Acute Treatment of Blood Pressure After Ischemic Stroke and Intracerebral Hemorrhage

J. Dedrick Jordan, MD, PhD, Kathryn A. Morbitzer, PharmD, Denise H. Rhoney, PharmD, FNCS

KEYWORDS
• Acute ischemic stroke • Intracerebral hemorrhage • Blood pressure
• Hemorrhagic conversion • Hematoma expansion • Cerebral edema • Hypertension

KEY POINTS
• Aggressive blood pressure (BP) reduction in patients with acute ischemic stroke who do not qualify for thrombolysis has not been shown to improve outcomes.
• For patients who qualify for intravenous thrombolysis with alteplase, BP elevated more than 185/110 mm Hg before initiation of thrombolytic therapy or 180/105 mm Hg during the 24 hours after treatment has been associated with worse clinical outcomes.
• BP variability seems to be linked to poor functional outcomes and increased risk of hemorrhagic transformation of cerebral infarction.
• Aggressive BP reduction in patients with intracerebral hemorrhage does not cause significant cerebral hypoperfusion and ischemia in the perihematomal region.
• Aggressive BP reduction is safe in patients with intracerebral hemorrhage but has been shown to not significantly improve clinical outcomes.

ISCHEMIC STROKE

Management of the early elevation in blood pressure (BP) following acute ischemic stroke (AIS) is a major unresolved issue in current clinical management. Although it may seem logical to decrease BP acutely with antihypertensive medications, there...
are reasonable arguments physiologically to support both lowering BP and refraining from early BP reduction (permissive hypertension). The rationale for lowering BP is to reduce or prevent cerebral edema and limit hemorrhagic transformation of the infarct. Alternatively, the concern with lowering BP in AIS is the expansion of the central ischemic core by worsening hypoperfusion within the ischemic penumbra, because this area may have disrupted cerebral autoregulation. The key clinical questions that are reviewed based on the currently available evidence include the following: (1) When should antihypertensive therapy be started following AIS? (2) How fast and what goal BP should be targeted? (3) Which is the best antihypertensive agent to use in AIS?

Abnormal Blood Pressure in Acute Ischemic Stroke

Many patients with AIS will present to the emergency department with hypertension; however, it is unclear whether this represents a natural compensatory mechanism or is related to a wide array of other causes, such as pain, dehydration, or chronic illness.1,2 Several studies have been helpful in describing the natural history of BP changes following AIS (Table 1).

Two large multicenter trials, the Chinese Acute Stroke Trial (CAST) with 21,106 patients and the International Stroke Trial (IST) with 19,435 patients, were originally designed to assess antiplatelet use in AIS; however, these trials also produced significant information regarding hypertension in the acute phase following ischemic stroke.3,4 CAST reported hypertension (defined as systolic BP [SBP] greater than 140 mm Hg) in 75% of patients with an acute stroke within the first 2 days, whereas the IST reported the incidence as 80%. Marked hypertension (defined as SBP >180 mm Hg) was seen in 25% of patients in CAST and 28% of patients in IST. The findings of CAST and IST have been supported by a large observational trial. Qureshi and colleagues5 evaluated the prevalence of elevated BP using a large data set comprising 276,734 patients presenting to the emergency department with AIS. An SBP of 140 mm Hg or greater was observed in 76.5% of patients based on their initial measurement.

Although not universal, the natural history of hypertension postischemic stroke has seemed to involve an initial acute increase, followed by a reduction over the next several days.1,2,6,7 The Barcelona Downtown stroke registry found that an early decrease of SBP by 20% to 30% was associated with a full recovery.8 In patients treated with intra-arterial thrombolysis, decreases in SBP early after AIS have been associated with recanalization of the vessel.9

Recently, findings have suggested that for BP measured within 3 hours of stroke onset, the mean first SBP is only slightly higher than the premorbid level (a 17.9 mm Hg increase vs most recent SBP and a 10.6 mm Hg increase vs 10-year mean premorbid level).10 This finding contrasts with the significant increase in BP compared with premorbid levels in intracerebral hemorrhage (ICH), which may provide reasoning behind the differences seen in the risks and benefits of lowering BP acutely after stroke.

Cerebral Autoregulation in Acute Ischemic Stroke

Under normal conditions, cerebral blood flow is maintained within a tight range despite variation in systemic pressure. This equilibrium is achieved through cerebral autoregulation (Fig. 1).11 The dynamic cerebral vasculature either constricts or dilates in response to changes in mean arterial pressure (MAP) ranging from 50 to 150 mm Hg in order to maintain a stable cerebral blood flow.12,13 On the lower end of this zone of autoregulation, cerebral ischemia eventually occurs when the pressure remains less than the lower limit of autoregulation. Conversely, cerebral vessels constrict as
MAP increases and the vascular endothelial cells become stretched. Eventually, the cerebral vessels can no longer constrict effectively against the high perfusion pressure and autoregulation fails, which may lead to cerebral edema or hemorrhage. Chronic untreated hypertension may impact autoregulation whereby the zone of autoregulation is shifted to the right toward higher pressures. Cerebral autoregulation may be impaired following AIS as cerebral blood flow more closely reflects the systemic arterial BP, although this is controversial with inconsistent data from human and animal studies. Therefore, hypertension following an AIS may reflect a compensatory or protective physiologic response aimed at maintaining perfusion of the ischemic penumbra.

If the hypertensive response is protective it raises the clinical controversy as to if and when acute hypertension should be treated following AIS. Increased BP raises concern for secondary complications, such as hemorrhagic transformation and exacerbating cerebral edema. However, if cerebral autoregulation is not maintained, then lowering the BP acutely could worsen hypoperfusion within the penumbra. This clinical response provides theoretic reasoning behind maintaining or raising the BP during the acute period following AIS.

**Blood Pressure as a Prognostic Indicator in Acute Ischemic Stroke**

The optimal targets for BP management in patients with AIS remain uncertain, as several observational studies have demonstrated a U-shaped correlation with poor outcomes. In these studies, poor outcomes were seen with either very high or very low admission BP.

Baseline BP data from the IST were analyzed to explore the relationship between SBP and clinical events and functional outcomes. In evaluating greater than 17,000 patients with confirmed ischemic stroke, the investigators found that both high BP and low BP were independent prognostic indicators for poor outcomes (death within 14 days or death or dependency at 6 months). A baseline SBP of 140 to 179 mm Hg, with the nadir at 150 mm Hg, resulted in the lowest frequency of poor outcomes. A prospective observational study comprising greater than 900 patients with AIS also demonstrated early and late mortality in relation to a U-shaped curve admission SBP pattern. Vemmos and colleagues found that the relative risk of 1-month and 1-year mortality increased with a 10-mm Hg SBP change greater than or less than 130 mm Hg. Although both of these studies demonstrated an association with poor outcomes and a U-shaped SBP curve, the reference point for the ideal SBP differs, resulting in an unclear prognostic indicator.

Other studies have found associations between one direction of SBP and patient outcomes. In a cohort of 357 patients with AIS, Stead and colleagues found that patients with SBP less than 155 mm Hg were more likely to die within 90 days than patients presenting with an SBP between 155 and 220 mm Hg. Alternatively, 265 patients with AIS were analyzed in the Intravenous Nimodipine West European Stroke Trial and found differing results. The study defined high initial BP as an initial BP greater than 160/90 mm Hg. They found that high initial BP was a predictor for death or dependency at 21 days compared with patients who had a normal initial BP (SBP 120–160 mm Hg and diastolic BP 60–90 mm Hg). Conversely, Jensen and colleagues found that although a higher initial SBP reduced the odds of a good outcome, after adjusting for other prognostic indicators, it was not an independent predictor of a good outcome. This finding suggests that hypertension on admission may be a marker of other factors, such as the severity of the stroke or a sign of premorbid hypertension, rather than an independent prognostic guide.

A limitation of these studies is the use of only admission BP in making these outcome assessments. An analysis of the Virtual Stroke International Stroke Trial...
<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Study Arms/Cohort</th>
<th>Number of Patients</th>
<th>Time from Onset to Presentation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CATIS</td>
<td>Randomized, single-blind, blinded end point, blinded end point, prospective</td>
<td>Antihypertensive treatment vs discontinue all antihypertensive medications</td>
<td>4071</td>
<td>&lt;48 h</td>
<td>No difference seen in death or major disability at hospital discharge or 2 wk or at 3 mo</td>
</tr>
<tr>
<td>VISTA</td>
<td>Academic collaboration with data obtained from randomized trials</td>
<td>Patients with hyperacute IS who received placebo treatment</td>
<td>1722</td>
<td>&lt;8 h</td>
<td>High SBP and large variability in SBP in hyperacute stages of IS are associated with increased neurologic impairment and poor functional outcome</td>
</tr>
<tr>
<td>Fukuoka Stroke Registry</td>
<td>Multicenter, prospective stroke registry</td>
<td>First-ever AIS who had been functionally independent before onset</td>
<td>1874</td>
<td>&lt;24 h</td>
<td>SBP range of 144–153 mm Hg and greater associated with lower probability of good neurologic recovery</td>
</tr>
<tr>
<td>AIS-Thrombolysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SITSISTR</td>
<td>Retrospective analysis of prospectively collected register</td>
<td>Hypertensive patients treated with antihypertensives vs hypertensive patients and withholding antihypertensives vs patients without history of hypertension and treated with hypertensives vs patients without history of hypertension and not treated with antihypertensives</td>
<td>11,080</td>
<td>Median (IQR) 145 h (115–170)</td>
<td>Increased SBP 2–24 h after thrombolytic therapy associated with worse outcomes at 3 mo Best outcomes observed with SBP between 141–150 mm Hg after thrombolysis</td>
</tr>
<tr>
<td>SAMURAI rt-PA Registry</td>
<td>Retrospective, observational</td>
<td>Patients with AIS who received IV rt-PA</td>
<td>527</td>
<td>Median (IQR) 141 min (121–165)</td>
<td>Early SBP variability positively associated with ICH and death</td>
</tr>
<tr>
<td><strong>AIS/ICH</strong></td>
<td><strong>Study</strong></td>
<td><strong>Design</strong></td>
<td><strong>Intervention</strong></td>
<td><strong>N</strong></td>
<td><strong>Follow-up</strong></td>
</tr>
<tr>
<td>------------</td>
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<td>------------</td>
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<td>------</td>
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</tr>
<tr>
<td><strong>CHHIPS</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Randomized, double-blinded, prospective</td>
<td>Labetalol vs lisinopril vs placebo</td>
<td>179</td>
<td>&lt;36 h</td>
<td>No difference in death or dependency at 2 wk</td>
</tr>
<tr>
<td><strong>SCAST</strong>&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Randomized, double-blinded, prospective</td>
<td>Candesartan vs placebo</td>
<td>2004</td>
<td>&lt;30 h</td>
<td>Trend toward increased risk of poor functional outcomes at 6 mo in candesartan group</td>
</tr>
<tr>
<td><strong>COSSACS</strong>&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Open, blinded end point, prospective</td>
<td>Continue vs discontinue preexisting antihypertensive drug</td>
<td>763</td>
<td>&lt;48 h</td>
<td>No difference observed in death or dependency at 2 wk</td>
</tr>
<tr>
<td><strong>ENOS</strong>&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Randomized, single-blinded, blinded-outcome, prospective</td>
<td>Glyceryl trinitrate vs continuing premorbid antihypertensive therapy vs discontinuing antihypertensive medications</td>
<td>4000</td>
<td>&lt;48 h</td>
<td>No difference found in modified Rankin score at 90 d between continuing vs stopping premorbid antihypertensive therapy</td>
</tr>
<tr>
<td><strong>Liu-DeRyke et al, 2008</strong></td>
<td>Pseudorandomized, prospective</td>
<td>Labetalol vs nicardipine</td>
<td>54</td>
<td>—</td>
<td>Patients in nicardipine group achieved higher rate of goal BP within 60 min, had better maintenance of BP, had greater percentage of time spent within goal BP range, and had less BP variability</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th><strong>ICH</strong></th>
<th><strong>Study</strong></th>
<th><strong>Design</strong></th>
<th><strong>Intervention</strong></th>
<th><strong>N</strong></th>
<th><strong>Follow-up</strong></th>
<th><strong>Outcome</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERACT</strong>&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Randomized, blinded-outcome, prospective</td>
<td>Intensive- (SBP &lt;140 mm Hg) vs guideline- (SBP &lt;180 mm Hg) based BP control</td>
<td>346</td>
<td>&lt;6 h</td>
<td>Early intensive BP reduction is feasible and may reduce hematoma expansion</td>
<td></td>
</tr>
<tr>
<td><strong>ATACH</strong>&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Dose escalation, prospective</td>
<td>SBP 170–200 mm Hg vs SBP 140–170 mm Hg vs 110–140 mm Hg</td>
<td>60</td>
<td>&lt;6 h</td>
<td>Early intensive BP reduction is safe and feasible</td>
<td></td>
</tr>
<tr>
<td><strong>INTERACT2</strong>&lt;sup&gt;77&lt;/sup&gt;</td>
<td>Randomized, open-treatment, blinded-outcome, prospective</td>
<td>SBP &lt;140 mm Hg vs SBP &lt;180 mm Hg</td>
<td>2839</td>
<td>&lt;6 h</td>
<td>No difference found in modified Rankin score at 90 d</td>
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</tbody>
</table>

**Abbreviations:** ATACH, Antihypertensive Treatment of Acute Cerebral Hemorrhage; CATIS, Chinese Antihypertensive Trial in Acute Ischemic Stroke; CHHIPS, Controlling Hypertension and Hypotension Immediately Post-Stroke; COSSACS, Continue Or Stop post-Stroke Antihypertensives Collaborative Study; ENOS, Efficacy of Nitric Oxide in Stroke; ICH, intracerebral hemorrhage; INTERACT, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; IQR, interquartile range; IS, ischemic stroke; IV, intravenous; rt-PA, recombinant tissue plasminogen activator; SAMURAI, Stroke Acute Management With Urgent Risk-factor Assessment and Improvement; SBP, systolic BP; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register; SCAST, The Angiotensin-Receptor Blocker Candesartan for Treatment of Acute Stroke; VISTA, Virtual Stroke International Stroke Trial Archive.
The Archive (VISTA) collaboration examined the relationship between hemodynamic measures, variability in BP, and change in BP over the first 24 hours after AIS. High SBP measured initially and with subsequent measurement up to 24 hours was significantly associated with increased neurologic impairment and poor functional outcomes. The magnitude of change in BP over this first 24 hours was also significantly related to poor outcomes whereby patients having large decreases in BP (>75 mm Hg) or increases (>25 mm Hg) seemed to have the highest risk of poor outcomes.

Recognizing the controversy surrounding the association between postischemic stroke BP and patient outcomes, Ishitsuka and colleagues developed a large-scale stroke registry aimed at assessing this relationship. Analysis of the registry showed that the SBP (averaged over first 48 hours) range of 144 to 153 mm Hg and greater was associated with a lower probability of good neurologic recovery, even after multiple adjustments for potential confounders. Similar relationships were found in that higher SBP was also associated with elevated risks of neurologic deterioration and poor functional outcomes. These results give credence to the argument that a high postischemic stroke BP is associated with unfavorable clinical outcomes.

**Blood Pressure Management in Acute Ischemic Stroke**

As stated previously, multiple observational studies exist demonstrating that BP declines in the first several days following ischemic stroke without pharmacologic intervention. However, controversy still remains regarding whether it is optimal to actively intervene to pharmacologically lower or increase BP following AIS or to leave it untreated until it exceeds defined upper or lower thresholds.

Few studies have examined the impact of BP reduction in patients with AIS. In 2008, an updated Cochrane review was published to assess the effect of actively intervening...
to alter BP in patients with AIS on functional outcomes or death. Twelve small randomized studies, including a total of 1153 patients with stroke, were analyzed in the review; the investigators concluded that there was insufficient evidence to determine an effect of lowering BP on clinical outcomes. In the time since that publication, 3 large studies have provided further data.

The Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) trial was a randomized, placebo-controlled, double-blind study that compared labetalol, lisinopril, and placebo for lowering of BP in 179 patients with either cerebral infarction or primary ICH and an SBP greater than 160 mm Hg. BP was reduced by 21 mm Hg in the active treatment group versus 11 mm Hg in the placebo group; however, there was no significant difference in primary outcome of death or dependency at 2 weeks. Although there was no increase in serious adverse events in the treatment arm, the secondary outcome measure of 3-month mortality was reduced from 20.3% to 9.7% (hazard ratio 0.40, 95% confidence interval [CI] 0.2–1.0).

The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST) trial examined whether BP lowering treatment with candesartan was beneficial to patients with acute stroke with increased BP. The trial included 2029 patients with stroke (approximately 85% ischemic, 15% hemorrhagic) and randomized them to receive either candesartan or placebo for 7 days. More than 25% of patients enrolled also received concomitant therapy with antihypertensive agents at the physicians’ discretion. A minimal but statistically significant BP lowering effect was seen, with the SBP 5 mm Hg lower in the candesartan group at day 7 compared with the placebo group. No significant difference in death, myocardial infarction, or recurrent stroke at 6 months was observed between the two groups; a slightly higher risk of poor function outcome was seen in the candesartan group at 6 months.

Recently, He and colleagues evaluated the impact of moderate BP reduction within 48 hours of onset in patients with AIS on death and major disability at 14 days or hospital discharge in the Chinese Antihypertensive Trial in Acute Ischemic Stroke (CATIS) trial. This trial is the largest to date evaluating BP lowering in patients with AIS, with 2038 patients assigned to receive antihypertensive agents and 2033 patients in the control group. The patients randomized had SBP between 140 and less than 220 mm Hg at the time of randomization. Exclusion criteria included patients who qualified for thrombolysis and patients with heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, deep coma, or resistant hypertension. The BP goals in the intervention group were to lower SBP by 10% to 25% within the first 24 hours and to achieve a BP of less than 140/90 within 7 days. The patients enrolled had a median National Institutes of Health Stroke Scale (NIHSS) score of 4. The first-line intervention was intravenous angiotensin-converting enzyme inhibitors followed by calcium channel blockers (second-line) and diuretics (third-line). Patients in the control group were not allowed BP treatment except in extreme circumstances. Within 24 hours, the mean SBP was reduced by 21.8 mm Hg (12.7%) in the treatment group and 12.7 mm Hg (7.2%) in the control group (difference −9.1 mm Hg, P<.001). At day 7, the mean SBP in the treatment group was 137.3 mm Hg (65.7% achieved goal BP), whereas the control group mean SBP was 146.5 mm Hg (32.2% achieve goal BP). Finally at day 14, the mean SBP was 135.2 mm Hg (72% achieved goal BP) compared with 143.7 mm Hg (39.5% achieved goal BP) in the control group. The mean differences in SBP between the two groups at day 7 and 14 were −9.3 mm Hg and −8.6 mm Hg, respectively (P<.001). Even with this significant difference in BP, no difference was seen in death or major disability at 2 weeks or at 3 months. This trial follows the current guideline recommendation that unless patients qualify for thrombolysis or have BP greater
than 220/120 mm Hg, the decision to lower BP acutely does not improve outcomes and should be based on individual clinical judgment if patients have other comorbidities. However, larger trials with well-defined criteria are needed to establish the optimal BP threshold.

Debate also exists regarding whether to continue or withhold antihypertensive medications that patients were receiving before admission. The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) assessed the efficacy and safety of continuing or stopping preexisting antihypertensive medications in patients who had a stroke. Patients were randomized to continue (n = 379; 67% ischemic stroke) or stop (n = 384; 58% ischemic stroke) their preexisting antihypertensive drug within 48 hours of symptom onset. The difference in SBP at 2 weeks between the groups was 13 mm Hg (95% CI 10–17 mm Hg). However, no difference was observed in the primary outcome of death or dependency at 2 weeks. Although this study provides initial data suggesting that continuing prior antihypertensive medications is safe, the results of this study should be taken with caution because COSSACS was underpowered because of the early termination of the trial and patients with dysphagia were excluded, making most of the patients included those with a mild stroke (median NIHSS score of 4).

The most recent trial, Efficacy of Nitric Oxide in Stroke (ENOS), tested whether transdermal glyceryl trinitrate (5 mg for 1 week) is safe and effective in lowering BP and improving outcomes following stroke (4000 patients with AIS and ICH). Patients with baseline SBP of 140 to 220 mm Hg were randomized to active treatment glyceryl trinitrate (5 mg for 1 week), continuing premorbid antihypertensive therapy, or stopping their medication. This trial assessed 2 central concepts: the role of glyceryl trinitrate as a nitric oxide donor to lower BP in the acute phase of stroke and the value of continuing or stopping preexisting antihypertensive agents for 1 week after the stroke. The results of the study were presented at the XXII European Stroke Conference in May 2014. They found that there was a neutral effect on modified Rankin score at 90 days with the use of glyceryl trinitrate, but some benefit was reported in patients treated within 6 hours of symptom onset. The median time to symptom onset was 26 hours, and there was no differential effect seen in patients with AIS and ICH. Patients who received glyceryl trinitrate had higher rates of hypotension and headache. When assessing the role of continuing versus stopping a preexisting antihypertensive agent, they found similar results as COSSACS, with no difference in modified Rankin score at 90 days. However, the secondary analysis found an increase in pneumonia (in patients with dysphagia), disability and cognitive impairment in patients who continued their medications. Unlike the COSSACS trial, ENOS did enroll patients with dysphagia, which illustrates important considerations clinically as there seems to be no urgency in restarting treatment within the first week and safe swallowing should be established before restarting any oral medication.

There are limited data describing the most optimal intravenous antihypertensive to use in the acute stroke setting. Liu-DeRyke and colleagues evaluated the therapeutic response and tolerability of labetalol and nicardipine following acute stroke in 2 comparative studies. Both studies enrolled patients according to the American Heart Association/American Stroke Association’s (AHA/ASA) guidelines for requiring treatment and assessed patients for the first 24 hours in a mixed stroke population. The first study was a retrospective nonrandomized study that assessed MAP reduction and BP variability differences between labetalol and nicardipine. Most of the patients were experiencing ICH, with 19% in the nicardipine group and 25% in the labetalol group experiencing an AIS. Patients who received nicardipine were more likely to achieve their MAP goals within 1 hour than patients who received labetalol. Secondarily,
patients treated with nicardipine required fewer dosage adjustments or need for rescue therapy with additional antihypertensive agents than those who received labetalol.

As a follow-up to this study, the same investigators enrolled 54 patients prospectively in a pseudorandomized study where 35% of patients presented with AIS. Patients received either labetalol or nicardipine for the first 24 hours from admission. The investigators found that the nicardipine group achieved a higher rate of goal BP within 60 minutes of drug initiation, had better maintenance of BP, and a greater percentage of time spent within the goal BP range. None of the patients randomized to nicardipine required rescue medication, whereas 72.7% of those randomized to labetalol required an additional agent to achieve BP goals.35

Blood Pressure Management in Patients Eligible for Thrombolytic Therapy

Despite unclear data concerning BP management in patients with general AIS, BP lowering is clearly recommended above certain thresholds for patients with AIS who are eligible to receive thrombolytic therapy.

A pilot study evaluating the factors associated with ICH formation following the use of thrombolytic therapy found that an increased risk of ICH was associated with elevated diastolic BP.36 Therefore, in the National Institute of Neurologic Disorders and Stroke (NINDS) study, a strict BP of less than 185/110 mm Hg was required for enrollment into the study and tight BP control was maintained for 24 hours with a BP goal of less than 180/105 mm Hg.37

Although subsequent observational studies evaluating the association of elevated BP and ICH formation have been variable,38 a study examining associations between protocol violations and outcomes in community-based recombinant tissue plasminogen activator (rt-PA) use found that when the NINDS protocol is strictly followed, hemorrhage rates are similar to those in the NINDS trial.39 Furthermore, in 2009 Ahmed and colleagues40 published results from the Safe Implementation of Thrombolysis in Stroke registry evaluating the association of BP and antihypertensive therapy with clinical outcomes after thrombolytic therapy. The registry included 11,080 patients and categorized patients based on their history of hypertension and whether they were treated with antihypertensives following thrombolysis. Increased SBP 2 to 24 hours after thrombolytic therapy was associated with worse outcome (symptomatic hemorrhage, mortality, functional dependence) at 3 months. The best outcomes were observed in patients with SBP values between 141 and 150 mm Hg up to 24 hours after thrombolysis.

There is an ongoing international trial, Enhanced Control of Hypertension and Thrombolysis Study, that compares a low dose versus a normal dose of rt-PA and intensive BP reduction versus standard reduction in patients receiving thrombolysis. This study will attempt to answer the following 4 key questions: (1) Does low-dose (0.6 mg/kg) intravenous rt-PA provide equivalent benefits compared with the standard dose (0.9 mg/kg) rtPA? (2) Does intensive BP lowering (130–140 mm Hg SBP target) improve outcomes compared with the current guideline-recommended level of BP control (180 mm Hg SBP target)? (3) Does low-dose (0.6 mg/kg) intravenous rt-PA reduce the risk of symptomatic ICH? (4) Does the addition of intensive BP lowering to thrombolysis with rt-PA reduce the risk of any ICH?41

It is also important to note that thrombolytic therapy may be associated with improvement in SBP following successful recanalization. Mattle and colleagues9 reported that patients who underwent intra-arterial thrombolysis and had unsuccessful vessel recanalization had higher and sustained elevations in SBP compared with those patients with successful recanalization.
The AHA/ASA's current guidelines for the management of AIS recommend the use of labetalol and nicardipine as the first-line agents, although there are limited data to support this recommendation. Martin-Schild and colleagues also conducted a retrospective observational study of standard versus aggressive BP management in patients with AIS receiving rt-PA. Standard therapy consisted of labetalol, whereas aggressive therapy consisted of labetalol plus nicardipine or nicardipine alone. Standard and aggressive BP-lowering therapies were equally effective in reaching target BP goals in 3 hours; however, patients receiving aggressive BP lowering had a significantly shorter hospital length of stay (4 days vs 7 days; \( P = .01 \)) than those given labetalol alone.

**Minimizing Blood Pressure Variability**

BP variability has also become an important monitoring parameter while trying to optimize outcomes in patients with AIS. Stead and colleagues evaluated the impact of acute BP variability following the onset of ischemic stroke. The study cohort consisted of 71 patients, and BP measurements were obtained every 5 minutes throughout the patients’ stay in the emergency department. The investigators found that a wide fluctuation in BP (median of 44.5 mm Hg vs 25.0 mm Hg) was associated with an increased risk of death at 90 days. The VISTA collaboration reported that increased SBP variability over 24 hours was significantly associated with poor late functional outcomes, whereas diastolic BP variability did not have an impact on outcomes. Kang and colleagues showed that variability of BP, but not the average BP in the subacute stage (within 48 hours of onset) of AIS, is associated with poor 3-month functional outcomes.

Similar results have been seen when evaluating patients who received thrombolytic therapy. In a study consisting of 80 patients with AIS who received thrombolytic therapy, multiple repeated BP measurements were obtained during the 24 hours following admission. The mean SBP variability was 14.7 ± 5.6 mm Hg. BP variability was found to be associated with greater diffusion-weighted imaging lesion grown and worse clinical outcomes. Comparable results were also shown in a registry trial composed of 527 patients with stroke who received intravenous rt-PA. Patients had their BP measured 8 times within the first 25 hours. The investigators found that early SBP variability was positively associated with ICH and death.

It is important to consider when evaluating these data that BP variability may be a result of stroke severity and, thus, lead to poor functional outcomes because a deteriorating clinical course can result in a variable BP profile; however, most studies did control for stroke severity in their analysis. The Blood Pressure Variability in Acute Ischemic Stroke trial is currently enrolling to evaluate a comparison of BP variability indices and ambulatory arterial stiffness index as prognostic indicators in functional outcomes after AIS.

Minimal literature exist assessing the impact of the various antihypertensive agents on BP variability. However, the 2 trials published by Liu-DeRyke and colleagues also reported that nicardipine was associated with less BP variability than labetalol. Future studies describing intravenous antihypertensives following AIS should include an assessment of BP variability.

**Induced Hypertension**

Adding to the complexity of optimal BP management in patients with AIS, a few studies have suggested a benefit in increasing the BP. Olsen and colleagues demonstrated that increasing the systemic BP can restore cerebral blood flow to the brain and increase perfusion to the ischemic penumbra. However, they also stated that the risk of the development of cerebral edema may outweigh the benefit.
Several small pilot studies have further assessed the outcomes associated with elevating the systemic BP with vasopressor agents. Rordorf and colleagues performed a prospective study that elevated BP in patients with AIS treated within 12 hours of onset. The BP was increased using intravenous phenylephrine until a threshold was found where neurologic deficits improved. Responses were observed in 30% to 50% of the patients treated, and improvements in neurologic deficits were seen within minutes of elevating the BP.

A subsequent pilot study prospectively randomized patients to either induced hypertension with intravenous phenylephrine or conventional management. An MAP increase of 23% was seen in patients being treated with induced hypertension, and these patients demonstrated a reduction in neurologic deficits.

Despite these positive results, concerns still exist regarding the potential adverse effects of increased BP after ischemic stroke, particularly the risk of ICH and worsening cerebral edema. Additionally, vasopressor use may result in cardiac arrhythmias and renal insufficiency.

**INTRACEREBRAL HEMORRHAGE**

Elevated BP is commonly seen in patients presenting with acute ICH; however, there is continued debate on the best treatment approach. Physiologically, both relative hypotension and continued hypertension could be deleterious. If the BP is lowered too rapidly, one may develop cerebral hypoperfusion with the subsequent development of cerebral ischemia and worsening neurologic status. Conversely, if the BP is allowed to be continuously elevated, the course could be complicated by further hemorrhage or worsening cerebral edema also leading to neurologic decline. The key clinical questions that are reviewed based on the currently available evidence include the following: (1) Does aggressive BP reduction reduce the risk of hematoma expansion? (2) Does BP reduction lead to cerebral hypoperfusion and ischemia? (3) What is the optimal BP goal in patients with ICH and hypertension?

**Abnormal Blood Pressure in Intracerebral Hemorrhage**

An acute elevation in BP is commonly seen in the setting of ICH, with approximately 70% of patients having an SBP greater than 140 mm Hg within 1 hour of presentation. A history of hypertension has been shown to be associated with an elevated BP on admission. In fact, a large population-based study performed in the United Kingdom demonstrated that the SBP is increased substantially in comparison with the premorbid BP in patients with ICH. Furthermore, several studies have demonstrated that patients with elevated BP on admission or within the first 24 hours have an increased risk of death and severe disability after ICH. Hypotension on admission has also been found to be associated with worse outcomes, with 52% of those admitted with an SBP less than 100 mm Hg having an early neurologic decline. Cardiovascular disease was the most common cause of death in these cases, as these patients commonly had preexisting heart failure and coronary artery disease.

**Hematoma Expansion**

Patients with ICH are at risk for hematoma expansion and an associated neurologic decline. In observational studies, up to 38% of patients have a substantial increase in the volume of the hematoma within the first 24 hours, and neurologic decline is more common in this group of patients. Although several factors have been associated with hematoma expansion, elevated BP seems to have the strongest association across several studies. Additionally, analysis of the intensive blood pressure...
reduction in acute cerebral hemorrhage Trial (INTERACT) trial data demonstrated a reduction of hematoma enlargement in one-third of participants when the lowest target BP was achieved within the first 24 hours and overall BP reduction was shown to attenuate hematoma enlargement at 72 hours. However, in the larger INTERACT2 study, no difference in hematoma expansion was noted between the groups after adjustment for prognostic variables.

**Perihematomal Cerebral Perfusion and Ischemia**

Severely elevated BP in the setting of ICH is likely multifactorial; however, concerns about rapid reduction in BP leading to neurologic decline has been a clinical concern. Those with long-standing hypertension may have a shift in the range for cerebral autoregulation, and acutely reducing the BP to less than that range may lead to autoregulatory failure and cerebral ischemia. Furthermore, early studies raised the concern that the brain immediately surrounding the hematoma may be at risk for ischemia from reduced blood flow when the BP is reduced acutely. However, subsequent studies using various imaging modalities have not supported these findings. Powers and colleagues demonstrated that global and periclot cerebral blood flow does not change with acute reduction in BP by 17 mm Hg in patients with small-to moderate-sized hematoma volumes. Additionally, studies using computed tomography (CT) perfusion indicate that the perihematomal region has adequate perfusion and is without a penumbra. The study performed by Butcher and colleagues, the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial, was a randomized trial that enrolled 75 patients with ICH and SBP greater than 150 mm Hg to protocol-guided antihypertensive therapy with a goal of less than 150 mm Hg versus less than 180 mm Hg. The primary outcome was the relative change in perihematomal cerebral blood flow as measured using CT perfusion. Although BP was lower with 2 hours after randomization in the less than 150 mm Hg target group, there was no significant difference in the relative change in perihematomal cerebral blood flow in this group when compared with the less than 180 mm Hg target group. Furthermore, there was no relationship between the amount of reduction in BP and the perihematomal relative cerebral blood flow for those subjects in either of the groups. These data further indicate that rapid lowering of the BP in patients with ICH and elevated BP will not precipitate perihematomal cerebral ischemia. Given the results of these studies, several clinical trials have been completed or are ongoing evaluating the safety and efficacy of BP reduction in the setting of ICH.

**Blood Pressure Control and Intracerebral Hemorrhage**

Because of the association between stroke and elevated BP on admission as well as during hospitalization, several studies have been performed to determine if BP control in the acute setting would improve outcomes in this population. Several of these clinical trials have included patients with AIS or ICH, whereas others have focused strictly on patients with ICH. Three of the largest trials completed that enrolled patients with both types of stroke include CHHIPS, COSSACS, and SCAST. The trials in this group, CHHIPS, COSSACS, and SCAST, were previously described. However, these studies have limited insight into the ICH population. Only 43 patients with ICH were enrolled in CHHIPS, and the placebo arm only included 7 patients in the ICH subgroup.

Therefore, the interpretation of these results in this population is very limited. COSSACS included only 38 patients with ICH, and it too cannot provide adequate data as to the safety and efficacy of BP reduction after ICH. There were 274 patients...
with ICH randomized in SCAST; subgroup analyses of this group did not identify any significant effect for the prescribed outcomes.  

As described earlier, preliminary results from the recently completed ENOS trial have been presented. Although the complete results have yet to be published, this trial included 629 participants with ICH; hence, the results for this subgroup are highly anticipated.

Because of the association of BP elevation with ICH and the potential risk of neurologic decline caused by hematoma expansion, several clinical trials have been performed over the past decade with the goal of determining whether BP reduction is safe and efficacious. INTERACT was a randomized study that enrolled 404 patients to either intensive BP reduction with a goal SBP of 140 mm Hg versus standard guideline-based management with a goal SBP of 180 mm Hg. The primary end point was change in hematoma volume at 24 hours, and the secondary outcomes included safety and clinical outcomes at 90 days. The BP was significantly lower in the intensive group from 1 hour after enrollment until 24 hours, whereas mean proportional hematoma growth was significantly less at 13.7% versus 36.3% for the guideline group. There were no reported differences between groups in the 90-day clinical and safety outcomes. Although a reduction in hematoma volume was noted in this trial, the absolute difference was only 1.7 mL, which may not be clinically meaningful.

The antihypertensive treatment of acute cerebral hemorrhage (ATACH) trial was a relatively small phase I dose-escalation study aimed at determining the feasibility and safety of reducing BP in patients with ICH and SBP of greater than 170 mm Hg. Although the INTERACT study allowed for local sites to decide on which antihypertensive agents to use, the ATACH study has a prescribed algorithm for BP reduction using intravenous nicardipine. SBP reduction was tiered, with the first 18 patients having a target of 170 to 200 mm Hg, the next 20 patients having a target of 140 to 170 mm Hg, and the last having a target of 110 to 140 mm Hg. Although aggressive BP reduction was feasible, 9 of the 22 patients in the most aggressive reduction arm were treatment failures suggesting that their protocol was not optimal for such aggressive BP reduction. Additionally, although there were a larger proportion of patients with neurologic decline or serious adverse events in the most aggressive tier, the safety-stopping rule was not met for any of the groups. The study was not powered to determine differences in clinical outcome, which were no different between study arms. The INTERACT and ATACH trials were preliminary studies to determine the feasibility of the selected BP targets as well as safety. Neither study was powered to determine if BP reduction was efficacious for clinical outcomes. Based on the analysis of each study, larger randomized trials with similar study designs were undertaken, INTERACT2 and ATACH II.

INTERACT2 was a prospective, randomized, open-treatment, blinded end-point trial aimed at determining if aggressive BP reduction in patients with ICH and BP elevation would improve clinical outcomes. Participants were enrolled within 6 hours of onset and were randomly assigned to receive either intensive BP reduction with a goal SBP of less than 140 mm Hg or guideline-recommended treatment with a goal SBP of less than 180 mm Hg. The primary outcome was death or major disability (score of 3–6 on the modified Rankin scale), and a prespecified ordinal analysis of the modified Rankin scale was also performed as the main secondary outcome. The ordinal analysis was added as a secondary outcome after completion of enrollment but before data analysis. This analysis allows for the statistical analysis to determine if there is a significant shift in the distribution of clinical outcomes an ordinal scale such as the modified Rankin scale. Although the mean SBP did differ between the two groups from 15 minutes to 7 days, 150 mm Hg in the intensive-treatment group versus 164 mm Hg in the guideline-treatment group, only 33.4% of patients achieved the
target BP in the intensive-treatment group. There was no difference in the primary outcome between the two treatment groups, whereas the ordinal analysis showed a significantly lower modified Rankin scale score with an odds ratio of 0.87 for greater disability ($P = .04$) in the aggressive-treatment arm. Furthermore, there was no difference in mortality or serious adverse events between the two arms of the study.62

ATACH II is an ongoing prospective randomized trial with a planned enrollment of 1280 subjects with ICH and an SBP greater than 180 mm Hg. Participants will be randomized to either a target SBP of less than 180 mm Hg or less than 140 mm Hg using a prespecified antihypertensive algorithm using continuous infusion of intravenous nicardipine. Treatment will begin within 3 hours of onset and continued for 24 hours. The primary outcome is death or disability (modified Rankin score 4–6) at 3 months with secondary outcomes including quality of life measures at 3 months, hematoma expansion at 24 hours, as well as treatment-related serious adverse events within the first 72 hours. Although this study is not projected to be complete until July 2016, the findings should further assist clinicians in determining the safest and most efficacious treatment of this population.75

**Continued Controversies**

Although much effort and funding has been put into the study of ICH, there continue to be areas of controversy surrounding the optimal management of the hypertensive response seen in patients with ICH. Two of the main areas of controversy have included the risk of perihematomal ischemia with BP reduction as well as the optimal BP targets that would improve clinical outcomes.

The concern for perihematomal ischemia has been well addressed in numerous studies.67–71,76 Although there may be individual cases of perihematomal reduction in cerebral blood flow and ischemia identified, we should feel confident that the reduction of BP does not lead to significant perihematomal ischemia when evaluated in prospective studies. Furthermore, the INTERACT, ATACH, and INTERACT2 studies did not demonstrate a significant neurologic decline with aggressive BP reduction when compared with guideline-based treatment.62,73,74 Clinicians may be faced with the case of a perfusion-dependent clinical examination that is assumed to be caused by perihematomal ischemia; in this rare case, clinical judgment would be necessary in light of the data that exist.

Even though we now have several clinical trials aimed at answering the question of what BP target is safe and efficacious for patients with ICH and hypertension, the answer is unfortunately still not clear. Although none of the trials to date have found BP reduction to improve clinical outcomes, these trials did not demonstrate any harm in aggressive BP reduction. Without further data, aggressive BP reduction is not supported by the current literature. Aggressive BP reduction may lead to an overall increased cost of providing care to this patient population through an increase in intensive-care-unit admissions and a longer length of hospital stay.

INTERACT2 failed to show a benefit for aggressive BP reduction in improving clinical outcome; however, post hoc analysis has raised the issue of whether BP variability may have affected the outcome measurement in the aggressive BP reduction arm. When BP standard deviation was evaluated during the hyperacute (first 24 hours) and acute (days 2–7) phase, a significant linear association was found with the primary outcome. Furthermore, the strongest predictor for outcomes during the acute phase of BP control was the standard deviation of the SBP.77 Although the outcome in INTERACT2 may have been affected by significant fluctuations in BP, the ongoing ATACH II study may help address this issue because of its use of continuous infusion nicardipine for BP control. However, the infusion is only for the initial 24 hours;
therefore, if BP variability affects outcome after this hyperacute period, then this question may remained unanswered.\textsuperscript{75}

SUMMARY

Questions remain regarding the optimal BP management in the hyperacute period following acute stroke. Complexities yet to be resolved include whether acute elevations in BP are physiologic and protective or are a result of the stress reaction that is harmful to the brain and whether lowering BP is beneficial. Adequately powered randomized trials are needed to help resolve these remaining conundrums.

Although the decision to initiate acute antihypertensive therapy has not been clearly delineated, the current evidence suggests that, in most patients with AIS who do not qualify for thrombolysis, antihypertensives can be safely withheld early except when the BP exceeds 220/120 mm Hg or in the presence of another acute, severe, and compelling indication, such as aortic dissection or myocardial infarction (T3, 3-0). The CATIS subgroup analysis of the time to randomization suggests that patients with mild AIS had better 6-month outcomes when BP lowering was withheld the first 12 hours and beyond 24 hours.\textsuperscript{30} This finding suggests that reinitiation of antihypertensives in the 12- to 36-hour period following stroke may be beneficial (T2, 2-1). However, considerations should be made regarding the route of administration in dysphagic patients with avoidance of oral agents until swallowing can be established based on the initial results from the ENOS trial (T2, 3-X).

For patients who qualify for thrombolysis, the current recommendations are that BP that is elevated more than 185/110 mm Hg should be carefully lowered before initiation of thrombolysis (T1, 1-1). For the first 24 hours after treatment, BP should be maintained at less than 180/105 mm Hg (T1, 1-1). When treatment is initiated, an agent should be selected that has rapid onset of action and that is titratable in order to avoid BP variability because BP variability seems to be linked to poor functional outcomes and an increased risk of hemorrhagic transformation of the infarct (T2, 2-1). The impact of the agent on comorbidities, heart rate, and intracranial pressure should also be considered. No large direct comparison trial has evaluated which of these antihypertensive agents is superior in clinical outcomes.

As in AIS, BP elevation is common in patients presenting with spontaneous ICH. Although early studies suggested an increased risk of perihematomal hypoperfusion and ischemia with BP reduction, multiple prospective follow-up studies have demonstrated that BP reduction does not lead to perihematomal hypoperfusion and ischemia (T3, 3-1).

Conversely, previous data have demonstrated that elevated BP is associated with hematoma expansion in patients with ICH and that aggressive BP reduction is not only safe but also leads to a reduction in hematoma expansion.\textsuperscript{73} However, the INTERACT2 trial did not demonstrate a reduction in hematoma expansion as a secondary end point; therefore, based on the best available data, aggressive BP reduction does not reduce the risk of hematoma expansion versus standard management using the current guidelines (T1, 1-0).\textsuperscript{78}

BP control in the setting of ICH has been evaluated in several randomized prospective studies with clinically meaningful end points. Based on the current literature, although it seems safe, aggressive BP reduction less than the AHA/ASA’s current guideline target of SBP less than 180 to 200 mm Hg is not supported (T1, 1-0).

REFERENCES


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