# Early Intensive Blood Pressure Reduction After Intracerebral Hemorrhage Is Associated With Worse Functional Outcome: The Risk of Overshooting Blood Pressure Goals

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**Study objective:** Blood pressure (BP) control is thought to be critical in acute intracerebral hemorrhage management. Here, we investigated whether reducing systolic BP ≤150 mm Hg within 2 hours of emergency department (ED) arrival is associated with improved outcomes and assessed the effect of excessive BP lowering ("overshooting") on functional recovery.

**Methods:** We conducted a retrospective cohort study of adult patients with spontaneous intracerebral hemorrhage (ICH) who presented to 2 academic medical centers between 2017 and 2023. We assessed the associations between blood pressure (BP) indicators, including BP control (≤150 mm Hg within 2 hours) and overshooting (<120 mm Hg), and the modified Rankin scale (mRS) score at discharge, dichotomized as a good (0 to 3) or poor (4 to 6) outcome, using logistic regression adjusted for ICH score, time from last seen well, and arrival BP.

**Results:** Among 420 included patients, 323 (76.9%) had arrival BP>150 mm Hg. Of these, 62.8% received antihypertensive medications within 1 hour of ED arrival, and 71.2% achieved goal BP within 2 hours. Achieving goal BP within 2 hours of ED arrival was associated with worse outcomes (OR 2.32, 95% CI 1.17 to 4.57). Overshooting within 6 hours was associated with worse outcomes (OR 2.55, 95% CI 1.27 to 5.13). Antihypertensive medication type (bolus versus infusion) did not influence overshooting risk.

**Conclusions:** Although successful early BP reduction is common in ICH care, excessive lowering is also common and is associated with worse functional outcome. Caution is warranted to avoid overshooting during acute BP management. [Ann Emerg Med. 2025;■:1-12.]

Please see page XX for the Editor's Capsule Summary of this article.

**Keywords:** Blood pressure, Hemorrhagic stroke, Intracerebral hemorrhage, Intraparenchymal hemorrhage.

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## INTRODUCTION

### Background

Intracerebral hemorrhage (ICH) is a devastating pathology that affects approximately 2 million people per year worldwide, with a 30-day mortality rate exceeding 50% and fewer than 40% of survivors achieving functional independence by 3 months.[1-3] Current treatment strategies include medical management to reduce hematoma expansion and optimize neurologic recovery, as well as surgical management to reduce final hematoma volume. Medical management strategies include blood pressure (BP) control,[4,5] anticoagulation reversal, and intracranial pressure management.[6-10] Among these, acute BP management has been a key therapeutic target.

### Importance

The 2022 American Heart Association (AHA)/American Stroke Association (ASA) guidelines recommend smooth but rapid systolic blood pressure (SBP) reduction to 130 to 150 mm Hg.[11] Specifically, guidelines recommend initiating treatment within 2 hours of ICH onset and reaching target within 1 hour of treatment.[11] These recommendations are based largely on post hoc analysis. The Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH-2) trial identified improved outcomes in a subgroup of patients who had increased BP and received treatment within 2 hours of symptom onset,[12] and the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial 2

**Editor's Capsule Summary**

*What is already known on this topic*

Many patients with spontaneous intracranial hemorrhage (ICH) have early systolic blood pressure (SBP) treatment.

*What question this study addressed*

What are the effects of SBP control (130 to 150 mm Hg) within 2 hours of emergency department arrival and of overshooting the target range (to <120 mm Hg) on functional outcomes in patients with spontaneous ICH?

*What this study adds to our knowledge*

In a retrospective observational design, early and rapid SBP control was associated with poor functional outcomes possibly because of overshooting the target SBP.

*How this is relevant to clinical practice*

Recognize the possible risks of blood pressure control approaches and overshoot in early care of those with spontaneous ICH.

(INTERACT-2) trial showed the greatest benefit when target BP was reached within 1 hour of initiating treatment.[13] However, neither randomized control trial demonstrated a statistically significant improvement in their primary outcome with intensive BP reduction alone. Only the more recent Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial 3 (INTERACT-3) trial, which employed a bundled care approach that included BP control, showed improved functional outcome.[14] However, the BP reductions achieved were modest, with only small differences between groups (mean SBP: 148.4 mm Hg versus 154.7 mm Hg at 1 hour; 136.1 versus 139.0 at 24 hours), making the specific effect of BP control on the observed benefit unclear.[14] Thus, the effect and optimal timing of BP lowering remains uncertain.[4,5]

Additionally, there is limited pragmatic data on how intensive BP targets are implemented in emergency care and whether they inadvertently contribute to adverse outcomes.[15] Post hoc analyses of ATACH-2 and INTERACT-2 found that intensive BP lowering was beneficial only for a narrow subset of patients under highly controlled trial conditions. In contrast, the authors have observed these intensive targets being applied broadly in real-world practice—often outside the strict eligibility criteria and without the standardized protocols used in the trials. This discrepancy confers the risk of generalizing trial-based strategies to heterogenous patient populations. Furthermore, the frequency and clinical consequences of excessive BP reduction ("overshooting" the recommended target range) remain poorly defined. Understanding how often overshooting occurs and its effect on outcomes is essential to refining BP management strategies and practically improving care for patients with ICH.

### Goals of This Investigation

To clarify the effect of early intensive BP lowering on functional outcome in real-world clinical settings, we conducted a retrospective cohort study of consecutive patients with spontaneous ICH who presented to 2 large academic medical centers within 24 hours of last seen well. We aimed to assess whether achieving goal BP (SBP≤150 mm Hg) within 2 hours of emergency department (ED) arrival was associated with improved or worsened functional outcome. Although not a guideline-specific goal, we chose the timepoint of 2 hours from ED arrival because we felt it is a widely adopted and clinically attainable target. Additionally, we investigated whether excessive BP reductions—defined as "overshooting" to SBP<120 mm Hg—contributed to poor recovery. By examining these variables in a routine clinical care setting, we sought to provide practical insights into how current BP management strategies may influence patient outcomes and to quantify the potential risks of overly aggressive BP lowering in the early phase of ICH care.

## METHODS

### Study Design and Setting

We conducted a retrospective cohort study using the AHA Get With The Guidelines stroke database from the Massachusetts General and Brigham & Women's Hospitals in Boston, Massachusetts. Both hospitals are urban academic medical centers, designated as Comprehensive Stroke Centers,[16] and use Epic as the electronic medical record.

### Selection of Participants

All patients aged 18 years or older admitted with a diagnosis of acute spontaneous ICH between January 1, 2017 and December 31, 2023 were eligible for inclusion in this study. In line with prior literature, we used last seen well time as a proxy for ICH onset. We excluded those with unknown or missing last seen well times, or last seen well >24 hours, to focus on acute-phase interventions for ICH management.[4,5] Patients transferred from outside hospitals were excluded, to focus on the effect of initial ED

care. Those with no or only 1 recorded BP measurement after admission were excluded due to inability to assess BP trend. Patients without a documented modified Rankin Score (mRS) at discharge were excluded, as this was the primary outcome. Additionally, patients with tumor-associated hemorrhage, arteriovenous malformation-associated hemorrhage, or ischemic stroke with hemorrhagic conversion were excluded. This study was approved by the Institutional Review Boards of Massachusetts General Hospital and Brigham & Women's Hospital under protocols #2002P000955, #2018P001173, and #2001P001933. Given the retrospective nature of the study, the requirement for informed consent was waived by the Institutional Review Boards.

## Data Collection

Patient demographics; dates and times of ED arrival, last seen well, first brain imaging completion, hospital discharge; initial ICH score, NIH Stroke Scale (NIHSS), and Glasgow Coma Score (GCS); home medications prior to admission; arrival BP; whether they received surgery; time of first documented comfort measure only status; discharge disposition; and mRS at hospital discharge were collected from the Get With The Guidelines database. All BP measurements and antihypertensive medications administered within the first 24 hours of ED arrival were extracted from Epic's Enterprise Data Warehouse. Additionally, 2 trained reviewers conducted manual chart review of medical notes and imaging reports of all included patients to confirm presence of acute ICH and exclude patients who did not have spontaneous ICH; 100% of patients excluded were confirmed by both reviewers.

Some patients in the Get With The Guidelines database were missing recorded ICH scores. The ICH score estimates mortality and is calculated using GCS (3 to 4, 5 to 12, or 13 to 15), age $\geq$80 years, ICH volume $\geq$30 mL, presence of intraventricular hemorrhage, and whether the hemorrhage is infratentorial in origin.[17] For patients missing ICH scores, the Research Patient Data Registry[18] was used to search notes for ICH score and GCS. For the remaining 64 patients still missing ICH score data, 2 trained reviewers manually extracted data from the electronic medical record, using a data abstraction form. ICH score, GCS, ICH volume, presence of intraventricular hemorrhage, and infratentorial origin of ICH were recorded. For those without recorded GCS, review of the physical examination description on the ED arrival note was used to determine the GCS category. For the 7 patients without recorded ICH volume within the radiology report or notes, 2 trained reviewers independently measured the size of each hemorrhage, determined the volume using the ABC/2 formula, and recorded whether it was greater or less than 30 mL, with 100% agreement between both reviewers. Thus, ICH scores were either recorded or calculated for all patients included in the study.

## Study Outcome

The primary outcome studied was functional status, defined by mRS at hospital discharge. The mRS is a measure of global disability scored from 0 to 6, where 0 indicates no symptoms, 1 indicates symptoms without disability, 2 to 5 represents increasing levels of disability, and 6 indicates death.[19] Functional outcome was dichotomized to mRS 0 to 3 as "good outcome" and 4 to 6 as "poor outcome," consistent with much of prior ICH literature and to reflect the functional significance of being ambulatory. Furthermore, because our study assessed mRS at discharge—an earlier time point than when most trials measure recovery—we chose the 0 to 3 cutoff rather than the more conservative 0 to 2. Because the decision to transition to comfort measure only status may confound outcomes, we included sensitivity analyses that excluded comfort measure only patients, defined as patients with a documented comfort measure only status at any time during the hospital admission.

## Arrival BP

Arrival BP was defined as the first blood pressure taken in the ED, and were categorized by SBP: $\leq$150, 151 to 180, 181 to 210, and >210 mm Hg. We compared arrival BP category and functional outcome (mRS 0 to 3 versus 4 to 6). We also included a sensitivity analysis using mRS 0 to 2 versus 3 to 6.

## Time to Goal BP

Goal BP was defined as SBP $\leq$150 mm Hg, in line with the AHA Guidelines.[11] Time to goal BP was the time from ED arrival to the first, single SBP$\leq$150 mm Hg. Those with subsequent BPs documented that rose back up to >150 mm Hg were still considered to have met goal BP. Among patients with arrival BP>150 mm Hg, we compared functional outcome in those that achieved goal BP within 2 hours of ED arrival versus those that did not. Those that did not achieve goal BP within 24 hours of ED arrival, or who did not have any BP measurements within 2 hours were included in the latter group. Patients with arrival BP already $\leq$150 mm Hg were excluded from this analysis. We conducted sensitivity analyses using mRS 0 to

2 versus 3 to 6. We conducted subgroup analyses limiting arrival BP to >150 mm Hg, between 151 and 180 mm Hg, >180 mm Hg, between 181 and 210 mm Hg, and >210 mm Hg. We conducted subgroup analyses limiting last seen well to ≤12 hours, ≤6 hours, and ≤2 hours.

### Overshooting

Among patients with arrival BP>150 mm Hg who received antihypertensive treatment, "overshooting" was defined as the occurrence of any single SBP<120 mm Hg following treatment. We assessed whether overshooting first occurring within 6 hours or within 24 hours of ED arrival was associated with outcomes. Sensitivity analyses used alternative timeframes from ED arrival (overshooting within 4, 8, 12, and 18 hours of ED arrival). The threshold of 120 mm Hg was selected to provide a buffer below the target range of 130 to 150 mm Hg, accounting for the variability inherent in relying on a single BP measurement. Sensitivity analyses used alternative SBP thresholds to define overshooting (<130, <110, and <100 mm Hg). Furthermore, we tested whether achieving goal BP within 2 hours was associated with overshooting. Finally, using all patients with arrival BP >150 mm Hg, we tested whether staying within target range (achieving goal BP within 2 hours, and not overshooting to <120 mm Hg) for the first 6 hours was associated with differences in outcomes compared to those that did not achieve goal BP within 2 hours.

### Antihypertensive Medication Type

We explored whether the type of first antihypertensive medication administered—bolus or infusion—was associated with overshooting within 6 hours of ED arrival. There were no institutional protocols regarding whether antihypertensives should be given as a bolus or infusion, though infusions would require disposition to an ICU.

### Data Analysis

We reported descriptive statistics for patients' demographic and clinical characteristics, stratified by time to goal BP. We used a logistic regression model to evaluate the associations between SBP indicators (arrival BP, time to goal BP, and overshooting) and functional outcome. We first conducted univariable analyses. We then conducted multivariable analyses to adjust for variables selected a priori that we felt could affect outcomes, particularly those that reflect severity of illness. For arrival BP analyses, we further adjusted for last seen well time in a multivariable model. For time to goal BP and overshooting analyses, we adjusted for last seen well time, ICH score, and arrival BP category in multivariable models. All statistical analyses were performed with R.

## RESULTS

### Patient Characteristics and BP Trends

During the study period, a total of 2,436 patients were recorded in the Get With The Guidelines Stroke database with intracerebral hemorrhage. Figure 1 shows the patient inclusion/exclusion criteria. After excluding those who arrived as interhospital transfers, had unknown or last seen well time >24 hours, without BP measurements, without mRS at discharge, or who were later deemed not to have acute, spontaneous ICH, 420 patients were included in this study. The mean age of patients included was 68.6 (standard deviation [SD] 14.9) years, with 45.5% female. The median ICH score was 1 (IQR 1 to 3), the median mRS at discharge was 4 (IQR 4 to 6), and the mean arrival BP was 180 (SD 38.7) mm Hg. The full set of patient characteristics are shown in Table 1. Patient characteristics for those with arrival BP >150 mm Hg are shown in Table E1, available at http://www.annemergmed.com.

### High Arrival BP Is Associated With Poor Functional Outcome

Among the 420 patients, 97 (23.1%) had an arrival BP≤150 mm Hg, 127 (30.2%) had 151 to 180 mm Hg, 103 (24.5%) had 181 to 210 mm Hg, and 93 (22.1%) had >210 mm Hg (Table 2). In the univariable analysis, we found that patients with a higher arrival BP had an increased risk of poor functional outcome in a dose-responsive manner (trend test $P$=.002). After adjusting for last seen well, the association between higher arrival BP and poor outcomes remained (arrival BP 151 to 180 versus ≤150 mm Hg: odd ratio [OR] 1.55, 95% confidence interval [CI] 0.85 to 2.84; 181 to 210 versus ≤150 mm Hg: OR 1.93, 95% CI 0.99 to 3.74; >210 versus ≤150 mm Hg: OR 2.89, 95% CI 1.36 to 6.15; Table 2). This trend persisted despite excluding comfort measure only patients (Table E2, available at http://www.annemergmed.com). Sensitivity analysis using mRS 3 to 6 (rather than 4 to 6) as the definition of poor outcome showed similar trends (Table E3, available at http://www.annemergmed.com).

### Successfully Achieving Goal BP Within 2 Hours Is Associated With Poor Outcomes

Among the 420 patients, 323 (76.9%) patients had an arrival BP>150 mm Hg, thus requiring BP control (Figure 2A). Of these, 230 (71.2%) achieved goal BP within 2 hours of ED arrival, and 203 (62.8%) received antihypertensive medications within 1 hour of ED arrival

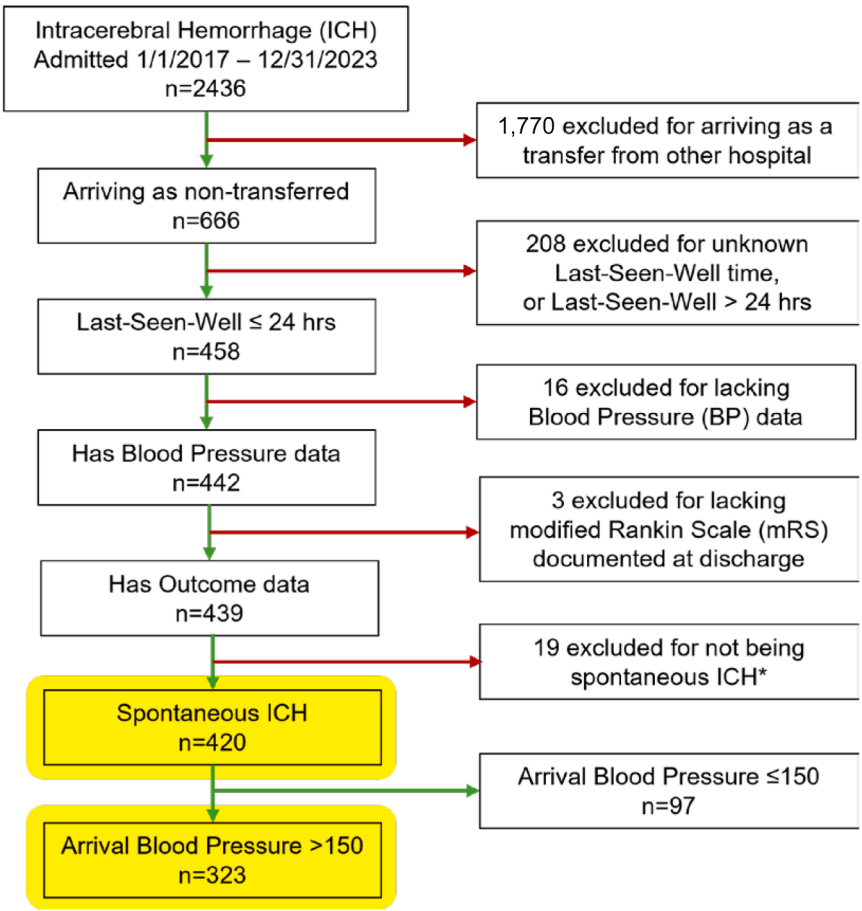


**Figure 1.** Cohort selection diagram. Of 2,436 patients with intracerebral hemorrhage (ICH) in the Get With The Guidelines Stroke database, 1,770 were excluded as interhospital transfers. Among 666 primary ED presentations, 458 had last seen well times ≤24 hours. After excluding 19 with nonacute or secondary hemorrhage (*5 tumor-associated bleed, 4 hemorrhagic conversion of ischemic infarct, 5 arteriovenous malformation-associated interventricular hemorrhage, and 5 without acute ICH), and 19 with missing BP or mRS data, 420 patients were included in the final analysis. Of these, 323 patients arrived with BP>150, necessitating BP control. *BP*, blood pressure; *ED*, emergency department; *mRS*, modified Rankin scale.

(Figure 2C). Overall, 327 (77.9%) of the total patients achieved goal BP of ≤150 mm Hg within 2 hours of ED arrival (Figure 2B).

Figure 3 shows the distribution of mRS for the 323 patients with arrival BP>150 mm Hg, by time to goal BP. Those that achieved goal BP within 2 hours had a median mRS at discharge of 5 (IQR 4 to 6), whereas those that took longer to achieve goal BP had a median mRS of 4 (IQR 3 to 5). In the univariable analyses, we found that patients who achieved goal BP within 2 hours had a 2.53-fold increased odd of having a poor outcome compared to those who did not (Table 3). After adjusting for last seen well time, ICH score, and arrival BP category, the association remained strong (OR 2.32, 95% CI 1.17 to 4.57; Table 2). In both the sensitivity analysis using mRS 3 to 6 as the definition poor outcome, and excluding comfort measure only patients, this association persisted (Table 3).

Subgroup analyses limiting to different arrival BP categories continued to show that achieving goal BP within 2 hours was associated with increased risk of poor outcomes in most subgroups (Table 3). Arrival SBP of >150 and >180 mm Hg had worse outcomes when achieving goal BP early, whereas those arriving with SBP >210 was no longer significant. Further limiting arrival SBP to 151 to 180 mm Hg had the most dramatic difference in worse outcome, whereas those with SBP 181 to 210 or >210 did not have significant harm. Subgroup analyses limiting to shorter last seen well times also continued to support the same association (Table 3).

## Early Overshooting Is Associated With Poor Outcomes

We then explored whether overshooting within the first 6 hours of ED arrival was associated with

**Table 1.** Baseline patient characteristics and BP control, stratified by time to goal BP.

| | Time to Goal Blood Pressure | |
|---|---|---|
| **Patient Characteristics** | **≤2 h** | **>2 h** |
| n | 230 | 93 |
| Age, y (SD) | 70.6 (13.9) | 68.8 (15.0) |
| % Female | 43.9 | 48.4 |
| Race, n (freq %) | | |
| White | 148 (64.3%) | 58 (62.4%) |
| Black/African American | 35 (15.2%) | 13 (14.0%) |
| Asian | 19 (8.3%) | 9 (9.7%) |
| Unknown | 28 (12.2%) | 13 (14.0%) |
| Last seen well, min (SD) | 306.6 (343.9) | 426.5 (378.7) |
| Initial illness severity score (IQR) | | |
| ICH score | 2 (1-3) | 1 (0-2) |
| NIHSS Score | 12 (5-17.5) [147] | 8.5 (2.75-17) [64] |
| Glasgow Coma Score | 14 (8-15) [168] | 15 (10-15) [59] |
| Home medications, n (Freq %) | | |
| Prior anticoagulant | 30 (5.6%) | 12 (12.9%) |
| Prior antiplatelet | 86 (13.1%) | 28 (30.1%) |
| Prior antihypertensive | 150 (28.1%) | 60 (64.5%) |
| Time to brain imaging, min (SD) | 42.0 (58.5) [227] | 88.5 (124.0) [92] |
| Arrival SBP, mm Hg (SD) | 191.5 (28.4) | 202.4 (31.4) |
| Maximum SBP, mm Hg (SD) | 206.7 (31.3) | 219.5 (32.6) |
| Minimum SBP, mm Hg (SD) | 108.7 (18.7) | 126.8 (32.2) |
| Received surgery (freq %) | 18 (3.3%) | 7 (7.5%) |
| mRS at discharge (IQR) | 5 (4-6) | 4 (3-5) |
| Comfort measures only status, n (freq %) | | |
| On day 0 or 1 of admission | 33 (14.3%) | 10 (10.8%) |
| On day 2 or later of admission | 41 (17.8%) | 10 (10.8%) |
| Not documented | 156 (67.8%) | 73 (78.5%) |
| Time to discharge, d (SD) | 9.7 (10.6) | 11.8 (14.4) |
| Disposition at discharge (Freq %) | | |
| Home | 32 (10.3%) | 22 (23.7%) |
| Hospice - home | 4 (0.9%) | 2 (2.2%) |
| Hospice - facility | 6 (0.9%) | 2 (2.2%) |
| Acute Care facility | 1 (0.5%) | 1 (1.1%) |
| Other health care facility | 112 (22.0%) | 47 (50.5%) |
| Expired | 74 (8.9%) | 19 (20.4%) |
| Left against medical advice | 1 (0.0%) | 0 (0.0%) |

Notes: Of the 420 overall patients included, 323 arrived with BP >150 mm Hg, of which 230 (71.2%) achieved goal blood pressure (systolic ≤150 mm Hg) within 2 hours of ED arrival. Mean (standard deviation, SD); Median (interquartile range, IQR); or number (n) with frequency (%) are reported. For those with n that differed from the first row, the number included is denoted [n].

differences in functional outcome. There were 302 patients with arrival BP>150 mm Hg and received antihypertensives within the first 6 hours, 152 (50.3%) of whom overshot within 6 hours. Overshooting within the first 6 hours was associated with poor outcome in univariable analysis and remained strong despite adjustment (adjusted OR 2.55, 95% CI 1.27 to 5.13, Table 2). These findings remained strong despite excluding comfort measure only patients (Table E2).

When we analyzed overshooting anytime within the first 24 hours, we included 315 patients who received antihypertensive treatment, 204 (64.7%) overshot within 24 hours. In contrast to the 6-hour analysis, overshooting within the first 24 hours was not associated with poor outcomes (Table 2). In the sensitivity analyses, we found that overshooting within the first 12 hours of ED arrival was associated with worse outcomes (Table E4C, available at http://www.annemergmed.com). Sensitivity analyses using alternative SBP thresholds to define overshooting continued to have the same findings (Table E4A, E4B, available at http://www.annemergmed.com).

## Associations Among Time to Goal BP, Early Overshooting, and Antihypertensive Medications

Given that achieving goal BP within 2 hours was associated with poor outcomes and that early overshooting was associated with poor outcomes, we next tested whether achieving goal BP within 2 hours was associated with early overshooting. Indeed, achieving goal BP within 2 hours was associated with overshooting within 6 hours (OR 2.64, 95% CI 1.59 to 4.40). When adjusting for overshooting, achieving goal BP within 2 hours was no longer associated with poor outcomes (OR 0.54, 95% CI 0.29 to 1.03).

Regarding the type of antihypertensive medication used, of the 302 patients analyzed, 157 patients received a bolus medication first, whereas 145 received an infusion first (144 patients received nicardipine, 1 patient received clevidipine). There was no difference in overshooting within the first 6 hours in those that received bolus versus infusion medications (45.9% of those that received bolus overshot, 55.2% of those that received infusions overshoot).

Ultimately, of the 323 patients that arrived hypertensive, there were no significant differences in outcomes among 3 groups: (1) those who did not achieve goal BP within 2 hours and did not overshoot within 6 hours, (2) those who did not achieve goal BP within 2 hours but did overshoot within 6 hours, and (3) those who

**Table 2.** Blood pressure management and functional outcomes in intracerebral hemorrhage.

| | | n (Freq %) | mRS (IQR) | % Poor Outcome (mRS 4 to 6) | Simple OR (95% CI) | Adjusted OR (95% CI) | Abs. Diff. % Poor Outcome (95% CI) |
|---|---|---|---|---|---|---|---|
| A. Arrival BP, mm Hg (n=420) | | | | | | | |
| ≤150 | | 97 (23.1%) | 4 (3-5) | 69.1% | Ref | Ref | Ref |
| 151-180 | | 127 (30.2%) | 4 (4-5) | 78.0% | 1.58 (0.87-2.89) | 1.55 (0.85-2.94) | 8.9% (−2.8% to 20.5%) |
| 181-210 | | 103 (24.5%) | 4 (4-6) | 81.6% | 1.98 (1.02-3.82) | 1.93 (0.99-3.74) | 12.5% (−0.6% to 24.3%) |
| >210 | | 93 (22.1%) | 5 (4-6) | 87.1% | 3.02 (1.44-6.36) | 2.89 (1.36-6.15) | 18.0% (6.6%-29.5%) |
| B. Time to goal BP (n=323) | | | | | | | |
| >2 h | | 93 (28.8%) | 4 (3-5) | 71.0% | Ref | Ref | Ref |
| ≤2 h | | 230 (71.2%) | 5 (4-6) | 86.1% | 2.53 (1.41-4.53) | 2.32 (1.17-4.57) | 15.1% (4.9%-25.4%) |
| C. Overshot within 6 hours? (n=302) | | | | | | | |
| No | | 152 (50.3%) | 4 (3-5) | 73.0% | Ref | Ref | Ref |
| Yes | | 150 (49.7%) | 5 (4-6) | 90.6% | 3.32 (1.74-6.33) | 2.55 (1.27-5.13) | 17.5% (8.3%-25.3%) |
| D. Overshot within 24 hours? (n=315) | | | | | | | |
| No | | 111 (35.3%) | 4 (4-6) | 79.3% | Ref | Ref | Ref |
| Yes | | 204 (64.7%) | 4 (4-6) | 82.4% | 1.22 (0.68-2.19) | 1.04 (0.55-1.99) | 3.1% (−6.1% to 12.3%) |
| E. Goal BP, Overshot within 6 hours? (n=323) | | | | | | | |
| >2 h | No | 70 (21.7%) | 4 (3-5) | 47 (67.1%) | Ref | Ref | Ref |
| >2 h | Yes | 23 (7.1%) | 4 (4-5) | 19 (82.6%) | 2.32 (0.71-7.63) | 2.29 (0.64-8.23) | 15.5% (−3.5% to 3.4%) |
| ≤2 h | No | 93 (28.8%) | 4 (4-6) | 69 (77.5%) | 1.68 (0.84-3.37) | 1.76 (0.79-3.91) | 10.4% (−7.1% to 21.2%) |
| ≤2 h | Yes | 137 (42.4%) | 5 (4-6) | 126 (92.0%) | 5.61 (2.54-12.39) | 4.38 (1.8-10.59) | 24.9% (12.9%-36.7%) |

Note: Number (n) and frequency (Freq %) of patients in each category, median modified Rankin Score (mRS) at discharge, percentage of patients with poor outcome (mRS 4 to 6 at discharge), simple odds ratio with from univariable analysis, adjusted odds ratio from multivariable analysis, and the absolute difference in percentage of poor outcome between groups are displayed. Interquartile range (IQR) and 95% confidence intervals (95% CI) are reported. *A*, The 420 patients with ICH were grouped by arrival systolic blood pressure (arrival BP). Higher arrival BP was associated with progressively increased odds of poor outcome, even after adjusting for last seen well. *B*, The 323 patients with arrival BP >150 mm Hg were grouped by either achieving the goal BP of ≤150 mm Hg within 2 hours (time to goal BP ≤2 h) or not (time to goal BP >2 h). Achieving goal BP ≤2 hours was associated with worse outcomes, even after adjusting for ICH score, last seen well time, and arrival BP category. *C*, The 302 patients who received antihypertensive medications within the first 6 hours of ED arrival were grouped by those who overshot to a BP <120 mm Hg (Overshot Yes) and those who did not (Overshot No). Overshooting within the first 6 hours of ED arrival was associated with worse outcomes, including after adjusting for ICH score, time from last seen well, and arrival BP category. *D*, The 315 patients who received antihypertensive medications within the first 24 hours of ED arrival were grouped by those who overshot to a BP <120 mm Hg (Overshot Yes) and those who did not (Overshot No). Overshooting within the first 24 hours of ED arrival was not associated with worse outcomes. *E*, Overall, of the 323 patients with arrival BP >150 mm Hg, those that achieved goal BP within 2 hours and did not overshoot within 6 hours (≤2 h, No) had similar outcomes to those that did not achieve goal BP within 2 hours and did not overshoot (>2 h, No). However, those that achieved goal BP within 2 hours and overshot within 6 hours (≤2 h, Yes) was associated with worse outcomes.

achieved goal BP within 2 hours and did not overshoot within 6 hours. The only group with increased risk of poor outcome was those that achieved goal BP within 2 hours but overshot to within 6 hours (OR 3.34, 95% CI 1.52 to 7.32 compared to those that achieved goal without overshooting, Table 2). These findings remained consistent in adjusted models.

## LIMITATIONS

This study has several limitations. First, as a retrospective study, it cannot define causality and is subject to unmeasured confounders such as (1) differences in disease severity that were not accounted for by ICH score; (2) potential variability in individualized treatment decisions regarding BP targets; (3) premorbid functional status; (4) use of do not resuscitate or comfort measure only orders, which can powerfully affect outcome. Second, we chose one way of defining BP and BP goals—using a single BP measurement without considering subsequent readings or frequency of recorded measurements. It is possible that the frequency of recorded BP measurements could be confounding. There are also a variety of ways to define BP parameters which may lead to different findings. However, we addressed some of these with sensitivity analyses, choosing the optimal definitions is inherently challenging, and we could only rely on recorded BP measurements. Third, mRS at 90 days, which is commonly used in ICH clinical trials, was not available. Instead, we relied on the available mRS at hospital discharge, which is subject to differences in recovery depending on a patient's length of stay in the hospital. We also dichotomized "good" versus "poor" outcome as 0 to 3 versus 4 to 6, rather than some literature that uses 0 to 2 versus 3 to 6; we felt this to be appropriate because of the

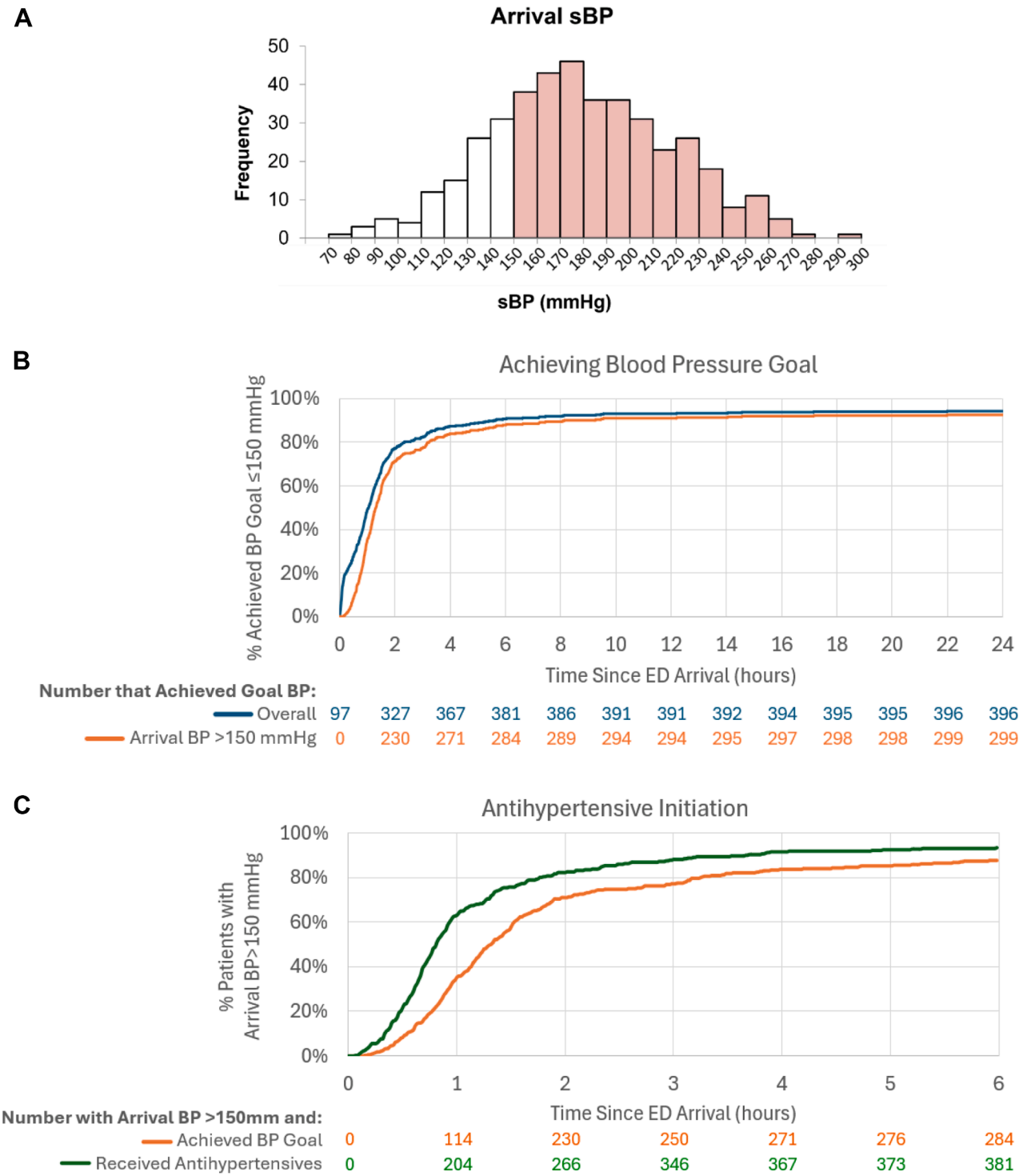


**Figure 2.** Arrival BP and timing of BP management. *A*, Histogram of arrival systolic blood pressures (SBP), with a mean of 180 (SD 38.7) mm Hg. *B*, Cumulative percentage of all patients (in blue) and those presenting with BP >150 mm Hg (in orange) who achieve goal BP ≤150 mm Hg over time since ED arrival (hours). Numbers of patients that have achieved goal BP over time since ED arrival are listed below the x-axis. *C*, Cumulative percentage of patients achieving BP goal (in orange) and received antihypertensive medication (in green) over time since ED arrival. Numbers of patients that achieved goal BP and received antihypertensives are listed.

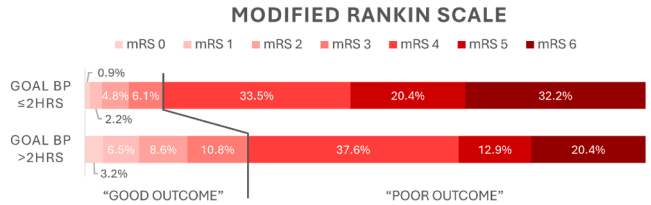


**Figure 3.** Distribution of functional outcome by time to goal BP. Discharge mRS scores among patients with arrival systolic BP>150 mm Hg, grouped by whether goal BP (≤150 mm Hg) was achieved within 2 hours ("goal BP ≤2 h") or after 2 hours ("goal BP >2 h"). Achieving goal BP within 2 hours was associated with higher risk of poor functional outcome (mRS 4 to 6).

shorter timeframe to recovery, and this better reflected the distribution of mRS in our cohort. Fourth, although we analyzed the association of overshooting and poor outcomes, it is challenging to disentangle whether it is the rapid BP lowering itself or the patient's inherent vulnerability to hemodynamic instability leading to worse outcomes. Fifth, our cohort was drawn from 2 academic medical centers, which may limit generalizability to other hospital settings with different BP management practices. Lastly, although our study relied heavily on automated methods of data extraction, some data was manually extracted; our 2 trained reviewers were not blinded to each other and were not blinded to the study hypothesis.

**Table 3.** Subgroup analyses of early blood pressure reduction and functional outcomes.

| | | % Poor Outcomes | | |
|---|---|---|---|---|
| | n | Goal BP ≤ 2 h | Goal BP >2 h (Ref) | OR (95% CI) |
| A. Arrival BP (mm Hg) | | | | |
| >150 | 323 | 86.1% | 71.0% | 2.56 (1.46-4.53) |
| >180 | 196 | 87.8% | 76.9% | 2.25 (1.09-4.83) |
| >210 | 93 | 91.1% | 81.1% | 2.30 (0.74-9.12) |
| 151-180 | 127 | 83.8% | 57.1% | 3.88 (1.53-10.01) |
| 181-210 | 103 | 85.3% | 71.4% | 2.32 (0.80-6.74) |
| B. Last seen well (h) | | | | |
| ≤24 | 323 | 86.1% | 71.0% | 2.52 (1.41-4.54) |
| ≤12 | 260 | 85.3% | 71.0% | 2.44 (1.22-4.51) |
| ≤6 | 209 | 83.7% | 71.4% | 2.17 (1.03-4.36) |
| ≤2 | 138 | 83.4% | 79.3% | 1.35 (0.49-3.74) |

Note: Number (n) of patients in each subgroup category, the percentage of patients with poor outcome (mRS 4 to 6 at discharge) in those who achieve goal BP within 2 hours (goal BP ≤2 h) vs those who did not (goal BP > h) as the reference group, and the simple odds ratio with 95% Confidence Interval (95% CI) are displayed.
*A*, Subgroup analyses based on arrival BP categories. *B*, Subgroup analyses based on time since last seen well (h).
*BP*, blood pressure.

## DISCUSSION

Our study supports prior findings that higher arrival BP is associated with worse outcomes in ICH patients.[20-22] Elevated SBP has been associated with hematoma expansion[23,24] and poor functional recovery.[25,26] Studies have shown conflicting results regarding the effect of BP control on hematoma growth[27-29] and perihematomal edema,[30-32] leaving both the potential benefits of BP reduction—and the mechanisms by which it might confer benefit—uncertain.

Surprisingly, we found that early BP control (which we defined as achieving goal BP≤150 mm Hg within 2 hours of ED arrival) was associated with worse outcomes. This paradoxical finding may be driven by early overshooting: those with early BP control were also more likely to overshoot, and those with early overshooting had higher risk of poor outcomes. Even the use of a continuously infused antihypertensive medication (typically nicardipine in our centers), which is titratable and theoretically could allow for tight BP control, did not prevent early overshooting. Moreover, those that achieved early BP control but overshot early did worse than those that did not achieve early BP control at all; those that achieved early BP control and remained in target range did not have better outcomes than those that did not achieve early BP control. These findings suggest that in our real-life data set, although a majority of patients achieved early BP control, overshooting was common and potentially detrimental.

Our results extend prior findings from the ATACH-2 and INTERACT-2 trials, which failed to show an overall benefit of intensive BP lowering to SBP <140 mm Hg compared to <180 mm Hg on functional outcome,[4,5] despite some subgroup benefits.[12,13] Our findings challenge the assumption that earlier is always better: rapid BP lowering was frequently associated with overshooting, possibly contributing to worse outcomes. In contrast to the controlled conditions of clinical trials (the mean minimum SBP during the first 2 hours of intensive treatment in ATACH-2 was 129 mm Hg and in INTERACT-2 was 141 mm Hg), 45% (74 of 164) of our patients dropped below 120 mm Hg within 2 hours. Recent data from the INTERACT-4 trial found that out-of-hospital reduction of SBP did have a functional outcome benefit compared to usual care, but the mean hospital arrival BP in the BP lowering group was 159 mm Hg versus 170 mm Hg in the usual care group, a more modest reduction in BP than seen in our cohort.[33] Furthermore, a

similar paradoxical association was found in ICH patients requiring interfacility transfer: those with longer door-in-door-out times had worse outcomes,[34] again challenging the assumption that faster intervention leads to better outcomes.

Prior studies have linked large BP reductions and wide BP variability to significant adverse events[35,36] and worse outcomes.[30,37-40] Several mechanisms have been proposed to explain how excessive BP lowering might worsen outcomes, though few have been confirmed in clinical studies. Aggressive BP lowering may cause acute ischemic kidney injury,[35,41,42] though reducing SBP to 140 mm Hg has generally been safe.[5,43,44] In the brain, lowering BP to 140 versus 180 mm Hg does not appear to significantly alter perihematomal perfusion or global hypoperfusion.[45-49] However, ischemic lesions—present in 15% to 35% of ICH patients[50,51]—are associated with worse outcomes,[45,52,53] raising concerns that rapid and excessive BP reduction could exacerbate ischemic injury. Some studies have found larger BP decreases or greater BP variability to be associated with more ischemic lesions,[50-53] whereas others found no clear link between the magnitude of BP lowering and ischemia risk.[54,55] Notably, allowing SBP to fall below 120 mm Hg was associated with increased ischemic lesions and worse neurologic outcomes.[50] Furthermore, although blood–brain barrier damage and perihematomal edema develop after ICH,[56] BP lowering has not been shown to significantly influence these processes.[44,57,58] Thus, the precise effect of acute BP lowering on secondary brain injury mechanisms such as ischemia, blood–brain barrier integrity, and edema remains uncertain.

Overall, our findings highlight the need for a more nuanced approach to BP management in ICH. Although current AHA/ASA guidelines emphasize achieving SBP 130 to 150 mm Hg rapidly in mild-to-moderate severity ICH of recent onset, our results emphasize the importance of having a floor to the BP goal. The INTERACT-3 trial was a pragmatic trial implementing bundled care for patients within 6 hours of ICH onset, including a goal of achieving BP <140 mm Hg within 1 hour of initiating treatment, with a SBP of 130 mm Hg being the threshold for the cessation of treatment; bundled care with an SBP goal of 130-140 mm Hg resulted in better functional outcome than the usual care group.[14] Taken altogether, a target range that avoids both high BP and excessive reductions may optimize outcomes in real-world settings. Only providing intensive BP lowering on patients with recent ICH onset may also optimize outcomes. Future research should explore individualized BP targets based on patient characteristics, such as baseline BP, hemorrhage onset, underlying vasculopathy, and hemorrhage size.

In conclusion, in this retrospective cohort study of ICH patients, early intensive BP lowering was associated with worse functional outcome, possibly due to overshooting below target BP range. Our results suggest that BP management, if not well executed in the clinical setting, can lead to excessive and abrupt BP reductions, associated with worse outcomes. Future studies should refine BP targets and timing to balance the risks of hematoma expansion with those of hypoperfusion-related injury, potentially with more individualized BP targets. Prospective, pragmatic trials of how BP goals are implemented and achieved would be insightful for future guidelines in the acute management of ICH. Any approach to BP management should emphasize targets with not just an upper, but also a lower, boundary.

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