Blood pressure management in stroke

Five new things

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Summary
Hypertension is a major modifiable risk factor for stroke, with an estimated 51% of stroke deaths being attributable to high systolic blood pressure globally.1,2 The management of hypertension in stroke is determined by timing, the type of stroke, use of thrombolysis, concurrent medical conditions, and pharmacologic variables. We highlight the details of elevated blood pressure management in the hyperacute/acute, subacute, and chronic stages of ischemic stroke and intracerebral hemorrhage.

The relationship between hypertension and stroke is dynamic and multifaceted. Be it in the context of managing ischemic or hemorrhagic stroke, selecting an appropriate blood pressure (BP) agent involves integration of several issues that must be recognized in order to formulate an effective strategy for BP control.

Blood pressure, ischemic stroke, and thrombolysis
More than 60% of patients with acute ischemic stroke (AIS) present with elevated BP within 1 hour of symptom onset.3 Elevated BP can affect thrombolytic eligibility and has been associated with delay in administration of IV tissue plasminogen activator (IV tPA).4 Since <30% of patients have door-to-treatment times less than the recommended 60 minutes, timely management of elevated BP is crucial when patients are otherwise eligible for IV tPA.3 Earlier thrombolytic treatment of patients with AIS is not only associated with more frequent independent ambulation at discharge and discharge to home, but is also associated with reduced mortality and symptomatic intracerebral hemorrhage (sICH).6

One factor that has been associated with delays in treatment times is the need for prethrombolytic BP goal of <185/110 mm Hg,7,8 a target extrapolated from prior studies of thrombolysis in acute myocardial infarction.9,10 In cases where such a target is not achieved, tPA may even be withheld, given the association of elevated BP and risk of sICH leading to poor clinical outcomes.11 Withholding tPA based solely on persistently uncontrolled BP, however, can lead to as many as 10% of otherwise eligible patients not receiving tPA. This is a significant

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number considering that <10% of patients meet the current eligibility criteria for the use of IV tPA within 4.5 hours. Thus, a proficient attempt must be made to reduce BP to the thrombolytic range, even if it involves using multiple BP agents or continuous infusions. Keeping in mind the importance of not making the patient relatively hypotensive, the safety of aggressively lowering BP to <185/110 mm Hg using continuous IV BP agents has been demonstrated to be safe in patients eligible for IV tPA presenting within 3 hours of symptom onset without adverse effect on clinical outcomes. With a synchronized effort, we propose that most thrombolytic eligible patients can have their BP brought down to the treatment range quickly enough so that thrombolysis remains an option for this debilitating disease.

The addition of intra-arterial (IA) therapy to the AIS treatment regimen requires special attention to BP with multiple variables involved. While uncertainty remains around optimal BP parameters, pending more definitive data, there are some concepts that can be considered in this scenario.

Prior to the procedure, BP <180/100 mm Hg is often designated, especially if IA lysis with tPA is planned. During the procedure, target BP within 10%–20% of the admission BP is a reasonable goal if IA recanalization is used as monotherapy, or <180/105 mm Hg if used adjunctively with IV tPA. Extreme caution should be taken to avoid relative hypotension during the procedure, especially when general anesthesia is used. In addition, systolic BP (SBP) >140 mm Hg is generally targeted during the procedure, as BP below this threshold has been shown to be independently predictive of poor neurologic outcomes after endovascular treatment. Postprocedure, BP can be titrated according to the degree of arterial recanalization and the patient’s neurologic examination. If complete recanalization is achieved, then goal BP may be lowered to a SBP of 120–140 mm Hg to lower the risk of reperfusion hemorrhage. In cases of partial recanalization, it is reasonable to maintain SBP up to 185 mm Hg for 24–48 hours in order to augment collateral blood flow and clear emboli from distal vasculature, unless the patient has received IV tPA. BP must ultimately be optimized to minimize the rate of sICH and reperfusion injury and to promote adequate cerebral perfusion.

BP and ischemic stroke when thrombolysis is not an option
In cases of AIS where thrombolysis is not a consideration, there is uncertainty surrounding the optimal management of BP in the acute setting. The decision to reduce BP in the first 24 hours of a stroke must take into consideration the potential of compromising collateral blood flow and hastening the interval to infarction (range 6–18 hours after large vessel ischemic stroke), vs the potential for adverse systemic effects as a result of persistently elevated BP. As a result, it is best to observe current guidelines, which recommend a 15% reduction within the first 24 hours of ischemic stroke only in cases where BP exceeds 220/120 mm Hg.

Given the association between clinical outcomes in AIS and the direction and magnitude of BP changes over the first 24–48 hours, antihypertensive therapy is routinely initiated 24 hours after AIS. Although it is intuitive that BP control at all timepoints after AIS would be beneficial, recent evidence has suggested that BP control beyond 15 hours from onset of an ischemic stroke (even up to 2 weeks) may have little effect on clinical outcome. Given the limitations in these studies and until more definitive evidence is available, our practice is to gently normalize BP during hospitalization. Regardless of when BP medication is resumed, a management strategy must ensure a patient’s neurologic stability prior to BP control and minimize BP variability, given the association of wide BP fluctuations and poor outcomes at 1 and 3 months.
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**Specific goals for specific conditions**

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**Small-vessel disease**

The Secondary Prevention of Small Subcortical Strokes trial demonstrated that lowering SBP to a goal <130 mm Hg vs a range of 130–149 mm Hg at least 2 weeks after MRI-confirmed lacunar strokes was not only safe and well-tolerated, but also reduced the rate of all stroke (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.64–1.03, \( p = 0.08 \)), disabling or fatal strokes (HR 0.81, 0.53–1.23, \( p = 0.32 \)), other major vascular events (HR 0.84, 0.68–1.04, \( p = 0.32 \)), and intracerebral hemorrhage (ICH) (HR 0.37, 0.15–0.95, \( p = 0.03 \)) over a period of 3–4 years.\(^{26}\) This study excluded patients with alternate stroke etiologies, such as ipsilateral carotid stenosis, high-risk cardioembolic strokes, and disabling strokes, where other clinical variables may also play a role in devising a BP management plan.

**Intracranial atherosclerosis**

Regarding recurrent strokes related to severe atherosclerotic disease of large intracranial vessels, prior evidence has indicated an increased stroke risk with elevated diastolic BP in patients with \( \geq 70\% \) stenosis of a major intracranial artery.\(^{27,28}\) Recent evidence, however, has demonstrated the importance of SBP control as well in preventing strokes in a similar cohort of patients. In this study, patients who had nondisabling strokes or TIAs attributable to 70%–99% stenosis of a major intracranial artery (carotid artery, middle cerebral artery, vertebral artery, or basilar artery), and in whom an aggressive medical management strategy was employed (goal SBP \(< 140 \) [\(< 130 \) mm Hg in diabetes], low-density lipoprotein [LDL] \(< 70 \) mg/dL, dual antiplatelet therapy with aspirin and clopidogrel for 90 days, and lifestyle modifications), had fewer cerebrovascular events in the subsequent 30 days compared with those who had a similar medical management strategy plus intracranial angioplasty and stenting. This beneficial effect was sustained in the long term over a median duration of 32.4 months (absolute risk reduction from medical treatment was 8.9% at 30 days and 9.0% at 3 years). While the findings from this study are partly attributable to the nature of the management strategy of using dual antiplatelet agents and targeting a lower LDL goal, it is notable that 70% of patients at 1 year continued to meet the target SBP goal of \(< 140 \) mm Hg (compared to 34% at enrollment).\(^{29}\) The fact that such BP goals were attainable within a framework of other key prevention strategies overseen primarily by neurologists and study coordinators is a testament to the important role that all providers play in taking care of stroke patients, including both general neurologists and stroke specialists.

**Acute reduction of BP in ICH is safe**

One aspect of the controversy regarding the safety of rapidly lowering BP in acute hemorrhagic stroke has been a concern for acute ischemia resulting from decreased cerebral blood flow (CBF) as a result of rapid BP reduction. Neuroimaging evidence has suggested otherwise, with PET studies showing neither a reduction in global and perihematomal CBF after acute reductions in mean arterial pressures nor a significant compromise in cerebral blood volume as a result of lowering SBP to a target of \(< 150 \) mm Hg.\(^{30,31}\) Similar markers of ischemia, such as diffusion restriction on MRI in the perihematomal region, have been attributed to nonischemic pathologies, such as vasogenic edema, inflammation, or mechanical cellular injury.\(^{12,32}\)
### Blood pressure management and stroke

#### Ischemic stroke and TIA

**Acute setting**

- **Patients eligible for acute reperfusion**
  - For BP >185/110 mm Hg: administer labetalol 10–20 mg over 1–2 minutes, may repeat 1 time; or start nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes for maximum 15 mg/h; or add other agents (hydralazine, enalaprilat).

- **BP goal**: 180/105 mm Hg

- **During and after reperfusion therapy**
  - Patients not eligible for acute reperfusion therapy
    - For SBP >220 mm Hg or DBP 121–140 mm Hg, administer labetalol IV or nicardipine as IV infusion, aiming for a 10%–15% reduction of BP.
  - If DBP >140 mm Hg, give sodium nitroprusside as IV infusion, titrating the dose for a 10%–15% reduction of BP.

#### Subacute setting

- **Previously untreated patients with SBP ≥140 mm Hg or DBP ≥90 mm Hg**
  - Initiate BP therapy (Class I; Level of evidence B)

- **Patients with SBP <140 mm Hg and DBP <90 mm Hg**
  - Initiation of BP therapy is of uncertain benefit (Class IIb; Level of evidence C)

- **Previously treated patients with known hypertension**
  - Resume BP therapy (Class I; Level of evidence A)

- **Specific indications**
  - **Recent lacunar stroke**
    - SBP <130 mm Hg (Class I; Level of evidence B)
  - **Intracranial atherosclerosis (50%–99% stenosis of a major intracranial artery)**
    - Target SBP <140 mm Hg (Class I; Level of evidence B)
  - **Intracerebral hemorrhage**
    - When SBP is 150–220 mm Hg, acute lowering to 140 mm Hg is reasonable

#### Table: Medications

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Dose</th>
<th>Onset of action</th>
<th>Duration of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Labetalol</strong></td>
<td>10–20 mg IV bolus, over 1-2 min or 0.5–2.0 mg/min infusion; may repeat at 10 min</td>
<td>5 min</td>
<td>8–12 h</td>
<td>Bradycardia, bronchospasm</td>
</tr>
<tr>
<td><strong>Nicardipine</strong></td>
<td>5-15 mg/h as IV infusion, increasing the rate 2.5 mg/h every 5 min (maximum dose: 15 mg/h)</td>
<td>1–5 min</td>
<td>15–120 min</td>
<td>Hypotension</td>
</tr>
<tr>
<td><strong>Hydralazine</strong></td>
<td>10-20 mg as IV bolus or intramuscularly; repeat every 4–6 h (maximum dose: 40 mg)</td>
<td>10-20 min</td>
<td>3–8 h</td>
<td>Reflex tachycardia, myocardial injury</td>
</tr>
<tr>
<td><strong>Nitroglycerine</strong></td>
<td>5-100 mg/min as IV infusion</td>
<td>2–5 min</td>
<td>5–10 min</td>
<td>Venous dilation can cause preload reduction</td>
</tr>
<tr>
<td><strong>Sodium nitroprusside</strong></td>
<td>0.25-10 μg/kg/min as IV infusion; maximal dose for 10 min only</td>
<td>Seconds to 2 min after initiation of infusion</td>
<td>1–3 min</td>
<td>Raised ICP</td>
</tr>
</tbody>
</table>

Continued
The second component of this debate has focused on the clinical safety of acutely lowering BP, since elevated BP after ICH is not only predictive of outcome but is associated with recurrent hemorrhage.\textsuperscript{e4,e5} The safety and effect on hematoma growth of lowering BP was demonstrated in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) trials, which not only supported the safety of an intensive BP-lowering strategy (SBP range of 130–140 mm Hg)\textsuperscript{e6} but also showed a reduction of hematoma enlargement (a factor associated with poor outcome) at 24 and 72 hours in patients who had intensive BP lowering vs a guideline-based management (SBP, 180 mm Hg) when treatment was initiated within 6 hours of symptom onset.\textsuperscript{e7} A similar safety trend was also demonstrated with the acute reduction of SBP to a goal 110–140 mm Hg within 6 hours of symptom onset of an acute ICH in the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial.\textsuperscript{e8}

With regards to clinical efficacy, no significant reduction was seen in the primary outcomes of the INTERACT-2 trial (odds ratio [OR] with intensive treatment 0.87; 95% CI 0.75–1.01; \( p = 0.06 \)). An ordinal analysis of the modified Rankin score, however, did suggest that intensive BP treatment improved functional outcomes (OR for greater disability 0.87; 95% CI 0.77–1.00; \( p = 0.04 \)). There was also meaningful evidence for better physical and psychological well-being in patients in whom the BP was intensively lowered, without a concomitant increase in the rate of death or serious adverse events.\textsuperscript{e6,e7} The ATACH II trial that is currently investigating the effectiveness and safety of lowering SBP to a goal <140 mm Hg within 4.5 hours will provide additional information on whether an antihypertensive treatment strategy targeting a more stringent time metric is safe and can improve clinical outcomes.\textsuperscript{e10} Based on the INTERACT and ATACH trials, the current American Heart Association recommendations endorse the safety of acutely lowering BP in acute ICH with an intensive strategy and suggest that antihypertensive treatment is safe and may improve outcomes when initiated within 6 hours of symptom onset.

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<th>Onset of action</th>
<th>Duration of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esmolol</td>
<td>500 ( \mu )g/kg as IV bolus over 1 min, followed by maintenance infusion of 50 ( \mu )g/kg/min for 4 min (maximum dose: 300 ( \mu )g/kg/min)</td>
<td>2–10 min</td>
<td>10–30 min</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>1 mg as IV bolus followed in 30 min by 10 mg</td>
<td>15 min</td>
<td>12–24 h</td>
<td>Onset of action and duration makes titration difficult, hypotension</td>
</tr>
</tbody>
</table>

#### Primary care setting\textsuperscript{e17}

<table>
<thead>
<tr>
<th>Age ( \geq 60 ) y</th>
<th>Goal BP &lt; 150/90 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( \leq 60 ) y</td>
<td>Goal BP &lt; 140/90 mm Hg</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Goal BP &lt;140/90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Initial drug option: thiazide diuretic, ACEI, ARB, or CCB</td>
</tr>
<tr>
<td>Age &gt;18 y and chronic kidney disease</td>
<td>Goal BP &lt;140/90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Initial drug option: ACEI or ARB</td>
</tr>
<tr>
<td>Non-black population</td>
<td>Thiazide diuretic, CCB, ACEI, or ARB</td>
</tr>
<tr>
<td>Black population</td>
<td>Thiazide diuretic or CCB</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- **ACEI** = angiotensin converting enzyme inhibitor
- **ARB** = angiotensin receptor blocker
- **BP** = blood pressure
- **CCB** = calcium channel blocker
- **DBP** = diastolic blood pressure
- **ICP** = intracranial pressure
- **SBP** = systolic blood pressure
- **TIA** = transient ischemic attack
lowering SBP to 140 mm Hg in patients with ICH presenting with a SBP of 150–220 mm Hg.

**Antihypertensive agents in stroke**

As discussed, the need for rapid BP control in both AIS and ICH often requires IV agents. Such agents should be rapidly acting, be easy to titrate, and have few side effects and short half-lives.

Some of the commonly used IV medications are nicardipine, labetalol, sodium nitroprusside, nitroglycerine, enalaprilat, and hydralazine. Sodium nitroprusside is not an ideal agent for acute reduction of BP due to its unpredictable dose–response relationship, risk of rebound hypertension, possibility of cyanide toxicity during prolonged use, and potential to cause raised intracranial pressure.

Although hydralazine is used frequently for acute reduction of BP, its use in routine clinical practice is limited due to its selective arteriolar vasodilator effect resulting in reflex tachycardia leading to myocardial injury.

Recently, new data have been published investigating the use of different BP medications in the acute stroke setting. To compare the therapeutic response and tolerability of labetalol boluses vs IV nicardipine infusion, Liu-DeRyke et al. conducted a small pseudorandomized trial in the acute stroke setting (n = 54; 19 ischemic stroke, 29 ICH, 6 subarachnoid hemorrhage). Their findings demonstrated that a higher proportion of patients in the nicardipine group achieved goal BP within 60 minutes of treatment initiation (100% vs 61%) and spent a greater amount of time in the goal BP range compared to the labetalol group. In addition, the number of dose adjustments required to reach goal BP was also lower (0 vs 2, \(p < 0.001\)) in the nicardipine group, indicating a reliable dose response. While there are several limitations to this small, single-center trial, it is one of the first studies comparing 2 commonly used medications in the acute stroke setting.

Owing to its rapid onset of action, short half-life, and selective arterial vasodilator effect, clevidipine, a new calcium channel antagonist, is being increasingly studied in the critical care setting. The Evaluation of Patients with Acute Hypertension and Intracerebral Hemorrhage with Intravenous Clevidipine Treatment study tested the efficacy and safety of clevidipine in a multicenter, single-arm, open-label design that included spontaneous ICH patients presenting to the emergency department within 6 or 12 hours of symptom onset and with SBP \(>160\) mm Hg. Target BP was achieved in 96.9% of patients in a median time of 5.5 minutes. While the results of this study do not warrant a change in current clinical practice given that this was a pilot study involving a small cohort of patients, the ability to rapidly control high BP is notable and merits further study to determine whether this type of medication should be incorporated into the routine management of hypertension in the acute setting of stroke.

While IV agents are the mainstay of proficient BP management in the hyperacute stroke setting, oral agents are the cornerstone of BP control in the outpatient setting. Recent guidelines from the 8th Joint National Committee (table) can serve as a foundation for clinicians to supplement their clinical expertise in achieving successful long-term outcomes for both primary and secondary stroke prevention goals.

**REFERENCES**

Blood pressure management in stroke


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