Title: **Impact of Antihypertensive Therapy on Hematoma Expansion in Acute Intracerebral Hemorrhage**

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Background:

Intracerebral Hemorrhage (ICH) is a devastating type of stroke with high rates of morbidity and mortality. Hematoma expansion (HE), which occurs in approximately one-third of ICH patients, significantly contributes to early neurologic deterioration and poor functional outcomes. Although rapid blood pressure (BP) control is essential in acute ICH management, overly aggressive BP reduction may compromise cerebral perfusion. Among intravenous (IV) antihypertensive agents, Clevidipine and Nicardipine are commonly utilized in neurocritical care; however, comparative data exist on their effects on HE are limited. This study aimed to evaluate whether treatment with Clevidipine, compared to Nicardipine, is associated with increased odds of hematoma expansion and in-hospital mortality in patients with acute ICH.

Methods:

In this retrospective, observational cohort study, we analyzed patients with acute spontaneous ICH admitted to Cleveland Clinic's Main Campus Neuro-ICU who received continuous IV antihypertensive therapy with either Clevidipine or Nicardipine. The primary outcome was hematoma expansion, defined as ≥ 33% increase from baseline ICH volume. The secondary outcome was in-hospital mortality. Clinical and demographic covariates included age, sex, race (Black vs. Non-Black), prior stroke, type 2 diabetes, admission Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), ICH score, baseline modified Rankin score (mRS), ICH location and volume, presence of intraventricular hemorrhage (IVH), and duration of continuous IV antihypertensive therapy. Propensity scores were estimated using logistic regression with the above covariates. Matching was performed using 1:1 nearest neighbor caliper matching (caliper =0.2) without replacement to optimize covariate balance. Additional analysis included propensity score weighting using inverse probability of treatment weighting (ATT) and generalized boosted modeling with ATT weighting (GBM+ATT). Generalized linear models were used to estimate odds ratio (OR) and 95% confidence intervals for the outcomes. Sensitivity analyses using Rosenbaum's Γ were conducted to assess robustness to unmeasured confounding.

Results:

Caliper-based 1:1 matching (n=52 per group) achieved optimal covariate balance and satisfied Rubin's diagnostics. In the matched cohort, Clevidipine was associated with

higher odds of hematoma expansion compared to Nicardipine (OR 2.3, 95% CI 1.2-4.3). Secondary analysis suggested a possible mortality benefit for Clevidipine (OR 0.55, 95% CI 0.3-0.95). Sensitivity analyses supported robustness of these findings to moderate unmeasured confounding (Γ up to 1.5). In contrast, ATT and GBM + ATT weighted models yielded inconsistent covariate balance and unstable estimates due to poor overlap and extreme weights.

Conclusion:

Clevidipine was associated with greater odds of hematoma expansion compared to Nicardipine in acute ICH, although a potential in-hospital mortality benefit emerged in matched analyses. Propensity score caliper matching outperformed weighting methods in achieving covariate balance and producing stable estimates. These results support the need for prospective validation, including the planned CLUTCH (Clevidipine for the Antihypertensive Treatment of Acute Intracerebral Hemorrhage) trial, to inform optimal BP management strategies in ICH care.