agents with rapid onset and short duration of action to allow precise titration (Table 2). BP can be monitored adequately with an inflatable cuff in most patients with acute hypertensive response, whereas intra-arterial monitoring should be considered in patients who require frequent titration with intravenous antihypertensive agents and in patients whose neurological status is deteriorating. ICP monitoring may be necessary in patients with a suspected increase in ICP. Patients with a poor level of consciousness, midline shift, or compression of basilar cisterns on computed tomographic scan may be considered for ICP monitoring when being treated with antihypertensive agents. Of note, cerebral perfusion pressure may overestimate regional perfusion because of its inability to measure regional pressure and autoregulatory disturbances.

Management of Chronic Hypertension in the Immediate Poststroke Period
Approximately 50% of patients are admitted with stroke while taking regular antihypertensive therapy. The abrupt discontinuation of antihypertensive medication may lead to enhanced sympathetic activity, rebound hypertension, and a consequent increase in cardiovascular events in patients with coronary artery disease using β-adrenergic blockers or those using high doses of centrally acting antiadrenergic drugs. In studies conducted in nonstroke patients, a slow

Table 2. Pharmacological Characteristics of Antihypertensive Agents Recommended in the Stroke Council, American Heart Association's Statements for Healthcare Professionals

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>CBF</th>
<th>ICP</th>
<th>Autoregulation</th>
<th>Platelet Activity‡</th>
<th>Cardiac Contractility‡</th>
<th>Dose</th>
<th>Onset of Action</th>
<th>Half-Life</th>
<th>Ischemic Stroke</th>
<th>ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>α- and β-Adrenergic blocker</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>-</td>
<td>-</td>
<td>5–20 mg bolus every 15 min up to 300 mg</td>
<td>5–10 min</td>
<td>3–6 h</td>
<td>SS, CS, ES92</td>
<td>ES92, ES93</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Direct relaxation of arteriolar smooth muscle</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5–20 mg bolus every 15 min</td>
<td>10–20 min</td>
<td>1–4 h</td>
<td>SS, ES53</td>
<td>SS, CS92</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Releases nitric oxide</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Infusion of 0.2 to 10 µg·kg⁻¹·min⁻¹</td>
<td>Within seconds</td>
<td>2–5 min</td>
<td>SS, CS, ES92</td>
<td>SS, CS92</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Releases nitric oxide</td>
<td>+</td>
<td>.</td>
<td>.</td>
<td>-</td>
<td>-</td>
<td>20 to 400 µg/min</td>
<td>1–2 min</td>
<td>3–5 min</td>
<td>SS, CS91</td>
<td></td>
</tr>
<tr>
<td>Nitropaste</td>
<td>Releases nitric oxide</td>
<td>+</td>
<td>.</td>
<td>.</td>
<td>-</td>
<td>-</td>
<td>0.2–0.4 mg/h up to 0.8 mg/h</td>
<td>1–2 min</td>
<td>3–5 min</td>
<td>SS, CS92</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Calcium channel blocker</td>
<td>+</td>
<td>.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5–15 mg/h</td>
<td>5–10 min</td>
<td>0.5–4 h</td>
<td>SS, CS, ES83</td>
<td>SS, CS, ES93</td>
</tr>
<tr>
<td>Esmolol†</td>
<td>β-Adrenergic blocker</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>+</td>
<td>-</td>
<td>250 µg/kg bolus followed by 25 to 300 µg·kg⁻¹·min⁻¹</td>
<td>5 min</td>
<td>9 min</td>
<td>SS</td>
<td></td>
</tr>
<tr>
<td>Enalapril*</td>
<td>ACE inhibitor</td>
<td>.</td>
<td>.</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1.25–5 mg every 6 h</td>
<td>15 min</td>
<td>1–4 h</td>
<td>CS, ES83</td>
<td>ES85</td>
</tr>
</tbody>
</table>

CBF indicates cerebral blood flow; SS, scientific statement; CS, clinical study; ES, experimental study; ACE, angiotensin-converting enzyme; +, increase or favorable effects; + +, substantial increase or favorable effects; -, decrease or negative effects; and . . . , no documented direct effect.

No conclusive evidence is present at this point to avoid any particular class of antihypertensive medication (including β-blockers). In general, medications with slow onset of action, long half-lives, or those known to cause precipitous BP reduction (sublingual nifedipine) should be avoided in the first 24 hours because they cannot be titrated to ensure controlled BP reduction.

*Data predominantly derived from other ACE inhibitors; †limited data available; ‡not derived from studies performed in acute stroke settings and unclear direct relevance.
increase in systemic BP and a low rate of cardiovascular events follows discontinuation of antihypertensive treatment. A small randomized trial was unable to demonstrate any difference in the rate of death or disability after discontinuation of antihypertensive treatment in patients with ischemic stroke within 72 hours of symptom onset. New multicenter trials are addressing this question (Table 1). In the interim, the decision to continue or discontinue antihypertensive agents must be made on a case-by-case basis with the intent to avoid hypotension, excessive hypertension, and myocardial ischemia. Reduction of the dose of the current agent or a change to a short-acting intravenous antihypertensive agent may be considered. Another issue is the timing of initiation or aggressive titration of oral antihypertensive treatment in patients with stroke who have chronic hypertension or undetected hypertension. In the California Acute Stroke Prototype Registry, great variability in practices between hospitals and considerable room for improvement was noted among two thirds of patients with acute ischemic cerebrovascular events discharged from the hospital who were given 1 or more antihypertensive medications. The heterogeneity in practice despite the definitive benefit demonstrated in clinical trials is concerning. Theoretically, oral hypertensive agents can be initiated at 24 to 48 hours after symptom onset, because most of the acute processes, such as ischemic penumbra and hematoma expansion, are uncommon after the first 24 hours. In the ACCESS trial (discussed above), treatment was started with daily candesartan or placebo on day 1. On day 2, the dosage was increased 2- or 4-fold if BP was >160/100 mm Hg. If patients in the candesartan group showed a hypertensive profile on day 7 (mean daytime BP >135/85 mm Hg), candesartan was increased or an additional antihypertensive drug was added. The results support early initiation of antihypertensive treatment with gradual titration to more aggressive BP treatment targets.

The JNC 7 report recommends that BP be maintained at intermediate levels (around 160/100 mm Hg) until neurological stability is achieved. Special circumstances such as elevated ICP, progressive cerebral edema, ongoing cerebral ischemia due to occlusive vessel disease or symptomatic cerebral vasospasm, and postoperative cerebral changes require individualized management. After the first week, or when neurological stability is achieved, a more aggressive treatment can be initiated for secondary prevention of recurrent stroke. The ASA recommends that antihypertensive therapy be considered for all patients with ischemic stroke or transient ischemic attack, because benefit is seen in persons with and without a history of hypertension. Special consideration may be necessary for patients with bilateral severe carotid stenoses, who may bear a high risk of stroke with aggressive BP lowering until carotid revascularization is performed.

Conclusions
Different strategies are required to manage the acute hypertensive response in different subtypes of stroke. Therefore, early diagnosis and differentiation are critically important for timely institution of the appropriate strategy. The management of high BP in acute ischemic stroke is highly controversial because of a lack of reliable evidence from randomized, controlled trials. Aggressive BP reduction is currently not recommended in patients with ischemic stroke in the acute phase because of potentially deleterious effects observed in some observational studies and absence of a documented benefit of acute BP lowering. A reduction in BP before administration of thrombolytics in patients with ischemic stroke is important to reduce the risk of secondary ICHs. Reduction of BP in patients with ICH requires further evaluation for efficacy given recent studies that have documented clinical tolerability due to reduced metabolism (hibernation) with preserved autoregulation in the peri-hematoma region.

Further studies are required to demonstrate the clinical benefits of treating the acute hypertensive response in patients with stroke and to determine whether these benefits are agent specific. Imaging modalities need to be developed that allow bedside measurement of regional cerebral blood flow and metabolism so that titration of antihypertensive treatment can be based on critical variables. Most recommendations are based on expert opinions and general principles defined by observational studies and small clinical trials. With the anticipated completion of several large clinical trials in the next 5 years, these recommendations can be established on the basis of superior levels of scientific evidence.

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References


**Key Words:** stroke ■ hypertension ■ blood pressure ■ cerebral infarction ■ cerebral ischemia ■ hemorrhage ■ thrombolysis
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