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EDITORIALS

# NOT TOO HIGH AND NOT TOO LOW: THE GOLDILOCKS APPROACH TO PREHOSPITAL TREATMENT OF SEVERE HYPERTENSION WITH STROKE

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Today more than ever, prehospital blood pressure (BP) lowering for stroke patients remains a hot topic, with many unanswered questions. First, how can we optimally lower BP before hospital arrival to help acute ischemic stroke (AIS) patients qualify for thrombolytics or mechanical thrombectomy? Secondly, how can we optimally lower BP before hospital arrival to prevent hematoma expansion for intracranial hemorrhage (ICH) patients? Thirdly, why are ambulances currently not lowering prehospital BP in stroke patients routinely and consistently already?

In an attempt to fill in some of these blanks, investigators from the Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke (INTERACT-4) trial published their findings in May 2024 in *The New England Journal of Medicine*. (Li, et al, 2024) Their study, conducted in China, utilized the anti-hypertensive drug urapidil, an $\alpha_1$-receptor blocker unavailable in the United States, during the ambulance phase of care for patients with "undifferentiated stroke." This term refers to patients with stroke-like symptoms without neuroradiographic confirmation yet – before computed tomography (CT) reveals ICH or AIS. The urapidil dose was titrated to achieve a target prehospital systolic BP (SBP) range of 130-140 mmHg but participants in this study only reached an average of 159 mmHg. Investigators found improved outcomes for ICH but worsening for AIS. Specifically, the odds of a poor functional outcome for ICH decreased by about 25% (common odds ratio, 0.75; 95% CI, 0.60–0.92) but increased by about 30% for AIS (common odds ratio, 1.30; 95% CI, 1.06–1.60).

From our perspectives as a vascular neurologist (DZR) and as an EMS quality improvement expert (MRG), we are concerned that overinterpretation of this data may lead some clinicians to refrain from appropriate prehospital antihypertensive therapy for severely hypertensive stroke patients. We suspect that INTERACT-4 may magnify the preexisting fear of neurologic worsening or exam decline from treatment with antihypertensives in the prehospital setting. This fear applies mostly to patients with known carotid disease or large-vessel atherosclerosis, because persistent hypotension can lead to decreased cerebral perfusion pressure and watershed infarction. While this is a valid risk, and potentially played a role in the worsened outcomes for AIS in INTERACT-4, it must be counterbalanced by the current treatment guidelines from the American Heart Association, American Stroke Association, and the European Stroke Organization, which require BP to be <185 systolic and <110 diastolic before treatment with thrombolytics or thrombectomy (Powers et al, 2019), for which we know exists significant benefit. Failure to reach these BP thresholds within guideline-directed time limits (4.5-hours for thrombolytics and 24-hours for thrombectomy, from last known well) may result in "throwing out the baby with the bathwater" as some patients may not receive thrombolytics or thrombectomy because BP could not be controlled fast enough prior to or even after arrival to the hospital. Prehospital adjustment of SBP to pre-specified "Goldilocks" levels that are not too high and not too low may make all the difference.

Feasibly, for undifferentiated stroke patients to receive guideline-compliant care, ambulance crews may indeed be able to attempt to lower the BP to <185 systolic and <110 diastolic during the treatment time window (which needs to occur anyway before thrombolysis or thrombectomy can proceed). Achieving this in the ambulance before ED arrival avoids a preventable delay after hospital arrival. Every minute a stroke goes untreated, a patient loses 1.9 million neurons, each hour results in a 120 million neuron loss (Saver, 2006)

Practically speaking, INTERACT-4 tried to address two problems with one solution: it succeeded with ICH but failed for AIS because, in our opinion, the SBP levels were not (on average) high enough to require acute antihypertensive therapy anyway and may have been clinically unnecessary. Practically and realistically, we find no need to reduce SBP from 185 mmHg to 159 mmHg in AIS; we only need to lower SBP to <185 mmHg in AIS patients. If SBP is <185 mmHg upon presentation to clinicians in the field, then it would be reasonable to simply maintain it at that level to qualify for thrombolytic or thrombectomy upon arrival to the hospital, and not drop it further which could expose the AIS patient to further risk. INTERACT-4 authors found that lowering SBP to below thrombolytic/thrombectomy-required levels may worsen outcomes and hence it may be unwise to use antihypertensives to go below those levels in the field. However, many AIS patients present with SBP >185, often >200 mmHg, some much higher at 220 mmHg, occasionally 250 mmHg, and rarely some unfortunate soul breaks the sphygmomanometer at 300 mmHg. Therefore, what we urgently need is this high systolic data (which INTERACT-4 did not provide) showing the effect of lowering SBP from these levels to a 160-185 mmHg range. Because this data remains unknown, we cannot discard the possibility that this may be ultimate answer to the AIS-BP question.

We therefore believe that since suspected stroke cases are 'undifferentiated' in conventional ground ambulances, getting the patient into a tight SBP goal of 160-185 mmHg

(lowered only if SBP were >185 mmHg) would enable immediate administration of thrombolytic after CT-scan confirms no ICH upon arrival to the emergency department (ED). This would save valuable "time-is-brain" minutes otherwise wasted bringing SBP down after ED arrival.

For ICH, data from INTERACT-4 and the Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage (ATACH-2) study (Qureshi et al, 2016) is somewhat more clear: lower is safe, and probably is better. The 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage from the American Heart Association/American Stroke Association recommends a SBP range of 130-150 mmHg. (Greenberg et al, 2022) If EMS has already reduced the SBP to the 160-185 mmHg range and ICH is confirmed on CT in the ED, physicians can lower the SBP even further to that 130-150 mmHg goal in a stepwise fashion. This is far more preferable to precipitously dropping it from >200 mmHg (if untreated in prehospital setting) to that 130-150 mmHg goal quickly and dangerously in the ED. In essence, by lowering the SBP to 160-185 mmHg prehospital, the ICH patient is halfway there upon ED arrival. Hence, extreme BP plummeting (which could be detrimental even in ICH patients) is averted.

Fast-acting intravenous antihypertensives, like clevidipine or labetalol, are decent candidates for prehospital use. Transdermal nitroglycerin use in the ambulance for presumed stroke has been studied in randomized fashion (4), but it was not used to acutely manage severe hypertension. Moreover, because of their potent vasodilatory effects, nitrates are well-known to increase intracranial pressure, which could be harmful for ICH and also harmful for AIS with cerebral edema.

While clevidipine and labetalol are often administered after ED arrival, the next logical step in optimization of the sequence of care for stroke patients would be to implement a protocol for administering them safely before ED arrival in ambulances with infusion pumps designed for field use. Ultimately, for undifferentiated stroke, the "Goldilocks Approach," with SBPs just in the ideal range, not too high and not too low, needs to be evaluated in a prehospital trial.

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