

Early Blood Pressure Reduction for Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective

Elevated systolic blood pressure in acute intracerebral hemorrhage (ICH) promotes hematoma expansion and poor neurological outcomes. Randomized trials of early blood pressure lowering (EBPL) initiated within six hours of symptom onset have yielded inconsistent results. We evaluated the efficacy and safety of EBPL in acute ICH.

Methods

We systematically searched major databases and ClinicalTrials.gov for randomized controlled trials comparing EBPL with guideline-based management or placebo in acute ICH. The primary outcome was 90-day ordinal modified Rankin Scale (mRS) shift. Secondary outcomes included good functional outcome (mRS 0–2), poor functional outcome (mRS > 2), 90-day mortality, hematoma expansion, neurological deterioration, and serious adverse events (SAEs). Prespecified subgroup analyses were performed according to treatment timing, setting, and intervention strategy.

Results

Eight randomized controlled trials comprising 12,582 patients were included. EBPL did not significantly improve 90-day ordinal mRS shift (OR 0.90, 95% CI 0.66–1.24). EBPL was associated with improved good functional outcome (RR 1.08, 95% CI 1.04–1.13), with no significant differences in other secondary outcomes. Subgroup analyses showed point estimates favoring in-hospital initiation and titrated intravenous regimens, but tests for subgroup interaction were not statistically significant.

Conclusions

EBPL initiated within six hours did not improve overall functional outcome but was associated with improved functional independence without increased adverse events. Apparent benefits of in-hospital initiation and titrated intravenous regimens were not statistically confirmed by interaction testing and should be considered hypothesis-generating.

PROSPERO registration: CRD42024563521.

1. INTRODUCTION

Elevated blood pressure (BP) is observed in up to 75% of patients with acute intracerebral hemorrhage (ICH)¹. Initially considered a protective response to preserve cerebral perfusion after rising intracranial pressure, early arterial hypertension is now recognized as a contributor to hematoma expansion, poor functional outcome and mortality². Hematoma expansion is most pertinent in the first 3–6 hours³, hence attenuation within this period remains the most plausible mechanism for BP lowering to produce improved outcomes in acute ICH^{4–5}. This pathophysiological rationale underpins the use of early blood pressure lowering (EBPL; ≤6 h from symptom onset); however, until recently trials have been unable to demonstrate clear functional benefits, leading to controversy over target, timing, intensity and agents used.

Current guidelines advocate for the prompt reduction of systolic blood pressure to a target of 140 mmHg in cases of acute ICH, with an acceptable range of 130–150 mmHg⁶. These recommendations are primarily informed by two pivotal trials, the INTERACT-2 and ATACH-2 studies, which assessed the effects of intensive blood pressure reduction within six hours of onset^{7–8}. INTERACT-2 indicated modest improvements in functional outcomes with minimal adverse effects⁷, whereas ATACH-2 did not demonstrate significant benefits and noted an increased risk of renal adverse events⁸. Recently, the INTERACT-4 trial revealed that prehospital administration of intravenous urapidil was associated with improved functional outcomes in ICH patients⁹. Conversely, trials utilizing fixed-dose glyceryl trinitrate (GTN) for ultra-early stroke treatment have paradoxically shown worse outcomes in ICH, perhaps due to residual blood pressure variability, delay in reaching target blood pressure, or other off-target effects^{10–12}. Previous meta-analyses have generally supported the safety of blood pressure reduction in acute ICH, although they frequently included interventions initiated beyond the hyperacute phase^{13–15}. This delay in treatment initiation may have diminished the potential benefits of EBPL by incorporating a larger cohort of patients with a lower risk of hematoma expansion. A consistent observation is that earlier or more intensive interventions, particularly within six hours, may mitigate early hematoma growth, although the effect on long-term functional outcomes remains uncertain^{13–15}.

To summarise the evidence, we conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of EBPL in patients with acute ICH. We further stratified outcomes by timing (< 2 hours vs 2–6 hours), setting (Pre-hospital vs In-hospital) and intervention type (fixed-dose GTN vs target-based titrated intravenous antihypertensives) to address the variability in functional outcomes across trials.

2. METHODS

This systematic review was registered in the PROSPERO database (CRD42024563521), conducted according to the Cochrane Handbook for Systematic Reviews and Interventions¹⁶, and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

2.1 Search Strategy

MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov, and Google Scholar were screened for RCTs assessing EBPL (either titrated to an intensive BP target or using fixed-dose antihypertensive therapy) in acute ICH (≤ 6 h from symptom onset) published in English from database inception to February 20, 2026. The reference lists of all included studies were screened. The search strategy, provided in Supplemental Table 1, used the following keywords: “stroke,” “cerebrovascular accident,” “blood pressure reduction,” “high blood pressure,” “early,” “pre-hospital,” “ambulance,” and “randomized trial.” The detailed search strategy is given in **Supplementary Table 1**.

2.2 Study Eligibility

Eligible RCTs (1) enrolled adult patients (≥ 18 years) with acute spontaneous ICH; (2) compared early BP lowering (either titrated to an intensive BP target or using fixed-dose antihypertensive therapy ≤ 6 h from symptom onset) with control (contemporaneous guideline-based BP target or placebo); and (3) recorded any of the outcomes. Studies with subpopulations that fulfilled this criterion were included. For trials enrolling undifferentiated stroke cohorts, we included them provided that separate baseline and outcome data for the confirmed ICH subgroup were available. The exclusion criteria were RCTs without a control arm, sample sizes < 20 , RCTs published as conference abstracts, and studies in which randomization was performed > 6 h after stroke onset.

2.3 Data Extraction and Quality Assessment

Two authors (G.R. and A.R.) independently screened titles and abstracts. Full texts were assessed for eligibility using the aforementioned criteria. Conflicts were resolved through discussions arbitrated by an independent third party (Y.S., L.P.). Data were collected from the included studies using a standard data-collection form. The collected data included study characteristics (author, year conducted, number of centers involved), patient characteristics (age, sex, comorbidities, severity scores, SBP at stroke onset), intervention details (antihypertensive use, dose, timing), control arm description, and clinical endpoints (mRS score at 90 days, death at 90 days, combined death or disability at 90 days, absolute hematoma expansion at 24 h, and SAEs as defined by the trial protocol). Two authors (G.R. and Y.S.) independently assessed the methodological quality of the trials using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions¹⁶ and the Cochrane Risk of Bias-2 (v2.0) tool¹⁸.

The certainty of evidence for each outcome was independently assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence was evaluated across the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias, and categorized as high, moderate, low, or very low certainty. A Summary of Findings table was generated using GRADEpro GDT.

2.4 Outcomes

The primary outcome was functional neurological outcome, evaluated as the distribution of scores across all categories (ordinal “shift” analysis) of the 90-day modified Rankin Scale (mRS). Pre-specified secondary outcomes were: combined death or disability (mRS > 2) at 90 days; good functional outcome (mRS 0–2) at 90 days; all-cause mortality at 90 days; radiographically defined hematoma expansion, according to the definition used in each individual trial; and serious adverse events (SAEs). Short-term mortality at 7 days and neurological deterioration were additionally evaluated as exploratory outcomes. The definition of hematoma expansion and SAEs across studies are detailed in **Supplementary Table 2**.

2.5 Statistical Analysis

Risk Ratios (RRs) with 95% confidence intervals (CIs) were calculated for binary outcomes, whereas Odds Ratios (ORs) were used for the ordinal primary outcome (90-day modified Rankin Scale [mRS] shift analysis), consistent with the reporting of the original trials. Heterogeneity was assessed using the I^2 statistic, with statistical heterogeneity defined by a Cochran Q test p-value < 0.10 . I^2 values of 0–40% were considered to represent low heterogeneity, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity, and 75–100% considerable heterogeneity, interpreted in the context of clinical and methodological diversity across studies. Random-effects meta-analyses were performed throughout. For binary outcomes, pooled RRs were calculated using the Mantel–Haenszel method with Restricted Maximum Likelihood (REML) estimation of between-study variance (τ^2).

Prespecified subgroup analyses were conducted according to: (1) intervention strategy (titrated intravenous antihypertensive regimens versus fixed-dose GTN regimens); (2) treatment setting (prehospital vs in-hospital initiation); (3) timing of treatment initiation (ultra-early < 2 hours versus early ≥ 2 hours). For prehospital trials enrolling undifferentiated stroke populations, only patients with confirmed ICH following neuroimaging were included. Subgroup differences were assessed using Cochran's Q test for interaction.

Leave-one-out sensitivity analyses were performed for all primary endpoints by sequentially excluding individual studies and recalculating pooled estimates. Baujat plots were constructed to identify studies contributing disproportionately to heterogeneity and overall effect size. Exploratory random-effects meta-regression analyses were performed using study-level covariates including baseline systolic blood pressure (SBP), achieved SBP, magnitude of SBP reduction, and time to treatment initiation. All statistical analyses were conducted using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

The database search yielded 1,398 unique articles, of which eight RCTs^{7–11,19–21} evaluating EBPL in patients with acute ICH were included (Fig. 1). All were multicenter trials conducted between 2008 and 2024. Six trials were open-label; however, all included trials employed blinded outcome assessments. Where trials recruited a mixed/undifferentiated acute stroke population^{9–12}, we included only the baseline characteristics and outcomes of patients with ICH. Broadly, the analyzed cohort (N = 12,582) comprised predominantly of males (~ 64%) in the seventh decade of life (mean 63.2 years) with mild-to-moderate severity ICH (mean GCS 13) and small-to-moderate hematoma volumes (mean 17 ml, SD 25.8 ml). The baseline characteristics of the included cohort stratified by study are summarized in Table 1. The trial protocols and extended patient characteristics are summarized in **Supplementary Tables 2 and 3**.

Table 1
Baseline characteristics of the included studies. C control; GCS Glasgow Coma Scale; I intervention; NIHSS National Institutes of Health Stroke Scale. Values are mean (SD) or median [IQR]. NA not available.

Study	Setting	Sample size, N (I/C)	Age, y (mean)		Female sex (%)		Median time from onset to randomization, mins		Baseline NIHSS Score		Baseline hematoma volume, mL		GCS score	
			I	C	I	C	I	C	I	C	I	C	I	C
INTERACT-4 2024*(9)	Pre-hospital [§]	1041 (522/519)	70 (12)	70 (13)	40.3	36.3	63 [41–93]	59 [41–93]	12 [6–18]	11 [6–17]	38.4 (33.4)	32.3 (34.9)	13 (10–15)	13 (10–15)
MR-ASAP 2022*(11)	Pre-hospital [§]	56 (35/21)	72 (13)	72 (13)	42	53	71 [39–114]	53 [33–94]	6 [3–13]	6 [2–11]	14.3 [5.2–36.4]	9.3 [7.0–32.1]	10	10
RIGHT-2 2019 (12)	Pre-hospital [§]	145 (74/71)	73.5 (12)	72.7 (14)	47	41	70 [45–121]	75 [45–101]	16.5 (7.0)	14.3 (7.4)	38.4 (33.4)	32.3 (34.9)	13.7	13.6
INTERACT-3 2023 (19)	In-hospital	7036 (3221/3815)	61.8 (12.6)	62.1 (12.6)	35.6	36.4	NA	NA	13 [7–23]	13 [6–22]	15 [7–30]	15 [8–30]	12 (9–14)	12 (9–14)
ATACH-2 2016 (8)	In-hospital	1000 (500/500)	62 (13.1)	61.9 (13.1)	29.2	36.8	182.2 (57.2)	184.7 (56.7)	11 [0–40]	11 [0–40]	10.3 (2.3–85.2)	10.2 (0.98–79.1)	13.2	13.3
INTERACT-2 2013 (7)	In-hospital	2839 (1399/1430)	63 (13.1)	64.1 (12.6)	35.8	39.3	222 [168–288]	222 [174–282]	10 [6–15]	11 [6–16]	11 [6–19]	11 [6–20]	14 [12–15]	14 [12–15]
INTERACT-1 2008 (20)	In-hospital	404 (203/201)	63 (12)	62 (13)	31	39	NA	NA	9 [5–14]	9 [5–16]	14.2 (14.5)	12.7 (11.6)	14 (12–15)	14 (13–15)
ENOS-ICH 2013 (21)	In-hospital [§]	61 (29/32)	68.3 (11.4)	70.8 (13.5)	44.8	31.2	270 (66)	264 (78)	12.7 (4.9)	12.8 (4.7)	13.0 (14.4)	20.8 (40.7)	12.7 (4.9)	12.8 (4.7)
*Data from the overall population (overall data for ICH only subgroup was not available)														
[§] BP lowering initiated prior to hospital admission, data collected from confirmed spontaneous ICH patients post admission.														

3.1 Primary outcome: Functional outcome (90-day mRS shift)

Compared with control, EBPL initiated within six hours of symptom onset did not significantly improve the overall distribution of 90-day mRS scores on ordinal shift analysis (OR 0.90; 95% CI 0.66–1.24; I²=66.7%; Fig. 2).

3.2 Secondary outcomes

Compared with control, EBPL was not associated with a statistically significant reduction in poor functional outcome (mRS > 2) at 90 days (RR 0.95; 95% CI 0.90–1.00; I²=58.9%; **Supplementary Figure S1**). In contrast, EBPL was associated with a significantly greater likelihood of achieving good functional outcome (mRS 0–2) (RR 1.08; 95% CI 1.04–1.13; I²=57.9%; Fig. 3).

EBPL was not associated with a statistically significant reduction in 90-day mortality (RR 0.89; 95% CI 0.77–1.03; I²=53.3%; **Supplementary Figure S2**) and 7-day mortality compared to control, although estimates were imprecise due to limited sample size (**Supplementary Figure S3**).

EBPL was not associated with statistically significant differences for hematoma expansion (RR 0.81; 95% CI 0.66–1.01; I²=52.3%; **Supplementary Figure S4**), risk of neurological deterioration (RR 1.05; 95% CI 0.87–1.27; I²=20.5%; **Supplementary Figure S5**) and risk of serious adverse events

(RR 0.98; 95% CI 0.83–1.16; $I^2=78.1\%$; **Supplementary Figure S6**) compared to control.

3.3 Subgroup Analysis

We performed subgroup analyses according to timing from symptom onset, treatment setting, and intervention strategy.

When stratified by timing from symptom onset to initiation of BP lowering, there was no evidence that ultra-early initiation (< 2 hours) modified treatment effect compared with early initiation (≥ 2 hours). Across all outcomes, subgroup interaction tests were non-significant, and effect estimates were directionally similar between groups (**Supplementary Figures S7-S13**).

When stratified by treatment setting (in-hospital versus prehospital initiation), no statistically significant interaction between subgroups was observed for any outcome. EBPL initiated in the in-hospital setting was associated with a significant improvement in good functional outcome (RR 1.07, 95% CI 1.03–1.12), whereas no benefit was observed in prehospital trials (RR 1.10, 95% CI 0.74–1.64). Similarly, a reduction in poor functional outcome was observed only among in-hospital studies (RR 0.94, 95% CI 0.91–0.98), while prehospital studies demonstrated no significant effect (RR 0.97, 95% CI 0.79–1.19). In-hospital trials also showed lower 90-day mortality (RR 0.87, 95% CI 0.76–1.00) compared with no significant reduction in prehospital studies (RR 0.98, 95% CI 0.65–1.46). No significant differences between settings were observed for neurological deterioration, serious adverse events, hematoma expansion, ordinal 90-day mRS shift, or all-cause mortality at 90 days, with all subgroup interaction tests remaining non-significant (**Supplementary Figures S14-S20**).

When stratified by intervention type (fixed-dose GTN vs titrated intravenous antihypertensives), no statistically significant interaction between subgroups was observed for any outcome. Within trials evaluating titrated intravenous antihypertensive regimens, pooled estimates favored EBPL, with statistically significant reductions in poor functional outcome (RR 0.93; 95% CI 0.90–0.96; $I^2=6.6\%$), improvement in good functional outcome (RR 1.08; 95% CI 1.04–1.13; $I^2=57.4\%$), reduction in 90-day mortality (RR 0.85; 95% CI 0.77–0.95; $I^2=0\%$), and reduction in hematoma expansion (RR 0.78; 95% CI 0.62–0.97; $I^2=54.4\%$), compared to control. In contrast, fixed-dose GTN trials demonstrated greater heterogeneity, and no significant change compared to control (**Supplementary Figures S21-S27**).

3.4 Meta-Regression

To investigate potential sources of heterogeneity, univariate random-effects meta-regressions were performed for baseline SBP, mean achieved SBP, SBP reduction magnitude, and time to treatment. No statistically significant linear relationships were identified between the evaluated study-level covariates and treatment effect across any efficacy or safety outcome.

3.5 Heterogeneity and Risk of Bias

Baujat plots and leave-one-out analyses were constructed to explore sources of heterogeneity (**Supplementary Figures S35-S41**). In leave-one-out analyses, exclusion of the RIGHT-2 trial reduced heterogeneity for the primary outcome ($I^2=26.3\%$) and shifted the pooled estimate toward statistical significance (OR 0.85; 95% CI 0.77–0.93) while substantially reducing heterogeneity ($I^2=26.3\%$). Exclusion of other individual trials did not materially alter effect estimates across outcomes.

Visual inspection of funnel plots (**Supplementary Figures S42-S48**) did not demonstrate clear evidence of publication bias, although interpretation is limited by the small number of studies per outcome. The risk of bias in the included RCTs is shown in Fig. 4. All eight trials were judged to be at high risk of bias for deviations from intended interventions (Domain 2), primarily reflecting the open-label design of six included trials despite blinded outcome assessment. All remaining domains were judged to be at low risk of bias.

3.6 Certainty of Evidence (GRADE)

The certainty of evidence, assessed using the GRADE framework, ranged from low to very low across outcomes (**Supplemental Table 5**). Evidence was rated as low for good functional outcome (mRS 0–2), poor functional outcome (mRS > 2), and neurological deterioration, and very low for 90-day mRS shift, mortality, hematoma expansion, and serious adverse events. Downgrading was primarily due to risk of bias from predominantly open-label trial designs, inconsistency across studies, and imprecision of several pooled estimates.

4. DISCUSSION

In this systematic review of eight randomized controlled trials comprising 12,582 patients with acute intracerebral hemorrhage, predominantly of mild-to-moderate severity, early blood pressure lowering (EBPL) initiated within six hours of symptom onset did not significantly improve overall functional outcome at 90 days. Likewise, no significant reductions were observed in 90-day mortality, neurological deterioration, hematoma expansion, or serious adverse events. However, EBPL was associated with improved functional independence (mRS 0–2). Exploratory subgroup analyses demonstrated consistent patterns of benefit among trials evaluating in-hospital initiation and titrated intravenous antihypertensive regimens, although formal subgroup interaction tests were not statistically significant. Collectively, these findings suggest that the strategy used to achieve blood pressure reduction, rather than treatment timing alone within the established therapeutic window, may represent an important determinant of treatment effect and warrants further investigation.

Previous meta-analyses evaluating blood pressure lowering in acute ICH have consistently demonstrated its safety but have yielded mixed conclusions regarding functional efficacy.^{13–15} Earlier syntheses generally reported no definitive improvement in overall functional outcomes despite trends toward reduced hematoma expansion.^{13,14} More recently, an individual participant data meta-analysis demonstrated that achieving and sustaining target systolic blood pressure was associated with improved functional recovery, emphasizing the importance of effective blood pressure control rather than simply treatment allocation.¹⁵ However, many previous meta-analyses combined studies initiating treatment across broad and heterogeneous therapeutic windows (up to 48 hours from symptom onset), potentially diluting any benefit achievable during the period of greatest risk for hematoma expansion. By restricting inclusion to interventions initiated within six hours of symptom onset, the present analysis provides a more clinically focused assessment of hyperacute blood pressure management. Furthermore, incorporation of recent trials, including INTERACT-4 and MR-ASAP, expands the evidence base into contemporary prehospital and ultra-early treatment strategies, allowing comparison of not only treatment timing but also differing approaches to blood pressure reduction.^{9,11} A recently published aggregate meta-analysis by Reginato et al. similarly evaluated intensive blood pressure lowering across eleven randomized trials and, consistent with our findings, reported no significant subgroup interaction according to randomization window (< 6 h versus ≥ 6 h).²² However, that analysis defined eligibility according to an achieved blood pressure target rather than restricting enrollment a priori to the hyperacute window, and did not include trials of fixed-dose transdermal glyceryl trinitrate (RIGHT-2, MR-ASAP) or stratify pooled estimates by intervention strategy. By restricting inclusion to trials initiating treatment within six hours and directly comparing titrated intravenous regimens against fixed-dose approaches, the present analysis extends this evidence base and identifies intervention strategy, rather than treatment window per se, as the more consistent correlate of benefit.

Although the primary outcome remained neutral, dichotomized analysis demonstrated a significantly greater likelihood of achieving functional independence (mRS 0–2). These analyses evaluate different aspects of neurological recovery. Ordinal analyses measure shifts across the entire disability spectrum, whereas dichotomized analyses emphasize transitions across clinically meaningful functional thresholds. The discrepancy observed in our analysis may therefore suggest that EBPL preferentially benefits patients close to the threshold of functional independence rather than producing uniform improvements across all degrees of disability. Similar differences between ordinal and dichotomized analyses have been observed in previous acute stroke trials and should not necessarily be interpreted as conflicting findings.²³

One of the more informative observations of the present analysis was that treatment timing itself did not appear to explain differences in treatment effect. Across prespecified subgroup analyses, initiation of blood pressure lowering within two hours was not associated with greater benefit than treatment initiated later within the six-hour therapeutic window. Although these analyses were limited by the relatively small number of available studies and should be interpreted cautiously, the absence of a significant temporal interaction suggests that reducing treatment delay alone may be insufficient to improve outcomes once patients remain within the accepted hyperacute treatment window. This finding is corroborated by an individual patient data pooled analysis of the four INTERACT trials, which likewise found no significant interaction between blood pressure-lowering treatment and time from symptom onset to randomization, despite point estimates suggesting the greatest reduction in hematoma growth and the largest improvement in functional recovery when treatment was initiated within three hours.²⁴ Taken together, these convergent null interaction tests, derived from independent aggregate- and individual patient-level analyses, suggest that once treatment occurs within the broadly accepted hyperacute window, incremental gains from earlier initiation alone may be modest, and that other factors, such as the adequacy and consistency of blood pressure control, warrant greater attention.

In contrast, a more consistent pattern emerged when studies were stratified according to treatment strategy. Trials evaluating titrated intravenous antihypertensive regimens demonstrated favorable effects across multiple clinically relevant outcomes, including functional independence, mortality, and hematoma expansion, whereas studies utilizing fixed-dose transdermal glyceryl trinitrate demonstrated no consistent benefit. Although formal subgroup interaction tests were not statistically significant and these analyses remain exploratory, the consistency of this pattern across several clinically relevant outcomes suggests that treatment strategy may represent an important source of clinical heterogeneity. This distinction is further reinforced by comparison with the INTERACT-restricted individual patient data analysis discussed above, which, by design, evaluated only trials employing titrated intravenous regimens and could not itself test whether alternative strategies, such as fixed-dose transdermal glyceryl trinitrate, achieve comparable benefit.²⁴ The present analysis, spanning multiple trial families and both intervention strategies, provides direct comparative evidence that titrated intravenous regimens, rather than early blood pressure lowering per se, may be principally responsible for the observed benefit.

The distinction between these approaches extends beyond the antihypertensive agent itself. Titrated intravenous regimens are specifically designed to achieve predefined systolic blood pressure targets rapidly while allowing continuous dose adjustment according to the patient's physiological response. In contrast, fixed-dose transdermal glyceryl trinitrate provides comparatively limited opportunity for individualized blood pressure control once administered. Consequently, these approaches differ not only pharmacologically but also in their ability to achieve, maintain, and stabilize target blood pressure throughout the period during which hematoma expansion is most likely to occur. Previous studies have demonstrated that sustained achievement of target systolic blood pressure and reduced blood pressure variability are independently associated with improved outcomes after acute ICH, providing a biologically plausible explanation for the consistent direction of effect observed among trials utilizing protocolized intravenous blood pressure management.^{25,26}

A parallel observation emerged when trials were stratified by treatment setting: significant benefit was confined to trials initiating blood pressure lowering after hospital arrival, whereas prehospital initiation showed no significant effect on any outcome. This pattern is consistent with a recent meta-analysis restricted specifically to prehospital blood pressure lowering in hemorrhagic stroke, which similarly found no significant improvement in functional outcome or survival with prehospital treatment and called for future trials evaluating protocolized, titratable regimens in this setting.²⁷ Ambulance-based protocols to date have relied predominantly on fixed-dose agents administered under logistical constraints that limit titration and monitoring, which may explain why setting and intervention strategy appear closely intertwined in the present analysis. Disentangling these two dimensions will likely require trials that test titrated intravenous regimens specifically within the prehospital environment.

Collectively, these findings raise the possibility that, within the first six hours after symptom onset, the quality of blood pressure control may be at least as important as the precise timing of treatment initiation. While earlier intervention remains biologically rational and should continue to be pursued, our findings suggest that future investigations should focus not only on how rapidly blood pressure is lowered, but also on how effectively target blood pressure is achieved and maintained. This interpretation remains hypothesis-generating but provides a potential framework for understanding the divergent findings observed across contemporary randomized trials.

Our findings are also consistent with the established pathophysiological rationale for early blood pressure reduction in acute ICH. Hematoma expansion, occurring in approximately 30–40% of patients during the first hours after symptom onset, is a major determinant of neurological deterioration and long-term disability.^{24,26,28} Elevated systolic blood pressure increases hydrostatic stress at the site of vascular rupture and is believed to promote continued bleeding, making prompt blood pressure control an attractive therapeutic target.^{24,26} Although the overall analysis demonstrated only a non-significant trend toward reduced hematoma expansion, the titrated intravenous subgroup demonstrated a significant reduction, providing a biologically plausible mechanism for the observed improvements in functional independence and favorable trends in mortality. Equally important, EBPL was not associated with increased serious adverse events or neurological deterioration, addressing longstanding concerns regarding cerebral hypoperfusion resulting from aggressive blood pressure reduction.²⁸ In the predominantly mild-to-moderate ICH populations included in these trials, preservation of perihematomal autoregulation may permit moderate systolic blood pressure reduction without compromising regional cerebral perfusion.²⁹

Recent ESO/EANS guidelines recommend rapid reduction of systolic blood pressure to below 140 mmHg as early as possible in eligible patients with acute intracerebral hemorrhage.³⁰ Our findings broadly support these recommendations by demonstrating that early blood pressure lowering is safe and may improve functional independence without increasing serious adverse events. Although the subgroup findings remain exploratory, they also suggest that future optimization of blood pressure management may depend less on further reducing treatment delay within the established therapeutic window and more on improving the consistency with which target blood pressure is achieved and maintained.

Several limitations warrant consideration. Heterogeneity across trials in antihypertensive agents, blood pressure targets, treatment protocols, and patient populations remained substantial for several outcomes, limiting the interpretability of pooled estimates. Although subgroup analyses were prespecified, the relatively small number of prehospital and fixed-dose glyceryl trinitrate studies limited statistical power to detect true subgroup interactions, and these findings should therefore be regarded as exploratory. Consistent with the GRADE assessment, the overall certainty of evidence ranged from low to very low, primarily reflecting risk of bias, between-study inconsistency, and imprecision. Furthermore, all included trials were judged to be at high risk of bias for deviations from intended interventions because six of the eight studies employed open-label treatment designs. Open-label administration of antihypertensive therapy inherently permits differences in co-interventions and clinical management that cannot be completely controlled, thereby lowering confidence in pooled treatment estimates. Most included studies also enrolled patients with predominantly mild-to-moderate ICH, limiting generalizability to patients with large hematomas, severe neurological injury, or markedly elevated intracranial pressure. Several trials were modest in size or terminated early, increasing the possibility of type II error. Finally, the absence of individual patient-level data precluded adjustment for important prognostic variables and more detailed exploration of treatment-effect modifiers, while assessment of publication bias remained limited by the relatively small number of studies available for each outcome.

5. CONCLUSION

In this meta-analysis of eight randomized controlled trials comprising over 12,500 patients with acute intracerebral hemorrhage, early blood pressure lowering initiated within six hours of symptom onset did not significantly improve overall functional outcome at 90 days. EBPL was associated with improved good functional outcome (mRS 0–2) without increasing serious adverse events. Although subgroup interaction tests were not significant, exploratory analyses demonstrated consistent patterns of benefit among trials evaluating in-hospital initiation and titrated intravenous antihypertensive regimens. These findings support current guideline recommendations for early blood pressure reduction in acute ICH and highlight the need for future trials to determine whether achieving and maintaining target blood pressure influences clinical outcomes more than treatment initiation alone.

Abbreviations

BP Blood Pressure

ICH	Intracerebral Hemorrhage
MAP	Mean Arterial Pressure
SBP	Systolic Blood Pressure
EBPL	Early Blood Pressure Lowering
RCT	Randomized Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CENTRAL	Cochrane Central Register of Controlled Trials
mRS	Modified Rankin Scale
SAEs	Serious Adverse Events
OR	Odds Ratio
CI	Confidence Interval

Declarations

Compliance with instructions to authors

The authors confirm that this manuscript complies with the Journal's Instructions for Authors.

Author contributions

Conception and design: Gokul Rajith, Lavienraj Premraj. Literature search and screening: Gokul Rajith, Aisha Rizwan Ahmed. Data extraction: Giovanni Noll, Vanisha Kumar. Risk of bias and quality assessment: Gokul Rajith, Yasmin Picanto Silva. Statistical analysis: Vanisha Kumar, Gabriel Erzinger. GRADE assessment: Ananya Vig. Drafting the manuscript: Gokul Rajith, Vanisha Kumar. Graphical abstract: Muhammad Khan. Critical revision of the manuscript for important intellectual content: Masaraf Hussain, Christopher Camarda, Ben Seymour, Gentle S. Shrestha, Romero-García Nekane, Denise Battaglini, Chiara Robba, Sung-Min Cho, Rafael Badenes, Andrew Udy. Supervision: Lavienraj Premraj. All authors reviewed and approved the final manuscript.

Authorship

All authors meet the ICMJE criteria for authorship, and the final manuscript has been approved by all authors.

Ethics approval

Ethical approval and informed consent were not required for this study, as it is a systematic review and meta-analysis of previously published aggregate data and did not involve new data collection from human participants.

Consent for publication

Not applicable.

Protocol registration

This systematic review was prospectively registered in PROSPERO (registration number CRD42024563521).

Reporting checklist

This systematic review and meta-analysis adheres to the PRISMA 2020 reporting guideline. The completed PRISMA 2020 checklist is provided in Supplemental Table 4.

Use of Artificial Intelligence Statement

Artificial intelligence (Claude Opus 5) was used to for editorial work (assisting proof-reading and revision of human-generated text) in the manuscript. No artificial intelligence tool was used for other tasks related to the preparation of this manuscript. We guarantee that there is no plagiarism in their paper, including in text and images produced by artificial intelligence tools.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

All data analyzed in this systematic review were extracted from previously published studies. The extracted dataset and analytic code are available from the corresponding author upon reasonable request.

Prior publication

This manuscript is original, has not been published elsewhere, and is not currently under consideration for publication elsewhere.

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Figures

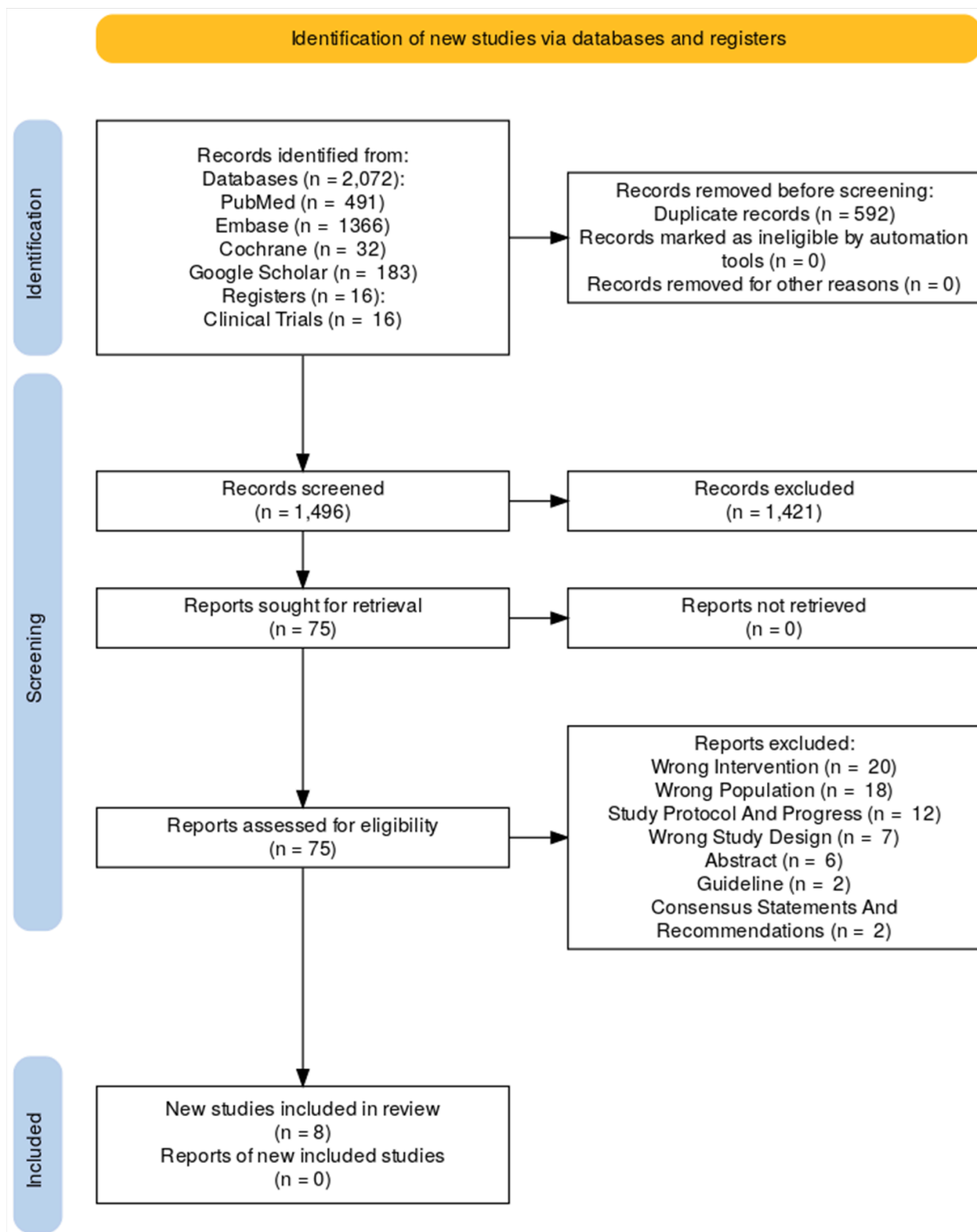


Figure 1

PRISMA flow diagram of study screening and selection.

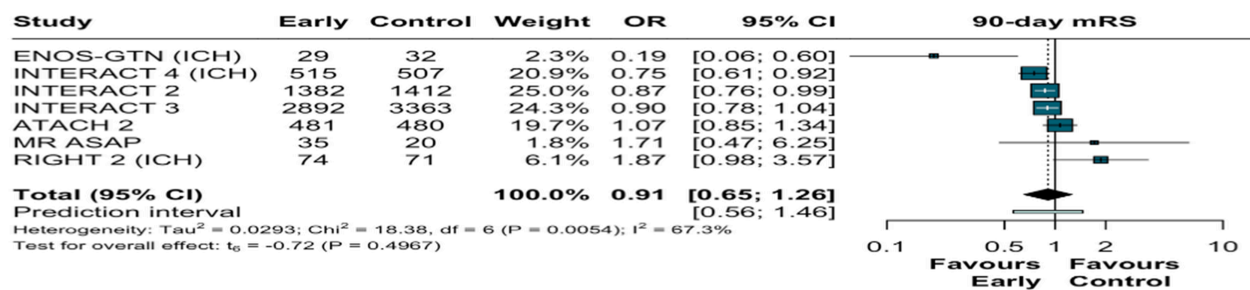


Figure 2

Forest plot showing the effect of early blood pressure lowering (EBPL) versus control on 90-day functional outcome assessed by ordinal modified Rankin Scale (mRS) shift analysis. EBPL was not associated with significant improvement in the overall distribution of mRS scores. CI confidence interval; OR odds ratio.

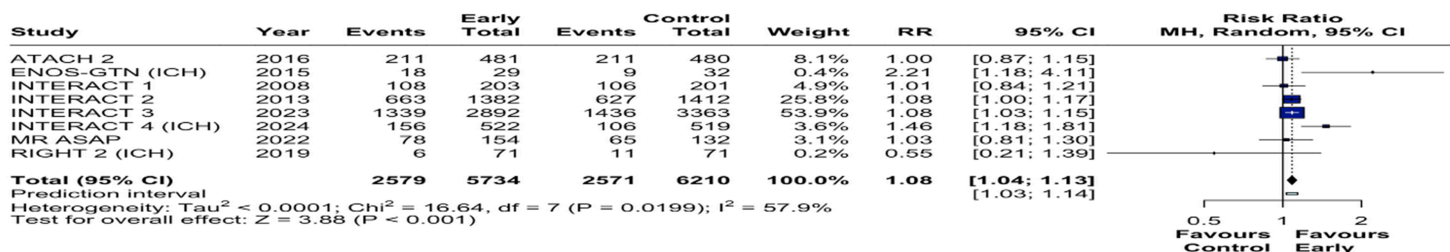


Figure 3

Forest plot showing the effect of early blood pressure lowering (EBPL) versus control on good functional outcome (mRS 0-2) at 90 ddays. EBPL was associated with significant improvement in good functional outcome compared to control. CI confidence interval; RR risk ratio.

Figure 4A.

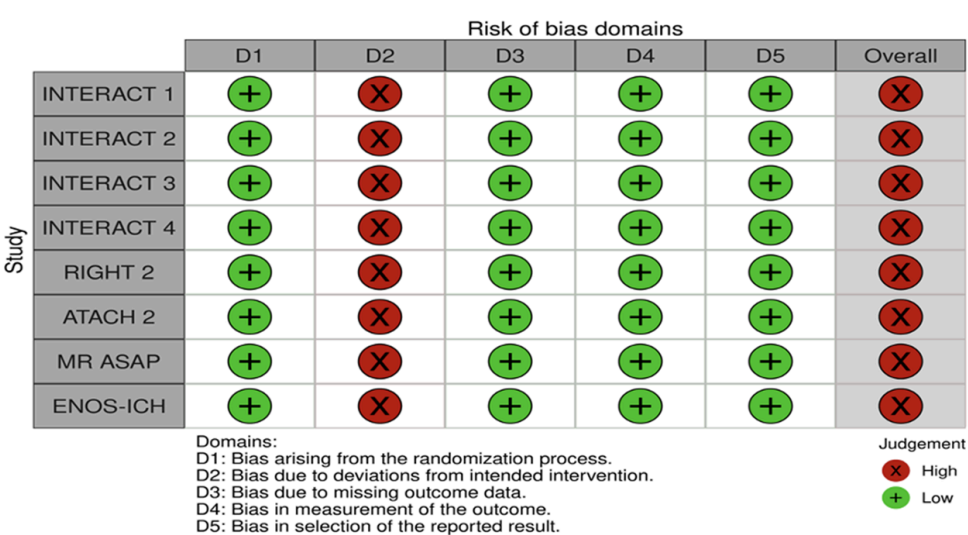


Figure 4B.

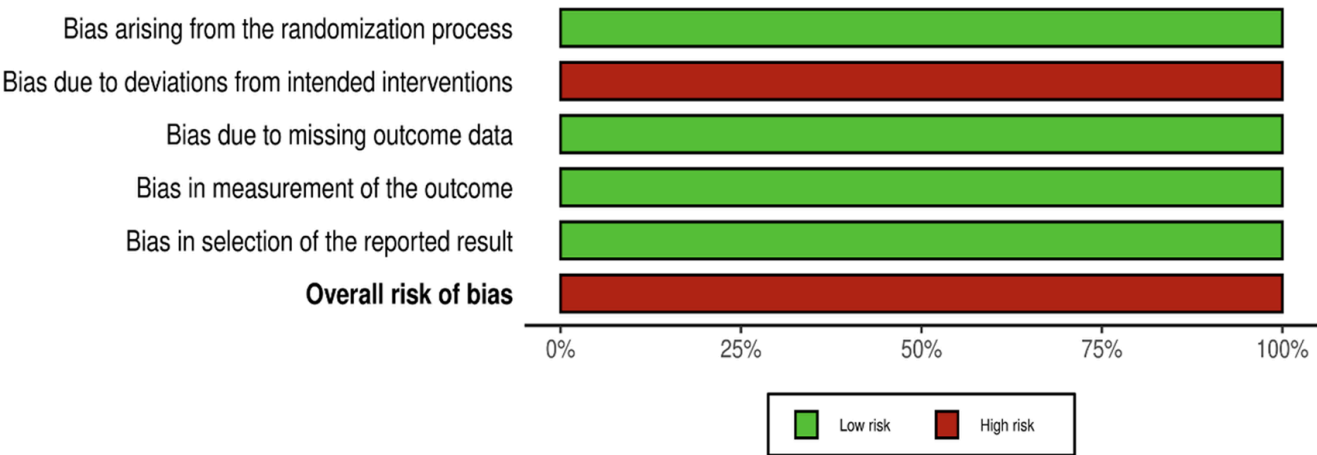


Figure 4

Risk of bias assessment using the Cochrane Risk of Bias 2 (RoB-2) tool.

(A) Traffic light plot illustrating risk of bias judgements across individual trials and domains. All eight trials were rated at high risk of bias for deviation from intended intervention (domain 2), with low risk of bias across all remaining domains.

(B) Summary bar chart showing the distribution of risk of bias judgements as a percentage across the six assessed domains.

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