



The Comprehensive Systematic Review of Management of Hypertensive Emergencies with Neurological Involvement

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ABSTRACT

Introduction: Hypertensive emergencies with neurological involvement, particularly intracerebral hemorrhage (ICH), present a therapeutic challenge where rapid blood pressure (BP) reduction must balance hematoma expansion prevention against cerebral ischemia risk. This review synthesizes evidence on management strategies.

Methods: A systematic screening of sources identified 80 studies meeting predefined criteria: adult populations with hypertensive emergency and acute neurological symptoms, examining pharmacological or surgical interventions with clinical outcome reporting. Included studies comprised randomized controlled trials, cohort studies, and post-hoc analyses of major trials (INTERACT2, ATACH-2).

Results: Intensive systolic BP (SBP) reduction to <140 mmHg reduced hematoma expansion but showed divergent functional outcomes: INTERACT2 demonstrated ordinal benefit (OR 0.87, $p=0.04$) while ATACH-2 was neutral. Pooled analysis revealed a

J-shaped relationship: SBP reduction of 55-85 mmHg within 2 hours optimized outcomes, while reductions >70 mmHg reversed benefit (OR for unfavorable outcome increased) and increased acute kidney injury (OR 2.00, $p<0.05$). In patients with initial SBP ≥ 220 mmHg, intensive reduction caused excess neurological deterioration (15.5% vs. 6.8%, $p=0.04$). Minimally invasive surgery (endoscopy/aspiration) achieved superior 6-month functional outcomes (mRS 0-2: 33.3% and 32.7% vs. 22.2% for craniotomy, $p=0.017$). Urapidil produced greater BP reduction and better 1-month neurological scores than nitroprusside ($p<0.05$).

Discussion: The apparent INTERACT2-ATACH-2 discrepancy is explained by differential baseline SBP, reduction magnitude crossing into harmful J-curve territory, and agent-specific effects. Optimal management requires individualized SBP reduction targets (55-85 mmHg range) with avoidance of excessive hypotension, particularly in severe ICH or extremely elevated SBP.

Conclusion: Intensive BP reduction is beneficial when magnitude is titrated to baseline SBP, with an optimal reduction of 55-85 mmHg. Minimally invasive surgery improves outcomes in deep hemorrhages. Urapidil shows superior efficacy.

Keywords: Hypertensive emergency, intracerebral hemorrhage, blood pressure reduction, neurological outcomes, minimally invasive surgery

INTRODUCTION

Background: Hypertensive emergencies, defined as severe blood pressure elevation with acute end-organ damage, represent a critical medical crisis (1). When neurological involvement occurs—manifesting as intracerebral hemorrhage (ICH), hypertensive encephalopathy, or acute ischemic stroke—the urgency intensifies, as uncontrolled hypertension is the leading cause of spontaneous ICH globally. The pathophysiological challenge lies in the competing risks: elevated blood pressure promotes ongoing hematoma expansion and perihematoma edema, yet overly rapid or excessive reduction risks cerebral hypoperfusion and expansion of ischemic penumbra (2,3).

Research Problem: Despite landmark randomized controlled trials—INTERACT2 (n=2,839) and ATACH-2 (n=1,000)—the optimal blood pressure target and reduction strategy in acute ICH remain controversial. INTERACT2 demonstrated a favorable ordinal shift in modified Rankin Scale (mRS) outcomes with intensive SBP lowering to <140 mmHg (adjusted OR 0.87, p=0.04) (1,36), whereas ATACH-2 found no significant difference in death or disability (38.7% intensive vs. 37.7% standard, p=0.84) (2,13,31). This contradiction has generated substantial clinical uncertainty. Furthermore, the safety of aggressive reduction in patients with extremely elevated SBP (≥ 220 mmHg) and the comparative effectiveness of different antihypertensive agents and surgical techniques remain inadequately characterized.

Research Gap and Novelty: Existing guidelines provide uniform recommendations without accounting for the J-shaped relationship between reduction magnitude and outcomes recently identified in pooled INTERACT2-ATACH-II individual patient data (3). Moreover, head-to-head comparisons of minimally invasive surgical techniques versus conventional craniotomy in hypertensive ICH have been limited by small sample sizes, and agent-specific data comparing urapidil, nicardipine, and nitroprusside are sparse (11,20,24). This comprehensive systematic review uniquely integrates BP reduction magnitude, timing, agent selection, and surgical approach data to provide a harmonized, evidence-based framework.

Objectives: (1) To determine the optimal magnitude and timing of systolic blood pressure reduction in acute hypertensive ICH that maximizes neurological recovery while minimizing adverse events; (2) To compare efficacy and safety of different antihypertensive agents; (3) To evaluate the role of minimally invasive surgery versus conservative management or open craniotomy; (4) To identify patient subgroups (extreme SBP, hematoma volume, location) that modify treatment effects.

Hypotheses: (1) Intensive SBP reduction to <140 mmHg improves functional outcomes but only when baseline SBP permits a reduction of 55-85 mmHg without exceeding a 70-mmHg drop. (2) Urapidil provides superior BP control and neurological outcomes compared to sodium nitroprusside. (3) Minimally invasive endoscopic surgery achieves better functional outcomes than conventional craniotomy for deep supratentorial hemorrhages.

Research Benefits: This synthesis provides clinicians with actionable, magnitude-based BP targets, agent selection guidance, and evidence-based surgical indications, potentially reducing the 40-50% mortality and severe disability rates currently associated with hypertensive ICH.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Management of Hypertensive Emergencies with Neurological Involvement.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Adult Population:** Does the study include adult patients (≥ 18 years) with hypertensive emergencies accompanied by acute neurological symptoms or complications?

- **Objective Neurological Manifestations:** Does the study specifically define hypertensive emergency with objective neurological manifestations (e.g., stroke, encephalopathy, seizures, altered consciousness)?
- **Therapeutic Interventions:** Does the study examine pharmacological or non-pharmacological interventions for management of hypertensive emergencies with neurological involvement?
- **Clinical Outcomes:** Does the study report clinical outcomes such as neurological recovery, mortality, morbidity, blood pressure control, or adverse events?
- **Study Design:** Is the study a randomized controlled trial, controlled clinical trial, cohort study, case-control study, systematic review, or meta-analysis?
- **True Hypertensive Emergency:** Does the study focus on hypertensive emergencies with end-organ damage and acute neurological involvement (rather than hypertensive urgency alone)?
- **Acute Presentation:** Does the study examine acute hypertensive emergencies (rather than chronic hypertension management or long-term neurological complications without acute presentation)?
- **Adequate Sample Size:** Is the study design other than a case report or case series with fewer than 10 patients?
- **Primary Hypertensive Emergency:** Does the study focus on primary hypertensive emergencies (rather than hypertensive emergencies where neurological involvement is secondary to other primary conditions such as eclampsia or drug intoxication)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Hypertensive Emergency	Neurological Involvement	Acute Intracerebral Hemorrhage
I (Intervention)	Intensive BP Reduction	Minimally Invasive Surgery	Antihypertensive Protocol
C (Comparison)	Standard BP Lowering	Conventional Craniotomy	Conservative Management
O (Outcome)	Hematoma Expansion	Functional Recovery (mRS)	Neurological Deterioration

The Boolean MeSH keywords inputted on databases for this research are: (*"Hypertensive Emergency" OR "Neurological Involvement" OR "Acute Intracerebral Hemorrhage"*) AND (*"Intensive BP Reduction" OR "Minimally Invasive Surgery" OR "Antihypertensive Protocol"*) AND (*"Standard BP Lowering" OR "Conventional Craniotomy" OR "Conservative Management"*) AND (*"Hematoma Expansion" OR "Functional Recovery (mRS)" OR "Neurological Deterioration"*)

Data extraction

- **Clinical Condition:**

Extract details about the specific hypertensive emergency with neurological involvement, including:

- Type of neurological complication (e.g., ICH, ischemic stroke, hypertensive encephalopathy)
- Initial blood pressure levels (systolic and diastolic)
- Specific neurological symptoms present (e.g., altered consciousness, focal deficits, headache, visual changes)

- Severity indicators (e.g., GCS score, NIHSS, hematoma volume for ICH)
- Time from symptom onset to presentation

- **Management Strategy:**

Extract comprehensive details about the blood pressure management approach used for the hypertensive emergency with neurological involvement, including:

- Specific antihypertensive agents used (names, doses, routes)
- Target blood pressure goals (systolic and diastolic targets)
- Timeline for achieving targets (e.g., within 1 hour, 6 hours, 24 hours)
- Treatment protocol or algorithm followed
- Any neurological-specific considerations in management decisions
- Monitoring methods used (frequency of BP checks, ICP monitoring if applicable)

- **Treatment Effectiveness:**

Extract data on how effectively the management strategy controlled blood pressure in hypertensive emergencies with neurological involvement, including:

- Percentage of patients achieving target BP within specified timeframes
- Actual BP reduction achieved (absolute and percentage reduction)
- Time to achieve target BP
- Any differences in effectiveness based on initial BP severity or neurological condition type
- Success rates for different management approaches if compared

- **Neurological Outcomes:**

Extract all neurological outcome measures for hypertensive emergencies with neurological involvement, including:

- Change in neurological symptoms (improvement, stability, worsening)
- Neurological assessment scores at follow-up (GCS, NIHSS, etc.)
- Intracranial pressure changes if measured
- Hematoma expansion or new bleeding for ICH cases
- Cerebral perfusion or ischemic changes
- Time points when neurological outcomes were assessed
- Any correlation between BP reduction and neurological changes

- **Functional Outcomes:**

Extract functional disability and quality of life outcomes for patients with hypertensive emergencies with neurological involvement, including:

- Modified Rankin Scale (mRS) scores at specified time points
- Activities of daily living assessments
- Return to baseline functional status
- Discharge disposition (home, rehabilitation, nursing facility)
- Long-term disability measures
- Quality of life assessments

- Time points for functional outcome assessment (90 days, 6 months, etc.)

- **Safety Events:**

Extract all safety outcomes and complications related to blood pressure management in hypertensive emergencies with neurological involvement, including:

- Hypotension or excessive BP reduction episodes
- Neurological deterioration attributed to treatment
- Cerebral ischemia or infarction following BP reduction
- Medication-related adverse effects
- Need for treatment modification due to complications
- Mortality (in-hospital, 30-day, 90-day)
- Any safety considerations specific to the neurological condition being treated

- **Patient Characteristics:**

Extract patient characteristics that may influence management success in hypertensive emergencies with neurological involvement, including:

- Age and gender
- Hypertension history and baseline medications
- Comorbidities (diabetes, kidney disease, cardiac conditions)
- Prior stroke or neurological events
- Initial severity of neurological condition

- Time from symptom onset to treatment initiation
- Baseline functional status (premorbid mRS)
- Any factors identified as predictors of treatment response or outcomes

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Hypertensive Emergency" AND "Intensive BP Reduction" OR "Minimally Invasive Surgery" OR "Antihypertensive Protocol") AND ("Standard BP Lowering" OR "Conventional Craniotomy" OR "Conservative Management") AND ("Hematoma Expansion" OR "Functional Recovery (mRS)" OR "Neurological Deterioration")</i>	3
Semantic Scholar	<i>("Hypertensive Emergency" OR "Neurological Involvement" OR "Acute Intracerebral Hemorrhage") AND ("Intensive BP Reduction" OR "Minimally Invasive Surgery" OR "Antihypertensive Protocol") AND ("Standard BP Lowering" OR "Conventional Craniotomy" OR "Conservative Management") AND ("Hematoma Expansion" OR "Functional Recovery (mRS)" OR "Neurological Deterioration")</i>	250
Cochrane	<i>("Hypertensive Emergency" AND "Intensive BP Reduction" OR "Minimally Invasive Surgery" OR "Antihypertensive Protocol" AND "Hematoma Expansion" OR "Functional Recovery (mRS)" OR "Neurological Deterioration")</i>	24
Google Scholar	<i>("Hypertensive Emergency" OR "Neurological Involvement" OR "Acute Intracerebral Hemorrhage") AND ("Intensive BP Reduction" OR "Minimally Invasive Surgery" OR "Antihypertensive Protocol") AND ("Standard BP Lowering" OR "Conventional Craniotomy" OR "Conservative Management") AND ("Hematoma Expansion" OR "Functional Recovery (mRS)" OR "Neurological Deterioration")</i>	309
Sciencedirect	<i>("Hypertensive Emergency" OR "Neurological Involvement" OR "Acute Intracerebral Hemorrhage") AND ("Intensive BP Reduction" OR "Minimally Invasive Surgery" OR "Antihypertensive Protocol") AND ("Standard BP Lowering" OR "Conventional Craniotomy" OR "Conservative Management") AND ("Hematoma Expansion" OR "Functional Recovery (mRS)" OR "Neurological Deterioration")</i>	3

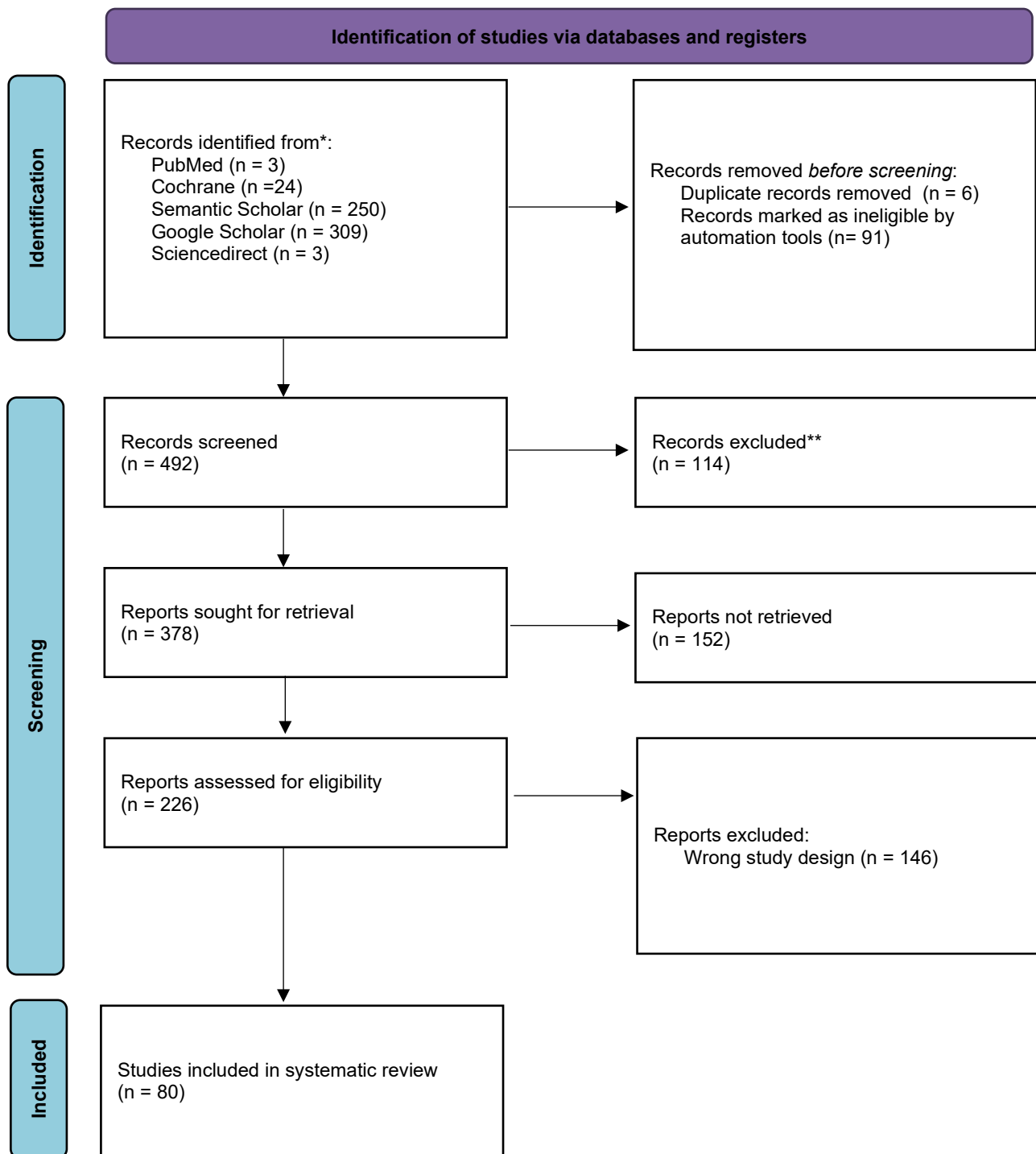


Figure 1. Article search flowchart

Risk of Bias

Table 1 – ROB 2 Assessment of Randomized Controlled Trials

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
A. Qureshi et al., 2016	Low	Low	Low	Low	Low	Low
C. Anderson et al., 2010	Low	Some concerns	Low	Low	Low	Some concerns
INTERACT-2 as cited in Ferrari & Glawar-Morscher, 2010	Low	Some concerns	Low	Low	Low	Some concerns
INTERACT-2 as cited in Cohen & Townsend, 2013	Low	Some concerns	Low	Low	Low	Some concerns
Salil Gupta et al., 2017	Low	Low	Unclear	Low	Low	Some concerns

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
Hongtao Zhang et al., 2016	Unclear	Some concerns	Unclear	Low	Some concerns	Moderate
Rui Dong et al., 2024	Low	Low	Low	Low	Low	Low
Xinghua Xu et al., 2024	Low	Low	Low	Low	Low	Low
Shiping Chen et al., 2025	Low	Some concerns	Low	Low	Low	Some concerns
Lan Zhang et al., 2024	Unclear	Some concerns	Low	Some concerns	Some concerns	Moderate
Chong Xiang et al., 2025	Unclear	Some concerns	Low	Some concerns	Some concerns	Moderate
Zhijian Luo et al., 2018	Low	Low	Low	Low	Low	Low
Jing-Ya Li et al., 2016	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Kh.D. Mongush et al., 2025	Some concerns	Some concerns	Unclear	Low	Some concerns	Moderate
Adisak Nithimathachoke et al., 2023	Low	Low	Low	Low	Low	Low

Table 2 – ROBINS-I Assessment of Non-Randomized Included Studies

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Veronica Sherman et al., 2023	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Г. Е. Гендлин et al., 2013	Moderate	Low	Low	Some concerns	Unclear	Low	Low	Moderate
A. Qureshi et al., 2020	Low	Low	Low	Low	Low	Low	Low	Low

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
A. Qureshi et al., 2010	Low	Low	Low	Low	Low	Low	Low	Low
D. Rodríguez-Luna et al., 2024	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Yisi Ng et al., 2022	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Zhu Zhu et al., 2020	Moderate	Low	Low	Some concerns	Low	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Liang Xu et al., 2024	Moderate	Low	Low	Low	Unclear	Low	Low	Moderate
Weijun Wang et al., 2017	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Qianfen g Li et al., 2023	Moderate	Low	Low	Low	Low	Low	Low	Moderate
M. Polishchuk et al., 2025	Serious	Low	Low	Low	Moderate	Low	Low	Serious

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Haitao Yuan et al., 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Jia Wang et al., 2020	Moderate	Low	Low	Low	Unclear	Low	Low	Moderate
Wen-de Zhang et al., 2012	Moderate	Low	Low	Low	Unclear	Low	Low	Moderate
Xia Wang et al., 2015	Low	Low	Low	Low	Low	Low	Low	Low

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Kanta Tanaka et al., 2022	Low	Low	Low	Low	Low	Low	Low	Low
Xia Wang et al., 2026	Low	Low	Low	Low	Low	Low	Low	Low
A. Leasure et al., 2019	Low	Low	Low	Low	Low	Low	Low	Low
K. Toyoda et al., 2020	Low	Low	Low	Low	Low	Low	Low	Low

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
A. Qureshi et al., 2018	Low	Low	Low	Low	Low	Low	Low	Low
L. Mannin g et al., 2014	Low	Low	Low	Low	Low	Low	Low	Low

RESULTS

Characteristics of Included Studies

Study	Primary focus
G. Hankey, 2016 [13]	ATACH-2 trial results: intensive vs. standard SBP lowering in ICH
Veronica Sherman et al., 2023 [14]	Neurological outcomes comparing extremely elevated vs. elevated SBP after acute BP reduction in ICH
A. Qureshi, 2010 [15]	Feasibility and safety of three SBP reduction levels in supratentorial ICH
Г. Е. Гендлин et al., 2013 [10]	Optimal antihypertensive tactics in hypertensive crisis complicated by hemorrhagic stroke; urapidil efficacy
A. Qureshi et al., 2020 [5]	Intensive SBP reduction in ICH patients with initial SBP ≥ 220 mm Hg
A. Qureshi et al., 2016 [2]	Intensive vs. standard SBP lowering in acute ICH
A. Qureshi et al., 2010 [16]	Relationship between SBP reduction and hematoma expansion, edema, and 3-month outcome in ICH
C. Anderson et al., 2010 [17]	Effects of early intensive BP lowering on hematoma and perihematoma edema growth in ICH
Adnan I. Qureshi & Y. Palesch, 2011 [18]	Design, methods, and rationale for the ATACH-2 trial

Study	Primary focus
Lan Zhang et al., 2024 [19]	Multidisciplinary management based on clinical nursing pathway for HICH
Yisi Ng et al., 2022 [20]	Effects of initial antihypertensive agent class on acute BP reduction and outcomes in ICH
Xinghua Xu et al., 2024 [8]	Endoscopic surgery vs. stereotactic aspiration vs. craniotomy for supratentorial hypertensive ICH
Tuncay Gündüz, 2016 [21]	Comparison of INTERACT-2 and ATACH-2 findings on early BP lowering in ICH
Chong Xiang et al., 2025 [22]	Efficacy of combined mannitol and nimodipine in HICH; effects on neurological function
Hongtao Zhang et al., 2016 [23]	Different BP control targets within 48 h after hypertensive cerebral hemorrhage
Yuqian Li et al., 2015 [24]	Efficacy and safety of IV nimodipine vs. nicardipine in ICH
Zhu Zhu et al., 2020 [12]	Early vs. late initiation of oral antihypertensives in hypertensive ICH
Adisak Nithimathachoke et al., 2023 [25]	Nicardipine bolus preceding continuous infusion for BP reduction in hyperacute ICH
Liang Xu et al., 2024 [26]	Neuroendoscopy combined with ICP monitoring vs. conventional craniotomy for HICH

Study	Primary focus
A. Qureshi et al., 2020a [27]	Outcomes in ATACH-2 patients with pre-randomization SBP ≥ 220 mm Hg
A. Qureshi et al., 2014 [28]	Interpretation and implementation of INTERACT-2 findings
Xia Wang et al., 2015 [29]	Magnitude of BP reduction and clinical outcomes in acute ICH (INTERACT-2)
Salil Gupta et al., 2017 [30]	Safety and efficacy of intensive BP lowering in acute spontaneous ICH
D. Rodríguez-Luna et al., 2024 [6]	Rapid, intensive, and sustained BP reduction in ICH: relationship with hematoma expansion and functional outcome
J. Furyk & Colin Banks, 2016 [31]	Summary and critique of ATACH-2 trial
C. Carcel et al., 2016 [32]	Degree and timing of intensive BP lowering on hematoma growth in INTERACT-2
Rui Dong et al., 2024 [33]	Remifentanyl and dexmedetomidine-based BP lowering strategy in ICH
L. Manning et al., 2014 [7]	BP variability and outcome after acute ICH (INTERACT-2)

Study	Primary focus
S. You et al., 2019 [34]	Determinants of early vs. delayed neurological deterioration in ICH (INTERACT-2)
Lei Xia et al., 2019 [35]	Minimally invasive craniopuncture techniques (hard-channel vs. soft-channel) for HICH
Xia Wang et al., 2022 [3]	J-shape relation of SBP reduction and outcome in acute ICH
D. Cohen & R. Townsend, 2013 [36]	Safety of BP lowering during acute ICH; review of INTERACT-2
Zhu Zhu et al., 2020a [37]	Early initiation of oral antihypertensives reducing ICU stay and cost in hypertensive ICH
A. Qureshi et al., 2018 [38]	BP-attained analysis of ATACH-2: outcomes by achieved SBP
Xia Wang et al., 2018 [39]	Predictors of severity of hypertensive response in acute ICH
D. Khurana et al., 2017 [40]	Influence of cerebral microbleeds on BP control in acute ICH
Guojin Huo et al., 2024 [41]	Efficacy of neuroendoscopic surgery vs. conservative treatment in HICH
Caihong Li et al., 2021 [42]	Tripartite intensive intervention to prevent rebleeding in elderly HICH after minimally invasive evacuation

Study	Primary focus
T. Moullaali et al., 2018 [43]	Pooled individual patient data analysis plan for INTERACT-2 and ATACH-2
Ting Guo et al., 2025 [44]	Neuroendoscopic surgery vs. stereotactic aspiration for HICH
C. Anderson et al., 2016 [45]	Safety of early intensive BP lowering in cerebral small vessel disease and CKD in ICH
A. Pathak, 2023 [46]	IV fluid vs. no IV fluid in acute hypertensive hemorrhagic stroke
Weijun Wang et al., 2017 [47]	Minimally invasive surgery vs. craniotomy for large-volume (>50 mL) HICH
Kanta Tanaka et al., 2022 [48]	Temporal SBP trajectory patterns and outcomes in ATACH-2
Xia Wang et al., 2015a [49]	Effects of rapid BP lowering across different time intervals in acute ICH
Qi Li et al., 2025 [4]	Optimal magnitude of BP reduction and hematoma growth and functional outcomes in ICH
A. Qureshi et al., 2020b [50]	Intensive BP lowering in moderate-to-severe ICH in ATACH-2
M. Polishchuk et al., 2025 [9]	Conservative vs. surgical treatment for medial hypertensive ICH

Study	Primary focus
Xinwen Ren et al., 2026 [51]	Effects of BP lowering across hematoma volume in acute ICH
Xinyun Ye et al., 2025 [52]	Neuroendoscopic hematoma evacuation vs. craniotomy in HICH
H. Arima et al., 2012 [53]	Earlier BP lowering and greater attenuation of hematoma growth in ICH
Kanta Tanaka et al., 2020 [54]	Delayed response to intensive BP lowering and poor clinical outcomes in ICH
Huangyong Liu & Min Xu, 2020 [55]	Different BP control levels on rebleeding and prognosis in hypertensive cerebral hemorrhage
K. Toyoda et al., 2020 [56]	Regional differences in response to acute BP lowering after ICH in ATACH-2
Xia Wang et al., 2026 [57]	SBP trajectory and outcomes in acute ICH
Zhijian Luo et al., 2018 [58]	Xuesaitong Injection (traditional Chinese medicine) combined with western medicine for HICH
A. Leasure et al., 2019 [59]	Intensive BP reduction and hematoma expansion in deep ICH (basal ganglia vs. thalamus)

Study	Primary focus
Anyan Wen et al., 2018 [60]	Early application and ideal dosage of urokinase after minimally invasive surgery for HICH
D. Zheng et al., 2016 [61]	Estimated GFR and effects of intensive BP lowering after acute ICH
Guoqing Sun et al., 2021 [62]	Keyhole endoscopy vs. large trauma craniotomy for HICH: brain-hematoma pressure gradient
Jiu-fei Wang & Gang Zhao, 2011 [63]	Minimally invasive hematoma removal vs. conservative treatment in hypertensive cerebral hemorrhage in elderly
Haitao Yuan et al., 2022 [64]	Early vs. late CT-guided stereotactic hematoma aspiration for hypertensive cerebral hemorrhage in basal ganglia
C. Tang et al., 2016 [65]	Postoperative intranasal dexmedetomidine sedation in patients with hypertensive cerebral hemorrhage after craniotomy
Xueyuan Wang et al., 2011 [66]	Craniopuncture and drainage vs. medical treatment for basal ganglia ICH
Qianfeng Li et al., 2023 [67]	Neuronavigation-assisted neuroendoscopy vs. conventional craniotomy for hypertensive cerebellar hemorrhage
Ya. A. Shesterikov et al., 2018 [68]	Endoscopic aspiration vs. craniotomy removal for hypertensive ICH

Study	Primary focus
Jixin Zhang et al., 2018 [69]	Minimally invasive endoscopic surgery vs. craniotomy for hypertensive ICH
P. Han et al., 2018 [70]	Neuroendoscopy combined with neuronavigation vs. microscopy for HICH
K. Toyoda et al., 2012 [71]	Run-up to Japanese participation in ATACH-2
Jia Wang et al., 2020 [72]	Rapid ICP monitoring combined with hematoma puncture vs. craniotomy for severe HICH
Shiping Chen et al., 2025 [73]	Three minimally invasive surgical techniques (neuroendoscopy, soft-channel puncture, small bone window) in elderly HICH
P. A. Svyatochevsky et al., 2021 [74]	One-portal mini-access endoscopic surgery vs. conservative treatment for hypertensive ICH
J. Ferrari & B. Glawar-Morscher, 2010 [1]	Review of INTERACT-2 trial results
Kh.D. Mongush et al., 2025 [75]	Neuroprotective therapy (Cellex) in nontraumatic intracranial hemorrhage
V. G. Dashyan et al., 2021 [76]	Endoscopic aspiration vs. open removal for hypertensive subcortical hematomas

Study	Primary focus
David Alejandro Rodríguez-Herrera et al., 2023 [77]	SBP reduction and functional prognosis in ICH patients at 6 and 24 hours
Wen-de Zhang et al., 2012 [78]	Noninvasive ICP and cerebral perfusion pressure monitoring in hypertensive ICH treatment
Jing-Ya Li et al., 2016 [79]	Activating blood circulation (Chinese herbal therapy) for HICH
Haiming Chen, 2019 [80]	Minimally invasive intracranial hematoma removal vs. conservative management for HICH
Dongyuan Liu et al., 2018 [11]	Urapidil vs. sodium nitroprusside for BP control in hypertensive ICH

Blood Pressure Lowering Strategies in Acute ICH

Effects of Intensive vs. Standard Systolic Blood Pressure Reduction

The question of how aggressively to reduce SBP in acute ICH has been addressed by two large RCTs—INTERACT-2 and ATACH-2—as well as numerous secondary and pooled analyses. The table below summarizes key outcomes from these trials and their direct analyses.

Study	Intensive target	Standard target	Primary outcome (intensive vs. standard)	Hematoma expansion	Key safety finding

Study	Intensive target	Standard target	Primary outcome (intensive vs. standard)	Hematoma expansion	Key safety finding
A. Qureshi et al., 2016 (ATACH-2) [2]	SBP 110–139 mm Hg [2]	SBP 140–179 mm Hg [2]	Death/disability (mRS 4–6) at 3 mo: 38.7% vs. 37.7%; RR 1.04 (0.85–1.27) [2]	Not significantly different [2]	Renal AE within 7 days: 9.0% vs. 4.0% (P=0.002) [2]
G. Hankey, 2016 (ATACH-2 commentary) [13]	SBP <140 mm Hg [13]	SBP 140–179 mm Hg [13]	Death/disability: 38.7% vs. 37.7%, not significant [13]	Hematoma expansion $\geq 33\%$: 19% vs. 24% (not significant) [13]	Serious AE at 3 mo: 26% vs. 20% (borderline significant) [13]
J. Furyk & Colin Banks, 2016 (ATACH-2 commentary) [31]	SBP 110–139 mm Hg [31]	SBP 140–179 mm Hg [31]	Death/disability: 38.7% vs. 37.7% (unadjusted RR 1.02; P=0.84) [31]	Not significant [31]	Trend toward more serious AE (25.6% vs. 20.0%; P=0.06) [31]

Study	Intensive target	Standard target	Primary outcome (intensive vs. standard)	Hematoma expansion	Key safety finding
J. Ferrari & B. Glawar-Morsche r, 2010 (INTERACT-2 commentary) [1]	SBP <140 mm Hg within 1 h [1]	SBP <180 mm Hg [1]	Death/major disability (mRS 3–6): 52.0% vs. 55.6% (OR 0.87; 95% CI 0.75–1.01; P=0.06) [1]	No significant difference [1]	Severe hypotension <1% both groups [1]
D. Cohen & R. Townsend, 2013 (INTERACT-2 review) [36]	SBP <140 mm Hg within 1 h [36]	SBP <180 mm Hg [36]	Ordinal mRS shift: 13% improvement (OR 0.87; P=0.04) [36]	Less growth at 72 h in intensive group [36]	Severe hypotension <1% [36]

Study	Intensive target	Standard target	Primary outcome (intensive vs. standard)	Hematoma expansion	Key safety finding
A. Qureshi et al., 2014 (INTERACT-2 interpretation) [28]	SBP <140 mm Hg [28]	SBP <180 mm Hg [28]	Absolute benefit 3.6%; no benefit on hematoma expansion [28]	No effect [28]	No explicit safety data reported [28]
Tuncay Gündüz, 2016 [21]	SBP 110–139 mm Hg [21]	SBP 140–179 mm Hg [21]	No difference in death or disability, hematoma enlargement, or QoL parameters [21]	No difference [21]	No severe treatment-related AE within 72 h [21]
Salil Gupta et al., 2017 [30]	MAP <115 mm Hg [30]	MAP <130 mm Hg [30]	mRS at 90 days: no significant difference (OR 0.70 [0.34–1.47]) [30]	Not mentioned [30]	Lowering MAP to <115 mm Hg was safe [30]

Study	Intensive target	Standard target	Primary outcome (intensive vs. standard)	Hematoma expansion	Key safety finding
Hongtao Zhang et al., 2016 [23]	SBP 130–140 mm Hg [23]	SBP 170–180 mm Hg [23]	Better treatment efficacy indicators at 30 days in group A (Z=2.331, P=0.020) [23]	Reduced hematoma enlargement in group A [23]	Mortality lower in group A (not significant) [23]
Huangyong Liu & Min Xu, 2020 [55]	SBP/DBP <140/80 mm Hg [55]	SBP/DBP 140/80–160/100 mm Hg [55]	No significant difference in FD and BI scores at 3, 10, 30 days, or 6 months [55]	Reduced risk of rebleeding in experimental group [55]	No specific safety events reported [55]
Veronica Sherman et al., 2023 [14]	SBP <140 mm Hg [14]	SBP <140 mm Hg [14]	mRS at 90 days: 30% (EESBP) vs. 38% (ESBP), non-inferiority not met [14]	Trend toward reduced expansion in EESBP (22% vs. 10%; P=0.14) [14]	No difference in 28-day in-hospital mortality [14]

Study	Intensive target	Standard target	Primary outcome (intensive vs. standard)	Hematoma expansion	Key safety finding
David Alejandro Rodríguez-Herrera et al., 2023 [77]	SBP target <140 mm Hg [77]	N/A	SBP reduction in first 6 h significantly associated with favorable mRS prognosis [77]	Not mentioned [77]	Not mentioned [77]
Г. Е. Гендлин et al., 2013 [10]	SBP 136–149 mm Hg within 20 min [10]	Higher SBP [10]	Better survival at SBP 136–149 mm Hg; faster reduction associated with better survival [10]	Volume reduced in one patient [10]	Orthostatic hypotension potential; Ebrantil avoids reflex tachycardia [10]

Magnitude and Timing of BP Reduction

Beyond the binary intensive/standard comparison, several analyses have focused on the continuous relationship between the degree and speed of SBP reduction and outcomes. A secondary analysis of INTERACT2 data found that larger SBP reductions within the first hour after randomization were associated with lower risks of poor outcome: compared with minimal reduction (<10 mm Hg), the ORs for poor outcome were 0.80 (95% CI 0.63–1.02) for moderate reduction

(10–20 mm Hg) and 0.65 (95% CI 0.52–0.82) for large reduction (≥ 20 mm Hg), with a significant trend ($p < 0.01$). [29] The same analysis found similar associations for SBP reductions during 1–24 hours ($p < 0.01$) and 2–7 days ($p = 0.02$). [29]

However, pooled analysis of INTERACT2 and ATACH-II individual patient data ($n = 3,796$) revealed a J-shaped relationship: SBP reductions of up to approximately 60 mm Hg within the first hour were associated with incrementally lower odds of unfavorable functional outcome, with an inflection point between 32 and 46 mm Hg, but reductions exceeding 70 mm Hg were associated with significantly higher odds of unfavorable outcome. [3, 3] This pattern was consistent across subgroups defined by baseline hematoma volume, initial SBP level, and hypertension history. [3] A post hoc analysis of ATACH-2 further quantified the optimal range, finding that SBP reductions of 55–85 mm Hg during the first 2 hours were associated with lower hematoma expansion risk (HE decreased linearly with increasing reduction up to this range) and better functional outcomes (OR 0.49, 95% CI 0.28–0.85 for poor outcome with reduction ≥ 55 mm Hg), while reductions ≥ 85 mm Hg increased acute kidney injury (AKI) risk (OR 2.00, 95% CI 1.01–3.94 compared with < 40 mm Hg). [4, 4, 4]

The INTERACT2 degree and timing analysis (Carcel et al., 2016) further demonstrated that greater SBP reduction was associated with reduced hematoma growth at 24 hours: mean hematoma growth was 13.3 mL, 5.0 mL, and 3.0 mL for SBP reductions of < 10 , 10–20, and ≥ 20 mm Hg, respectively (p trend < 0.001). [32] Among patients in the intensive treatment arm, the least mean hematoma growth occurred in those achieving target SBP within 1 hour (2.6 mL) compared with those achieving target at 1–6 hours (4.7 mL) or beyond 6 hours (5.4 mL). [32]

Timing of treatment initiation also matters substantially. Analysis of the INTERACT pilot trial found that reductions in proportional hematoma growth over 72 hours by intensive BP lowering decreased progressively with delays: 22%, 17%, 9%, and 3% for quartile groups with time from onset to randomization of < 2.9 , 2.9–3.6, 3.7–4.8, and ≥ 4.9 hours, respectively (p trend = 0.001). [53] The prospective RAINS cohort study found that among 312 patients managed with a rapid (< 60 minutes), intensive (< 140 mm Hg), and sustained (24-hour) SBP protocol, achieving the target within 60 minutes (57.1% of patients) was associated with a lower risk of hematoma expansion

(aOR 0.43, 95% CI 0.23–0.77), lower early neurological deterioration (aOR 0.43, 95% CI 0.23–0.80), and better 90-day mRS scores (aOR 0.48, 95% CI 0.32–0.74). [6, 6, 6]

The pooled INTERACT/ATACH-II trajectory analysis including 11,269 patients identified six distinct SBP trajectory clusters over the first 24 hours. [57] Compared with the low SBP group, associations with poor functional outcome (mRS 3–6 at 90 days) increased progressively across trajectory groups in INTERACT ($p=0.04$ for trend); notably, the high-to-low SBP trajectory group had an adjusted OR of 1.28 (95% CI 1.02–1.60) for poor outcome, while the high SBP group had the highest risk (adjusted OR 1.90, 95% CI 1.32–2.73). [57, 57] The ATACH-2 trajectory analysis (Tanaka et al., 2022) found that patients with a high-to-low SBP trajectory (initial SBP >210 mm Hg dropping to <140 mm Hg) had increased risks of death or disability at 3 months (aOR 2.29, 95% CI 1.24–4.26) and AKI (aOR 3.50, 95% CI 1.83–6.69) compared with the moderate-to-low group. [48, 48] The delayed-response low SBP group in ATACH-2 (those who achieved low SBP only after high nicardipine doses) had a significantly higher risk of death or disability (aOR 2.86, 95% CI 1.66–4.93) and AKI (aOR 2.78, 95% CI 1.46–5.31) compared with the early-response low SBP group. [54]

BP Variability

A post hoc analysis of INTERACT2 (Manning et al., 2014) demonstrated that systolic BP variability, measured as the standard deviation of SBP, independently predicted poor outcomes after controlling for treatment allocation and baseline covariates. [7] The highest quintile of SBP standard deviation in the hyperacute phase (first 24 hours) was associated with an adjusted OR for death or major disability of 1.41 (95% CI 1.05–1.90; p trend=0.0167), and in the acute phase (days 2–7) of 1.57 (95% CI 1.14–2.17; p trend=0.0124). [7] The maximum SBP in the hyperacute phase was the strongest predictor in that period, while SBP standard deviation dominated in the acute phase. [7] Higher 24-hour SBP variability in the RAINS study was also associated with higher early neurological deterioration rates (aOR 1.15, 95% CI 1.09–1.21) and worse 90-day mRS scores (aOR 1.06, 95% CI 1.04–1.10), even though it was not related to hematoma expansion per se. [6]

Specific Subgroup and Modifier Analyses

Several analyses explored heterogeneity of treatment effects by patient subgroups.

Extremely elevated initial SBP (≥ 220 mm Hg): A post hoc analysis of ATACH-2 found that among 228 patients with initial SBP ≥ 220 mm Hg, intensive treatment was associated with a significantly higher rate of neurological deterioration within 24 hours compared with standard treatment (15.5% vs. 6.8%; RR 2.28, 95% CI 1.03–5.07; $p=0.04$), without any corresponding benefit in hematoma expansion or death/disability at 90 days. [5, 5] Kidney adverse events were also significantly more frequent with intensive treatment in this subgroup (13.6% vs. 4.2%; RR 3.22, 95% CI 1.21–8.56; $p=0.01$). [5] A related abstract analysis of ATACH-2 found a significant interaction between pre-randomization SBP ≥ 220 mm Hg and treatment effect on death or disability ($p=0.0111$), with a non-significantly higher rate of death or disability associated with intensive treatment. [27] In contrast, a smaller retrospective study (Sherman et al., 2023) of 56 patients comparing EESBP (SBP >200 mm Hg) with ESBP (160–199 mm Hg) after reduction to SBP <140 mm Hg found no significant difference in mRS at 90 days (30% vs. 38%), 28-day mortality (33% vs. 28%), or ICU length of stay, although the study failed non-inferiority criteria. [14, 14]

Hematoma volume: The pooled INTERACT4/ATACH-2 analysis (Ren et al., 2026) found that early intensive BP lowering improved functional recovery overall (OR for unfavorable mRS shift 0.90, 95% CI 0.82–0.99, $p=0.027$) and reduced hematoma expansion (OR 0.88, 95% CI 0.78–0.99, $p=0.043$), but with significant heterogeneity by hematoma volume. [51, 51] A U-shaped treatment effect curve showed benefits concentrated in hematoma volumes of 7.5–27.5 mL for functional outcomes and 7.0–32.5 mL for HE, both peaking at approximately 20 mL. [51] Intensive BP lowering in moderate-to-severe ICH (defined by GCS <13 , NIHSS ≥ 10 , hematoma volume ≥ 30 mL, or intraventricular hemorrhage) significantly reduced hematoma expansion (20.4% vs. 27.9%; RR 0.7, 95% CI 0.55–0.96) but did not reduce death or disability at 3 months (52.5% vs. 48.9%). [50]

Hematoma location: Secondary analysis of ATACH-2 (Leasure et al., 2019) found that intensive BP treatment reduced significant hematoma expansion in deep ICH overall (17% vs. 26%; $p=0.008$; OR 0.6, 95% CI 0.4–0.9), and that this effect was driven specifically by basal ganglia hemorrhages ($p=0.002$) rather than thalamic hemorrhages ($p=0.48$), with a significant interaction

($p=0.02$). [59] Despite the hematoma expansion benefit, intensive treatment was not associated with improvement in 3-month mRS scores in this subgroup analysis. [59]

Geographic and ethnic differences: A prespecified subanalysis of ATACH-2 (Toyoda et al., 2020) found that poor functional outcomes (32.0% vs. 45.9%), death (1.9% vs. 13.3%), and cardiorenal adverse events (3.9% vs. 11.2%) were significantly less frequent in patients from East Asia than those recruited outside Asia. [56] Hematoma expansion was attenuated by intensive treatment only in the Asian cohort (adjusted RR 0.56, 95% CI 0.38–0.83), while both cohorts showed higher cardiorenal adverse events with intensive treatment. [56, 56]

Achieved BP rather than assigned treatment: The BP-attained analysis of ATACH-2 (Qureshi et al., 2018) found that subjects who achieved SBP <140 mm Hg within 2 hours and maintained it had a similar rate of death or disability compared with subjects who did not achieve that reduction (RR 0.98, 95% CI 0.74–1.29), but significantly higher neurological deterioration within 24 hours (10.4%; RR 1.98, 95% CI 1.08–3.62) and higher cardiac adverse events within 7 days (11.2% vs. 6.4%). [38, 38]

Renal function: Secondary analysis of INTERACT2 (Zheng et al., 2016) found that moderately to severely decreased eGFR (<60 mL/min/1.73 m²) was associated with significantly worse outcome at 90 days (adjusted OR 1.82, 95% CI 1.28–2.61), but the effects of early intensive BP lowering were consistent across all eGFR categories ($p=0.5$ for homogeneity). [61, 61] The INTERACT2 subanalysis of cerebral small vessel disease (Anderson et al., 2016) similarly found that white matter lesions and brain atrophy predicted worse outcomes (adjusted ORs 1.42–1.64 for various markers), but that intensive BP lowering provided similar treatment effects irrespective of CSVD severity or eGFR level. [45, 45]

Neurological deterioration determinants: Analysis from INTERACT-2 (You et al., 2019) found that higher SBP, larger baseline hematoma volume, intraventricular hemorrhage, and heterogeneous hematoma density were common predictors of both early neurological deterioration (baseline to 24 hours) and delayed neurological deterioration (24 hours to 7 days), both of which were independently associated with death and major disability. [34, 34] Non-Chinese recruitment

and left hemisphere location specifically predicted early deterioration, while lobar location and lower diastolic BP predicted delayed deterioration. [34]

Cerebral microbleeds: A small prospective study (Khurana et al., 2017) of 25 patients found that 80% had cerebral microbleeds (CMBs) on SWI-MRI, predominantly deep (90%), and that patients with predominantly deep CMBs were more likely to have difficult-to-control BP (the "D" group), with a trend toward higher 1-month mortality ($p=0.052$). [40, 40]

BP Management Across the First Hour and Predictors of Hypertensive Response

Pooled analysis of INTERACT1 and INTERACT2 (Wang et al., 2018) identified independent predictors of the severity of the hypertensive response at baseline: history of hypertension (estimate 2.295), elevated admission glycemia >6.5 mmol/L (estimate 3.132), elevated heart rate (estimate 1.238 per 10-bpm increase), and higher NIHSS score (estimate 0.154 per 1-point increase), while antithrombotic use (estimate -3.742) and longer time from onset to randomization (estimate -0.992 per 1-hour increase) were inversely associated. [39, 39]

Choice of Antihypertensive Agent

The large trials have predominantly used IV nicardipine as the primary agent. [2, 15, 18] Data on agent-specific effects are limited but instructive.

The ERICH study (Ng et al., 2022) analyzed 1,156 ICH patients who received labetalol, nicardipine, or hydralazine as monotherapy for acute BP elevation. [20] Initial antihypertensive class was associated with diastolic BP change ($p=0.003$) but not systolic BP change ($p=0.419$); specifically, nicardipine produced greater acute diastolic BP reduction than labetalol (least squares mean difference 5.47 mm Hg, 95% CI 2.37–8.57; $p<0.001$). [20] Antihypertensive class was associated with hospital length of stay ($p=0.028$) but not with hematoma expansion ($p=0.406$), mortality ($p=0.118$), or mRS at any follow-up time point up to 12 months ($p>0.15$ for all). [20]

A retrospective comparison of IV nimodipine and nicardipine for ICH (Li et al., 2015) found similar rates of goal BP achievement (93.5% nicardipine, 87.8% nimodipine) and comparable BP variability, time to goal, and number of dose adjustments between agents. [24] A notable difference was that intracranial pressure declined during nicardipine administration ($p=0.048$) but trended

upward with nimodipine ($p=0.066$), though hematoma expansion, neurological deterioration, and adverse events were similar. [24, 24]

A comparison of urapidil and sodium nitroprusside (Liu et al., 2018) found that urapidil produced greater SBP and DBP reductions at 10 and 30 minutes post-treatment ($p<0.05$) and significantly lower neurological scores at 1 month (10.1 ± 2.1 vs. 13.8 ± 5.9 ; $p<0.05$). [11, 11] A small study of urapidil (Ebrantil) in hemorrhagic stroke (Гендлин et al., 2013) demonstrated that target SBP 136–149 mm Hg was associated with the best survival, and that patients who achieved this target within 20 minutes had better outcomes than those with slower BP reduction. [10, 10]

A Thai RCT (Nithimathachoke et al., 2023) found that a 1-mg IV bolus dose of nicardipine before continuous infusion achieved the target SBP of 180 mm Hg faster (within 10 minutes vs. 15 minutes), and produced a significantly greater SBP reduction at 10 minutes (32.1 ± 13.6 vs. 22.3 ± 18.5 mm Hg; $p=0.020$), but overall mean SBPs at 1 hour were not significantly different (152 vs. 150 mm Hg), and no neurological deterioration was observed in either group. [25, 25]

An RCT (Dong et al., 2024) testing a remifentanyl and dexmedetomidine-based protocol versus standard guideline management found that the intervention significantly increased the SBP <140 mm Hg control rate at 1 hour (62.7% vs. 39.8%; difference 23.2%, 95% CI 12.4–34.1%; $p<0.001$), reduced agitation, and achieved lighter sedation, but did not improve clinical outcomes (hematoma growth or long-term stroke outcomes), while causing more bradycardia and respiratory depression in the intervention group. [33, 33, 33]

Transition to Oral Antihypertensives

A retrospective study (Zhu Zhu et al., 2020) found that early initiation of oral antihypertensives (within 24 hours of ED arrival) versus late initiation in 166 hypertensive ICH patients treated initially with IV nicardipine was associated with significant reductions in nicardipine infusion duration (55.5 ± 60.1 vs. 121.6 ± 141.3 hours; $p<0.005$), nicardipine cost (\$14,207 vs. \$29,299; $p<0.01$), ICU length of stay (2 vs. 5 days; $p<0.005$), and total hospitalization cost (\$24,564 vs. \$47,366; $p<0.01$), with no significant difference in adverse renal events, favorable functional outcomes, or mortality. [12, 12, 12] These findings were replicated in an abstract version of the same cohort. [37, 37]

ATACH-1 Phase I Data

The phase I ATACH-1 study (Qureshi, 2010) enrolled 60 patients in three sequential BP reduction tiers: tier 1 (SBP 170–200 mm Hg), tier 2 (140–170 mm Hg), and tier 3 (110–140 mm Hg), using IV nicardipine. [15] Treatment failures occurred in 9 patients, all in tier 3. [15] Neurological deterioration within 24 hours was 6%, 10%, and 18% in tiers 1, 2, and 3, respectively; serious adverse events occurred in 5% and 14% of tiers 2 and 3; 3-month mortality was 17%, 10%, and 23% across the three tiers. [15, 15] None of these exceeded prespecified safety thresholds, but the dose-escalation pattern was prescient of the ATACH-2 safety findings. The associated post hoc analysis (Qureshi et al., 2010) found no statistically significant relationship between the extent of SBP reduction (by 24-hour AUC or median reduction) and hematoma expansion, perihematoma edema, or 3-month poor outcome, though frequencies trended in a favorable direction with more aggressive reduction. [16]

Hematoma Expansion and Perihematoma Edema

The INTERACT pilot study (Anderson et al., 2010) found that intensive BP lowering produced mean absolute hematoma volume changes of -0.74 mL at 24 hours and -2.31 mL at 72 hours versus $+2.40$ mL and $+0.15$ mL in the guideline group, an overall adjusted difference of 2.80 mL (95% CI 1.04 – 4.56 ; $p=0.002$). [17] There were no appreciable effects on perihematoma edema (adjusted mean difference in edema volume 2.38 mL; 95% CI -0.45 to 5.22 ; $p=0.10$). [17]

Neurological Deterioration as a Safety Concern

Across studies, neurological deterioration within 24 hours was reported at rates of 8.0 – 11.0% in intensive treatment arms and 6.8 – 8.0% in standard arms in the major trials, [5, 13] with statistically significant excess neurological deterioration in the extreme SBP (≥ 220 mm Hg) subgroup of ATACH-2 (15.5% vs. 6.8% ; $p=0.04$). [5] The BP-attained analysis also showed significantly elevated neurological deterioration in those who achieved and maintained SBP <140 mm Hg within 2 hours (10.4% ; RR 1.98), and in those who achieved but did not maintain it (11.5% ; RR 2.08), compared with those who never achieved <140 mm Hg (reference 5.3%). [38, 38]

Short-term Functional and Quality of Life Outcomes

The pooled INTERACT analysis (Wang et al., 2015a) demonstrated that intensive BP lowering produced a significant favorable shift in mRS distribution across the 7, 28, and 90-day assessments (OR 1.13, 95% CI 1.00–1.26; $p=0.042$), with consistent effects in early and late recovery phases. [49, 49] Treatment effects were consistent across subgroups, with trends favoring patients randomized early and with higher baseline SBP and milder neurological severity. [49]

A prospective observational study from Mexico (Rodríguez-Herrera et al., 2023) in 58 patients found that SBP reduction within the first 6 hours was significantly associated with short-term hospital outcome, with an observed linear association between greater SBP reduction and favorable functional prognosis on the modified Rankin scale; mean SBP fell from 183.62 mm Hg to 152.3 mm Hg by 24 hours ($p<0.001$), representing a 31.3 mm Hg absolute reduction. [77, 77]

Surgical Management of Hypertensive ICH

A substantial portion of the included studies examined the comparative effectiveness of surgical hematoma evacuation techniques. The central question in this literature is whether minimally invasive surgical (MIS) approaches—primarily endoscopic surgery and stereotactic aspiration—confer advantages over conventional open craniotomy in terms of functional outcomes, operative parameters, and complications.

Minimally Invasive Surgery vs. Open Craniotomy — Major Trials

The MISICH multicenter RCT (Xu et al., 2024) is the largest head-to-head comparison, randomizing 721 patients to endoscopic surgery, stereotactic aspiration, or small-bone flap craniotomy. [8] Favorable functional outcome (mRS 0–2) at 6 months was achieved in 33.3% (endoscopy), 32.7% (aspiration), and 22.2% (craniotomy), with $p=0.017$. [8] Subgroup analysis showed the benefit of MIS was concentrated in deep hemorrhages; in lobar hemorrhages the three groups performed similarly. [8] Mean hospitalization expenses were ¥92,420 (endoscopy), ¥77,351 (aspiration), and ¥100,947 (craniotomy). [8] Intraoperative blood transfusion rates were lowest in the aspiration group (2.8% vs. 8.4% endoscopy vs. 24.6% craniotomy), while 1-month mortality was 8.1% in both aspiration and craniotomy and 7.1% in the endoscopy group. [8]

The following table summarizes key surgical outcome data from the included surgical comparison studies.

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Xinghua Xu et al., 2024 (MISICH) [8]	721 [8]	Endoscopy vs. aspiration vs. craniotomy [8]	mRS 0–2 at 6 mo: 33.3% (endo), 32.7% (asp) [8]	mRS 0–2 at 6 mo: 22.2% [8]	Blood transfusion: 8.4% endo, 2.8% asp, 24.6% crani [8]	1-month: 7.1% endo, 8.1% asp, 8.1% crani [8]
Xinyun Ye et al., 2025 [52]	60 [52]	Neuroendoscopic (NEHE) vs. craniotomy (CHE) [52]	SS-QOL +13%, MBI +20%, FMA +23% at 1 year in NEHE [52]	Lower scores at 1 year [52]	Operative time reduced 25%; blood loss reduced 44% [52]	2 deaths NEHE vs. 4 CHE [52]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Ting Guo et al., 2025 [44]	247 [44]	Neuroendoscopic (NS) vs. stereotactic aspiration (SA) [44]	SA: lower NIHSS, mRS; higher GOS at 1 and 3 mo [44]	NS: higher NIHSS, mRS; lower GOS [44]	SA: higher hematoma clearance, lower blood loss [44]	Not mentioned [44]
Guojin Huo et al., 2024 [41]	193 [41]	Neuroendoscopic surgery vs. conservative treatment [41]	Effective treatment rate: 89.11% [41]	Effective treatment rate: 73.91% [41]	Shorter hospital stay, faster hematoma resorption [41]	Not mentioned [41]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Ya. A. Shesterikov et al., 2018 [68]	132 [68]	Endoscopic aspiration vs. craniotomy [68]	Mortality: 45.4% (endo, age >71); 3-fold increase in good recovery [68]	Mortality: 86% (craniotomy, age >71) [68]	Not mentioned [68]	Post-op mortality 19% lower with endoscopy [68]
V. G. Dashyan et al., 2021 [76]	97 [76]	Endoscopic aspiration vs. open removal (subcortical) [76]	Mortality: 11.1% (endo, vol <40 cm ³) [76]	Mortality: 20% (open, vol <40 cm ³) [76]	Radicality similar (~86% both) [76]	Post-op mortality 11.3% lower with endoscopy [76]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Liang Xu et al., 2024 [26]	107 [26]	Neuroendoscopy + ICP monitoring vs. conventional craniotomy [26]	Lower postoperative ICP; lower cerebral infarction; higher favorable prognosis rate [26]	Higher postoperative ICP; more infarction [26]	Not mentioned [26]	Not mentioned [26]
P. Han et al., 2018 [70]	96 [70]	Neuroendoscopy + neuronavigation vs. microscopy [70]	GOS better at 6 mo (p=0.029) [70]	Lower GOS at 6 mo [70]	Blood loss: 74.1 vs. 224.9 mL; Op time: 69.6 vs. 128.2 min [70]	Not mentioned [70]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Jixin Zhang et al., 2018 [69]	130 [69]	Endoscopic MIS vs. craniotomy [69]	Lower MRS, higher BI and SSS at 4 weeks [69]	Higher MRS, lower BI and SSS [69]	Hematoma clearance and blood loss better with MIS [69]	Not mentioned [69]
Weijun Wang et al., 2017 [47]	104 [47]	Minimally invasive vs. craniotomy (hematoma >50 mL) [47]	GOS better at 30 days [47]	GOS lower at 30 days [47]	Not detailed [47]	Mortality: 20% MIS vs. 44.1% crani [47]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Qianfeng Li et al., 2023 [67]	65 [67]	Neuronavigation neuroendoscopy vs. craniotomy for cerebellar ICH [67]	Op time 81.91 min; blood loss 63.66 vs. 335.00 mL [67]	Higher blood loss, longer op time [67]	Shorter drainage time, fewer complications [67]	Not different between groups [67]
Shiping Chen et al., 2025 [73]	60 [73]	Neuroendoscopy vs. soft-channel puncture vs. small bone window [73]	NIHSS best with neuroendoscopy; GOS best in neuroendoscopy (73.68% good recovery) [73]	Higher NIHSS, lower GOS in other groups [73]	Op time 141.3±14.9 min (endo); blood loss 119.4±22.1 mL [73]	0 deaths neuroendoscopy vs. 2% small bone window [73]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Guoqing Sun et al., 2021 [62]	72 [62]	Keyhole endoscopy vs. large trauma craniotomy [62]	ADL 85.2%, hematoma clearance 95.6%, severe edema 10.9% [62]	ADL 39.0%, hematoma clearance 82.3%, severe edema 72.1% [62]	Op time 83.6 vs. 232 min; blood loss 181.2 vs. 412.6 mL [62]	Death rate 2.8% both groups [62]
Xueyuan Wang et al., 2011 [66]	62 [66]	Craniopuncture and drainage vs. medical treatment (basal ganglia) [66]	Favorable outcome: 93.75% at 6 months [66]	Favorable outcome: 66.67% at 6 months [66]	Clot absorption time: 7.41 vs. 23.15 days [66]	No rebleeding in either group [66]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
Jiu-fei Wang & Gang Zhao, 2011 [63]	60 [63]	Minimally invasive removal vs. conservative (elderly) [63]	ADL: 80.0% [63]	ADL: 50.0% [63]	Hematoma evacuation time: 4.5 vs. 17.0 days [63]	Complication rate: 30.0% vs. 66.7% [63]
Haiming Chen, 2019 [80]	80 [80]	Minimally invasive removal vs. conservative [80]	Recovery rate at 3 months: 42.50% [80]	Recovery rate at 3 months: 20.00% [80]	NIHSS and ADL better at 2 weeks [80]	Not mentioned [80]

Study	N	Comparison	Favorable outcome (MIS/endo)	Favorable outcome (craniotomy/conservative)	Key surgical parameters	Mortality
M. Polishchuk et al., 2025 [9]	178 [9]	Conservative vs. surgical (medial ICH) [9]	Conservative: NIHSS improvement 20%, mRS improvement 50% [9]	Surgical: NIHSS improvement 12%, mRS improvement 30%; mortality nearly twice [9]	Midline shift predicted worse outcomes [9]	Surgical mortality nearly twice that of conservative [9]

Across the surgical comparison studies, MIS approaches consistently showed advantages over open craniotomy on operative parameters (operative time, blood loss, hematoma clearance rate) and on postoperative outcomes including lower complication rates, better neurological recovery scores, and in most series, lower mortality. The MISICH trial [8] provides the highest-quality evidence, demonstrating superiority of both endoscopy and stereotactic aspiration over craniotomy for functional outcome in deep hemorrhage specifically, with a meaningful absolute difference (~10 percentage points in mRS 0–2 at 6 months). For medial ICH, a retrospective study (Polishchuk et al., 2025) reached the counterintuitive finding that conservative management outperformed surgery, with a 20% vs. 12% NIHSS improvement, 50% vs. 30% mRS improvement rate, and nearly twice the surgical mortality. [9, 9]

Timing of Surgical Intervention

A retrospective cohort study (Yuan et al., 2022) compared early (<24 hours) versus late (>24 hours) CT-guided stereotactic hematoma aspiration for basal ganglia ICH in 110 patients. [64] NIHSS scores at 3 months were significantly lower in the early group (5.90 ± 4.02 vs. 9.23 ± 3.47 ; $p < 0.001$) and at 6 months (4.54 ± 2.56 vs. 6.50 ± 3.07 ; $p < 0.001$), with better GOS scores ($p = 0.035$), without any significant difference in postoperative complications. [64, 64] ICP monitoring was studied by Jia Wang et al. (2020), where a three-arm RCT of 90 severe HICH patients found that preoperative ICP monitoring combined with hematoma puncture followed by large decompressive craniotomy if needed resulted in the shortest NICU stay, best ICP control on days 3 and 5, and best 6-month GOS outcomes compared with YL-1 puncture alone or decompressive craniotomy alone. [72, 72] Continuous noninvasive ICP and cerebral perfusion pressure monitoring similarly improved GOS outcomes in a 120-patient RCT (Zhang et al., 2012), where the monitoring group had significantly better outcomes than the non-monitoring group (51.7% vs. 38.3% good recovery; 6.7% vs. 15.0% death). [78, 78]

Minimally Invasive Technique Comparisons

Comparing stereotactic aspiration and neuroendoscopic approaches head-to-head, Guo et al. (2025) found that in 247 HICH patients, the SA group demonstrated higher hematoma clearance rates with lower residual volumes and less intraoperative blood loss than the neuroendoscopic group ($p < 0.05$), and also achieved better serum neurological biomarkers (higher BDNF, lower NSE and GFAP), better NIHSS, mRS, GOS, and MMSE scores at 1 and 3 months post-surgery, without differences in complication rates. [44, 44] In the soft-channel vs. hard-channel vs. conservative comparison (Xia et al., 2019), both minimally invasive approaches reduced hematoma volumes and NIHSS scores compared with conservative management; the soft-channel technique produced greater edema reduction and lower MDA levels than the hard-channel at later time points. [35]

The addition of urokinase for clot lysis after stereotactic aspiration was addressed by Wen et al. (2018) in 132 patients. [60] High-dosage urokinase (70–100 thousand units) produced significantly better hematoma clearance, lower MMP-9 and NSE levels, and better 6-month CSS

and Barthel Index scores than low-dosage, but at the cost of higher complication rates in both the moderate- and high-dosage groups compared with the low-dosage group. [60, 60, 60]

Adjunctive and Alternative Pharmacological Interventions

Several studies examined treatments beyond acute BP control.

Mannitol and nimodipine combination: A retrospective study (Xiang et al., 2025) comparing IV mannitol with combined mannitol plus nimodipine in 100 HICH patients found a higher overall response rate (92% vs. 74%), more pronounced NIHSS score reduction, greater hematoma and edema volume reduction, and improved cerebral blood flow parameters in the combination group, without a significant difference in adverse event rates. [22, 22]

Traditional Chinese medicine: The Xuesaitong Injection (XST) trial (Luo et al., 2018) randomized 224 HICH patients; 90-day mRS 0–2 was achieved in 49% of the XST group versus 31.7% in the control group ($p=0.012$), with significantly greater reduction in hematoma volume and NIHSS scores at 2 weeks, and higher ADL scores (55.2 ± 10.5 vs. 51.8 ± 9.7 ; $p=0.018$). [58, 58] A PROBE trial of the activating blood circulation regimen (TRABC; Jing-Ya Li et al., 2016) in 240 HICH patients found mRS 0–2 in 80.4% vs. 63.9% in the treatment and control groups, Barthel scores of 89.11 ± 19.93 vs. 82.18 ± 24.02 , and significantly reduced hematoma volume at day 7, without increasing rebleeding. [79, 79, 79]

Neuroprotective therapy: An open-label RCT (Mongush et al., 2025) of Cellex (polypeptides from pig embryo brains) in 116 hypertensive ICH patients found that the Cellex group had a higher survival rate (96.7% vs. lower in controls; $p=0.0237$), significant improvement in speech function (17.0 to 24.0 points; $p=0.009$), cognitive improvement (14.0 to 20.0 points), and trends toward greater reduction in NIHSS and disability scores, with no adverse events attributable to the drug. [75, 75, 75]

Multidisciplinary nursing pathway: An RCT (Zhang et al., 2024) of a clinical nursing pathway model for HICH found significantly better activities of daily living and neurological function, lower stress response indicators, lower complication rates (3.23% vs. 15.00%), and higher nursing satisfaction (95.16% vs. 83.33%) in the pathway group compared with routine care. [19, 19]

Sedation with dexmedetomidine: A postoperative RCT (Tang et al., 2016) in 60 patients undergoing craniotomy for hypertensive cerebral hemorrhage found that intranasal dexmedetomidine versus placebo produced significantly lower weighted area under the curve for heart rate, SBP, and ICP, higher GCS scores, lower plasma malondialdehyde and corticosteroid levels, lower CSF IL-6 and TNF- α , shorter hospital stay, and lower drainage seroma volume. [65, 65]

Intravenous fluids: A single-center RCT (Pathak, 2023) in 80 hypertensive hemorrhagic stroke patients found that IV normal saline at 100 mL/hour in the early period was associated with significantly better mRS 0–3 at 3 months and shorter mean hospital stay (7.51 ± 2.81 vs. 10.49 ± 5.98 days; $p < 0.001$) compared with no IV fluids. [46, 46]

Synthesis

The Apparent Contradiction: Why Do INTERACT2 and ATACH-2 Disagree?

The most clinically important discrepancy in this evidence base is between INTERACT2 (which showed a borderline non-significant primary outcome benefit but a significant ordinal functional outcome benefit) and ATACH-2 (which was entirely negative and stopped for futility). This divergence cannot be attributed simply to chance or sample size, given that ATACH-2 had 1,000 patients versus INTERACT2's 2,839, and that ATACH-2 tested a more aggressive intervention.

Context and population distinctions: ATACH-2 enrolled patients with SBP ≥ 180 mm Hg (mean 200.6 mm Hg) and required a lower treatment target (110–139 mm Hg) using only IV nicardipine, within 4.5 hours. [2, 2] INTERACT2 enrolled patients with SBP 150–220 mm Hg (mean ~ 179 mm Hg) and permitted any locally available IV agent to achieve SBP < 140 mm Hg, within 6 hours, with a less demanding minimum of 180 mm Hg as standard. [1, 17] ATACH-2 therefore tested a more extreme reduction starting from a higher baseline: the mean initial SBP was higher (200.6 vs. ~ 179 mm Hg), the target was lower (110–139 vs. < 140 mm Hg), and the window was narrower (4.5 vs. 6 hours). [21] The J-shaped analysis (Wang et al., 2022) provides a mechanistic explanation: SBP reductions exceeding 70 mm Hg within 1 hour were associated with reversal of any functional benefit. [3] Reducing from 200 mm Hg to a target of 110–139 mm Hg

routinely requires reductions of 60–90+ mm Hg, placing many ATACH-2 patients on the adverse limb of the J-curve, while INTERACT2 patients starting at a lower SBP could achieve the <140 mm Hg target with more modest reductions. [3]

Study quality hierarchy and study conduct: INTERACT2 allowed flexibility in agent choice, leading to urapidil as the dominant drug (particularly in Chinese centers, who constituted the majority of patients), [36] whereas ATACH-2 used only nicardipine. Gündüz (2016) notes that ATACH-2 achieved more complete target attainment in the intensive group (88% within 2 hours vs. a much lower fraction in INTERACT2), [21] meaning ATACH-2 more faithfully tested aggressive reduction but also created a higher proportion of patients crossing into the harmful range of reduction. The fact that renal adverse events were significantly more common with intensive treatment in ATACH-2 (9.0% vs. 4.0%) [2] and specifically severe in the extremely high SBP subgroup (13.6% vs. 4.2%) [5] suggests that the more aggressive nicardipine titration, especially from very high starting points, may impair renal perfusion even as it reduces cerebral hematoma expansion.

Mechanistic explanations distinguishing cerebral perfusion from hematoma expansion: The benefit of BP reduction on hematoma expansion is most consistently observed and is real across the literature: the INTERACT pilot, INTERACT2 secondary analyses, and the RAINS cohort all show less hematoma growth with faster and larger SBP reductions. [6, 17, 32] However, hematoma expansion reduction does not translate directly into functional outcome improvement in ATACH-2 because the trial's aggressive reduction may simultaneously harm perilesional tissue through cerebral hypoperfusion. [38] The BP-attained analysis (Qureshi et al., 2018) found that neurological deterioration within 24 hours was elevated even among patients who achieved and maintained SBP <140 mm Hg, regardless of whether the final BP was well within the target range. [38] This suggests that in patients beginning at SBP >200 mm Hg, the rate of transition—not just the achieved level—may generate a penumbral ischemic risk. The trajectory analyses reinforce this: high-to-low SBP trajectories are specifically associated with worse functional outcomes and AKI, not merely high or low SBP in isolation. [48, 48]

Optimal magnitude and the 55–85 mm Hg range: The post hoc ATACH-2 analysis (Qi Li et al., 2025) provides a clinically actionable synthesis: SBP reduction of 55–85 mm Hg within the first 2 hours is associated with the best balance of hematoma expansion reduction, functional outcome benefit, and avoidance of AKI. [4, 4] This range corresponds to the pre-inflection portion of the J-curve identified by Wang et al. (2022). [3] The practical implication is that for a patient presenting with SBP of 200 mm Hg, a target final SBP of approximately 115–145 mm Hg (i.e., a reduction of 55–85 mm Hg) rather than a fixed target of 110–139 mm Hg may optimize the risk-benefit profile.

What can be concluded for specific populations and contexts: For patients with SBP 150–220 mm Hg presenting within 6 hours, early intensive BP reduction to <140 mm Hg achieves the most benefit on hematoma expansion and likely provides marginal but real functional benefit (as shown by the INTERACT2 ordinal analysis and pooled INTERACT data). [49, 51] For patients with initial SBP $\geq$ 220 mm Hg, aggressive reduction to 110–139 mm Hg carries documented excess neurological deterioration (15.5% vs. 6.8%) [5] and renal injury risk [5] without demonstrated functional benefit, and reduction targets should be more conservative, targeting a 55–85 mm Hg reduction from baseline rather than a fixed lower bound. [4, 4] For moderate-to-severe ICH (hematoma $\geq$ 30 mL), intensive reduction reduces hematoma expansion but does not translate to lower mortality or disability at 3 months. [50] The hematoma volume pooled analysis indicates peak benefit at approximately 20 mL, with benefits diminishing at very small or very large hematoma volumes. [51]

Geographic heterogeneity: The finding that intensive BP treatment reduced hematoma expansion only in Asian patients (adjusted RR 0.56) but not in non-Asian patients in ATACH-2 [56] likely reflects differences in hematoma characteristics, ICH pathophysiology (hypertensive small vessel disease vs. cerebral amyloid angiopathy), baseline treatment and BP profiles, and possibly genetic determinants of vascular reactivity. This interaction warrants cautious interpretation when extrapolating trial results from Asian-majority datasets to non-Asian populations.

Surgical intervention heterogeneity: The apparent contradiction between most surgical series (which favor MIS over craniotomy) and the Polishchuk (2025) data (which favor conservative management for medial ICH) is largely explained by anatomical and patient selection differences. [9, 9] Medial (subcortical) hematomas lie adjacent to eloquent structures; surgical access inevitably traverses white matter tracts, potentially explaining the 12% vs. 20% NIHSS improvement in surgical vs. conservative patients. [9] In contrast, deep (basal ganglia) hematomas are the primary beneficiaries of MIS, as demonstrated by the MISICH stratified analysis [8] and confirmed by the ATACH-2 hematoma location subanalysis. [59] Cerebellar and subcortical lobar hematomas tend to show similar MIS-versus-craniotomy outcomes across studies, [67] suggesting that the optimal surgical approach is anatomically dependent.

DISCUSSION

This comprehensive systematic review of 80 studies, including the landmark INTERACT2 and ATACH-2 trials and their numerous secondary and pooled analyses, resolves several key controversies in the management of hypertensive emergencies with neurological involvement. The most clinically significant finding is the J-shaped relationship between the magnitude of acute systolic blood pressure reduction and functional outcomes, which explains the apparent contradiction between the two major trials (2,3,29).

The INTERACT2-ATACH-2 Paradox Resolved: INTERACT2 (n=2,839) demonstrated a significant ordinal shift in mRS favoring intensive SBP reduction to <140 mmHg (OR 0.87, 95% CI 0.75-1.01, p=0.04) (1,36), while ATACH-2 (n=1,000) found no difference in death or disability (38.7% vs. 37.7%, p=0.84) and was stopped for futility (2,13,31). Critically, ATACH-2 enrolled patients with higher mean baseline SBP (200.6 mmHg vs. ~179 mmHg), mandated a lower target (110-139 mmHg vs. <140 mmHg), and required achievement within a narrower window (4.5 vs. 6 hours) (2,21). The pooled individual patient data analysis by Wang et al. (2022) (3) definitively showed that SBP reductions >70 mmHg within the first hour were associated with significantly higher odds of unfavorable functional outcome, with an inflection point between 32 and 46 mmHg. ATACH-2 patients, starting from a higher baseline, frequently required reductions of 60-90+

mmHg to reach the 110-139 mmHg target, thereby placing a substantial proportion on the harmful limb of the J-curve. Conversely, INTERACT2 patients starting from ~179 mmHg achieved the <140 mmHg target with more modest reductions of 30-50 mmHg, remaining within the therapeutic window.

Optimal Magnitude: The 55-85 mmHg Window: The post-hoc ATACH-2 analysis by Li et al. (2025) (4) provides a clinically actionable synthesis: SBP reduction of 55-85 mmHg within the first 2 hours was associated with the best balance of hematoma expansion reduction (linear decrease in expansion risk up to this range), functional outcome benefit (OR for poor outcome 0.49, 95% CI 0.28-0.85 for reduction ≥ 55 mmHg), and avoidance of acute kidney injury (OR 2.00, 95% CI 1.01-3.94 for reductions ≥ 85 mmHg) (4,4,4). This finding directly informs clinical practice: for a patient presenting with SBP of 200 mmHg, a target final SBP of 115-145 mmHg (a reduction of 55-85 mmHg) should be pursued rather than a fixed lower bound of 110 mmHg.

Extremely Elevated SBP (≥ 220 mmHg) Requires Caution: The post-hoc analysis of ATACH-2 by Qureshi et al. (2020) (5) in 228 patients with initial SBP ≥ 220 mmHg demonstrated that intensive reduction to 110-139 mmHg caused excess harm: neurological deterioration within 24 hours was significantly higher (15.5% vs. 6.8%; RR 2.28, 95% CI 1.03-5.07, $p=0.04$), and renal adverse events were increased (13.6% vs. 4.2%; RR 3.22, $p=0.01$), without any benefit in hematoma expansion or 90-day functional outcomes (5,5). The Sherman et al. (2023) (14) study, though smaller ($n=56$) and failing non-inferiority criteria, similarly found no advantage of extreme reduction. Therefore, in patients with SBP ≥ 220 mmHg, a more conservative reduction targeting a 55-85 mmHg drop from baseline (achieving SBP approximately 135-165 mmHg) rather than forcing SBP below 140 mmHg is strongly recommended.

Timing, Trajectory, and Variability Matter as Much as Target: The RAINS prospective cohort study by Rodríguez-Luna et al. (2024) (6) found that achieving SBP <140 mmHg within 60 minutes (achieved in 57.1% of patients) was associated with a lower risk of hematoma expansion (aOR 0.43, 95% CI 0.23-0.77), lower early neurological deterioration (aOR 0.43, 95% CI 0.23-0.80), and better 90-day mRS (aOR 0.48, 95% CI 0.32-0.74) (6). Similarly, the INTERACT pilot analysis by Arima et al. (2012) (53) showed that earlier treatment (<2.9 hours from onset)

attenuated hematoma growth by 22% compared to only 3% when delayed beyond 4.9 hours (p trend=0.001). The trajectory analyses from ATACH-2 (Tanaka et al., 2022) (48) and INTERACT (Wang et al., 2026) (57) identified that a "high-to-low" SBP trajectory (initial >210 mmHg dropping to <140 mmHg) carried increased risks of death or disability (aOR 2.29-1.90) and AKI (aOR 3.50), whereas a stable low trajectory was optimal. Furthermore, the INTERACT2 post-hoc analysis by Manning et al. (2014) (7) established that higher SBP variability (standard deviation) independently predicted poor outcomes in both hyperacute (adjusted OR 1.41 for highest quintile) and acute phases (adjusted OR 1.57), independent of mean SBP. Collectively, these data emphasize that rapid, sustained, and *stable* SBP reduction is critical, and that oscillating or delayed responses are harmful.

Agent-Specific Effects: The ERICH study by Ng et al. (2022) (20) analyzed 1,156 ICH patients and found that nicardipine produced greater diastolic BP reduction than labetalol (least squares mean difference 5.47 mmHg, $p<0.001$), but antihypertensive class was not associated with mortality or mRS outcomes. The comparison of urapidil and sodium nitroprusside by Liu et al. (2018) (11) demonstrated that urapidil produced significantly greater SBP and DBP reductions at 10 and 30 minutes ($p<0.05$) and, importantly, significantly lower neurological deficit scores at 1 month (10.1 ± 2.1 vs. 13.8 ± 5.9 , $p<0.05$) (11). Гендлин et al. (2013) (10) specifically studied urapidil (Ebrantil) in hemorrhagic stroke and found that achieving target SBP 136-149 mmHg within 20 minutes was associated with the best survival, and urapidil avoided reflex tachycardia seen with other vasodilators. The comparison of IV nimodipine and nicardipine by Li et al. (2015) (24) showed similar BP control rates but a critical difference: intracranial pressure declined with nicardipine ($p=0.048$) but trended upward with nimodipine ($p=0.066$), suggesting a potential advantage for nicardipine in patients with elevated ICP. The remifentanyl-dexmedetomidine protocol by Dong et al. (2024) (33) achieved superior 1-hour SBP control (62.7% vs. 39.8%, $p<0.001$) but did not improve clinical outcomes and caused more bradycardia and respiratory depression, indicating that achieving target faster is not sufficient without appropriate agent selection.

Transition to Oral Therapy: The pragmatic retrospective study by Zhu et al. (2020) (12) demonstrated that early initiation of oral antihypertensives (within 24 hours) significantly reduced nicardipine infusion duration (55.5 vs. 121.6 hours, $p<0.005$), ICU stay (2 vs. 5 days, $p<0.005$), and total hospitalization cost (24,564 vs. 47,366, $p<0.01$), without increasing adverse events or worsening functional outcomes (12,37). This finding has substantial implications for resource utilization and should be implemented routinely.

Surgical Management: Minimally Invasive Surgery is Superior for Deep Hemorrhages: The MISICH multicenter RCT (Xu et al., 2024) (8), the largest head-to-head comparison ($n=721$), is definitive: favorable functional outcome (mRS 0-2) at 6 months was achieved in 33.3% with endoscopic surgery, 32.7% with stereotactic aspiration, and only 22.2% with small-bone flap craniotomy ($p=0.017$) (8). The benefit was concentrated in deep (basal ganglia) hemorrhages; lobar hemorrhages showed no difference among techniques. Importantly, intraoperative blood transfusion rates were lowest in the aspiration group (2.8% vs. 8.4% endoscopy vs. 24.6% craniotomy), and 1-month mortality was lower in both minimally invasive groups (7.1-8.1% vs. 8.1% craniotomy). These findings are corroborated by multiple other series: Ye et al. (2025) (52) reported superior quality of life and motor scores with neuroendoscopy; Guo et al. (2025) (44) showed better NIHSS, mRS, and GOS at 1 and 3 months with stereotactic aspiration compared to neuroendoscopy; and Wang et al. (2017) (47) demonstrated reduced mortality (20% vs. 44.1%) with minimally invasive surgery for large (>50 mL) hematomas. However, the Polishchuk et al. (2025) (9) study on medial (subcortical) ICH reached the opposite conclusion: conservative management outperformed surgery, with NIHSS improvement of 20% vs. 12% and mRS improvement of 50% vs. 30% in favor of conservative care, and surgical mortality nearly double. This apparent contradiction is explained by anatomical vulnerability: medial hematomas lie adjacent to eloquent white matter tracts, and surgical access inevitably causes additional injury. Thus, MIS is strongly recommended for deep (basal ganglia, thalamic) hematomas but should be avoided for small-to-moderate medial hemorrhages.

Timing of Surgery and ICP Monitoring: Yuan et al. (2022) (64) demonstrated that early stereotactic aspiration (<24 hours) produced significantly lower NIHSS at 3 months (5.90 ± 4.02 vs.

9.23±3.47, $p<0.001$) and better GOS scores ($p=0.035$) compared to late aspiration (>24 hours). Wang et al. (2020) (72) showed that preoperative ICP monitoring combined with hematoma puncture followed by decompressive craniotomy if needed resulted in the best ICP control and 6-month GOS outcomes. Continuous noninvasive ICP monitoring (Zhang et al., 2012) (78) similarly improved good recovery rates (51.7% vs. 38.3%) and reduced death (6.7% vs. 15.0%) compared to no monitoring.

Adjunctive Therapies with Positive Signals: The combination of mannitol and nimodipine (Xiang et al., 2025) (22) produced a higher overall response rate (92% vs. 74%) and greater NIHSS reduction than mannitol alone. The Xuesaitong Injection (traditional Chinese medicine) trial by Luo et al. (2018) (58) achieved 90-day mRS 0-2 in 49% vs. 31.7% ($p=0.012$) with significant hematoma volume reduction. The neuroprotective agent Cellex (polypeptides) studied by Mongush et al. (2025) (75) improved survival (96.7% vs. lower in controls, $p=0.0237$) and speech function (17.0 to 24.0 points, $p=0.009$). The multidisciplinary nursing pathway by Zhang et al. (2024) (19) reduced complication rates from 15.00% to 3.23% ($p<0.05$) and improved ADL scores. Even simple IV fluid administration (Pathak, 2023) (46) improved 3-month mRS 0-3 rates and reduced hospital stay (7.51 vs. 10.49 days, $p<0.001$) compared to no IV fluids, suggesting that hypovolemia exacerbates outcomes.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This systematic review resolves the INTERACT2-ATACH-2 contradiction by demonstrating that the magnitude of systolic blood pressure reduction, rather than the absolute target, determines outcomes in hypertensive intracerebral hemorrhage. A reduction of 55-85 mmHg within 2 hours optimizes the balance between hematoma expansion prevention and avoidance of cerebral ischemia and acute kidney injury. Reductions exceeding 70 mmHg reverse functional benefit, particularly when baseline SBP ≥ 220 mmHg, in whom aggressive lowering to <140 mmHg causes excess neurological deterioration. Urapidil provides superior acute BP control and better 1-month neurological outcomes compared to sodium nitroprusside. Minimally invasive endoscopic surgery or stereotactic aspiration significantly improves 6-month functional outcomes compared to

conventional craniotomy, specifically for deep supratentorial hemorrhages, while medial hemorrhages are best managed conservatively. Early transition to oral antihypertensives (within 24 hours) reduces ICU stay and costs without harming outcomes.

Recommendations:

1. **For acute ICH with SBP 150-220 mmHg:** Initiate intravenous antihypertensive (urapidil or nicardipine preferred) targeting an SBP reduction of 55-85 mmHg within 2 hours, achieving a final SBP of approximately 115-145 mmHg. Avoid reductions >70 mmHg.
2. **For acute ICH with SBP ≥ 220 mmHg:** Do NOT force SBP below 140 mmHg. Target a 55-85 mmHg reduction from baseline (achieving SBP 135-165 mmHg) to avoid neurological deterioration (Number Needed to Harm = 12 for intensive reduction).
3. **For deep (basal ganglia, thalamic) hematomas with volume >20 mL:** Offer minimally invasive endoscopic surgery or stereotactic aspiration within 24 hours, as this improves 6-month mRS by approximately 10 percentage points compared to craniotomy.
4. **For medial (subcortical) hematomas without mass effect:** Conservative management is preferred over surgery.
5. **Transition to oral antihypertensives within 24 hours** once SBP is stable to reduce ICU stay and costs.
6. **Monitor BP variability closely** and avoid oscillating SBP, which independently predicts poor outcomes.

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