# Stroke - Focused Updates in Cerebrovascular Disease

# Title: Blood pressure management after intracerebral and subarachnoid hemorrhage: the knowns and known unknowns

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**Abstract**

Blood pressure (BP) elevations often complicate the management of intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (SAH), the most serious forms of acute stroke. Despite consensus on potential benefits of BP lowering in the acute phase of ICH, controversies persist over the timing, mechanisms and approaches to treatment. BP control is even more complex for SAH, where there are rationales for both BP lowering and elevation in reducing the risks of rebleeding and delayed cerebral ischemia, respectively. Efforts to disentangle the evidence has involved detailed exploration of individual patient data from clinical trials through meta-analysis to determine strength and direction of BP change in relation to key outcomes in ICH, and which likely also apply to SAH. A wealth of hemodynamic data provides insights into pathophysiological inter-relationships of BP and cerebral blood flow. This focused update provides an overview of current evidence, knowledge gaps, and emerging concepts on systemic hemodynamics, cerebral autoregulation and perfusion, to facilitate clinical practice recommendations and future research.

# Introduction

The main forms of hemorrhagic stroke, intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (SAH), are often complicated by elevated blood pressure (BP),1,2 which in turn increases the likelihood for ongoing and recurrent hemorrhage,3,4 and death and disability.5,6 Despite considerable research effort undertaken to date, controversy persists as to the most appropriate management of BP in these two serious conditions, that globally contribute greater disability-adjusted-life-years than the more common, acute ischemic stroke. While consensus has formed as to there being benefits from initiating BP lowering early after the onset of ICH,7 uncertainty persists as to the optimal approach to such treatment in terms of timing, speed, agent(s), and target level of systolic BP to be achieved. The situation is even more complex for SAH, where BP lowering on the one hand can be justified to reduce the risk of rebleeding, but on the other hand may increase the already substantial risk of delayed cerebral ischemia (DCI).

In this review, we summarise the evidence for BP control in acute spontaneous ICH and aneurysmal SAH, acknowledge management issues germane to both conditions, and emphasize knowledge gaps and emerging concepts on systemic hemodynamics, cerebral autoregulation and perfusion. There exist similarities between cerebral small vessel disease-related ICH and aneurysmal SAH that justify this comparative consideration of approaches to acute management (Figure). We avoid reference to secondary causes of ICH, such as arteriovenous malformations or cavernomas, which are low pressure abnormalities without any relation to BP; and similarly of perimesencephalic SAH, which is characterized by a typical pattern of hemorrhage on CT and absence of an aneurysm,8 where BP is usually normal,9 rebleeding is extremely rare, and DCI does not occur.8 In drawing upon our recent epidemiological studies, systematic reviews, randomized controlled trials (RCTs) and individual participant data (IPD) meta-analysis of RCTs of BP control in acute ICH,10 we aim to provide guidance for clinical practice and future research.

## **Rationale for early BP lowering after ICH and SAH**

Elevated BP is common in acute stroke, but particularly so for hemorrhagic forms because of greater sympathomimetic activation which contributes to a worse outcome.11 In ICH, high BP is related to greater hematoma growth, most of which occurs in the first few hours after onset, and is more likely in patients presenting with large hematomas and in the context of using antithrombotic medications.12 Clinically, larger parenchymal hematomas in the cerebral hemispheres are more likely to compress vital structures and thus cause greater neurological deficits, and with extension into ventricular and subarachnoid spaces lead to hydrocephalus, which further compromises neurological function and functional recovery.13,14 It is plausible, therefore, that a key therapeutic mechanism of action for BP control in ICH is to attenuate hematoma growth,15 and thus BP should be controlled as early as possible in ICH, ideally within the first few hours of onset. Lower BP levels over the subsequent hours and several days could minimize hematoma expansion and perihematomal edema, and reduce the risks of recurrent ICH and serious ischemic events.16–18

A similar biphasic pattern of therapeutic action is also apparent for SAH. As high BP is associated with rebleeding3 and poor outcome,19 guidelines recommend to reduce high BP in the acute phase of SAH, but there is disagreement on an upper threshold for treatment, approach and target.20,21 Among the various potential triggers identified for SAH is a sudden surge in BP being responsible for rapid aneurysm growth and rupture,22 although this may have little relevance to clinical practice other than supporting the need to ensure good long-term BP control in hypertensive patients.23 Consequently, and as in ICH, patients often present with high BP after aneurysmal SAH, with increasing intracranial pressure (ICP) as a contributing factor, which can present a Scylla and Charybdis dilemma for clinicians: leaving the patient with untreated high BP runs the risk rebleeding, whilst reducing BP may increase the risk of DCI, which typically arises within several days and is the main contributor to death and disability in patients with SAH and secured aneurysms.19 Despite decades of research, the cause and treatment of DCI have not been fully resolved, and nimodipine is the only proven strategy for prevention. The mechanisms by which nimodipine exerts its beneficial effects have not been fully clarified, but its (modest) BP lowering effects may contribute.

Thus, given that early assessments of the effects of BP lowering in ICH are made within 24 hours (ie on hematoma growth and early neurological deterioration), and that guidelines recommend an early occlusion of ruptured aneurysms in SAH, preferably within 24 hours (i.e. to eliminate the risk of rebleeding, and as DCI occurs later), it seems reasonable to consider BP management in both forms of hemorrhagic stroke according to ‘acute’ and ‘subacute’ phases, defined by a 24 hour cut-point.

## **Evidence to support BP lowering after ICH**

*Acute phase*

Differing results of the two largest RCTs of early intensive BP lowering in ICH, the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT2) and Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II), intensified debate over the safety and efficacy of this treatment.24 However, a collaborative analysis that pooled IPD of the 3829 patients from these RCTs showed that achieving lower and more stable BP during 1-24 hours after ICH is associated with lower odds of hematoma growth and neurological deterioration, and better functional recovery over the subsequent 90 days.25 Moreover, there were no apparent cardiac or renal serious adverse events from achieving low systolic BP, with potential benefits evident to levels as low as 120-130 mmHg in 1-24 hours.

However, in a broader systematic review and IPD meta-analysis of 5895 patients from 16 RCTs that tested various interventions to lower BP within 7 days of ICH, there was no overall effect of the treatment on functional outcome at 90-180 days, despite a reduction in hematoma growth at 24 hours in the subset of 2510 patients from 5 RCTs with complete imaging data.10 Once again, the treatment was shown to be safe in regard to serious adverse events, including those separately defined as cardiac and renal, and for any early neurological deterioration. The IPD meta-analysis also showed heterogeneity in the effect of BP lowering treatment on functional outcome according to the strategy (fixed active agent vs. intensive BP lowering titrated to a systolic BP target) and agent. We will upon this evidence in a sectiondevoted tospecific BP targets and BP lowering agents.

Discordance between the effects of early intensive BP lowering treatment on the key outcome measures of hematoma growth and functional recovery may relate to several issues of study design and patient characteristics. First, ICH patients included in RCTs were randomized to BP lowering after a median of ~4 hours from symptom onset, which is outside the window of most hematoma growth.12 Second, these patients tended to have small-to-medium sized hematomas in deep brain locations (median ~11 mL), which are less likely to grow substantially.12 Third, there were only small differences in hematoma growth between treatment and control groups (absolute difference of ~1 mL at 24 hours); this may not be clinically relevant for individual patients but more appropriate across groups of patients as part of a standard of care protocol. Fourth, as ICH patients tend to be elderly and have multiple co-morbidities,26 the modest benefit of treatment will be diluted by medical complications, which are common in the acute period after ICH.27

Understandably, therefore, guidelines have been conservative by providing an intermediate Grade 2a level to support to their recommendations for intensive BP lowering to a systolic BP target <140 mmHg within 6 hours of symptom onset to reduce hematoma expansion and improve functional outcome after ICH.7,28

## Timing of BP lowering after ICH

A recent post-hoc subgroup analysis of the ATACH-II trial showed that intensive BP lowering (systolic target 110-139 mm Hg) with intravenous nicardipine delivered within 2 hours of ICH onset was associated with reduced hematoma growth and improved functional outcome.29 However, there was no heterogeneity in the effect of BP lowering treatment according to time to randomization in a broader IPD meta-analysis of 16 RCTs;10 but some 10-15% of the 945 patients in this subgroup received a glyceryl trinitrate (GTN) patch as part of a large pre-hospital ambulance-initiated treatment RCT (RIGHT-2) in patients with suspected acute stroke, where subgroup analysis showed patients treated with GTN had greater hematoma growth and poorer outcomes than sham-GTN controls.30 These data suggest that very early use of GTN might promote vasodilation or disrupt hemostatic mechanisms in ICH, and this may have modified the signal for potential benefits from other BP lowering interventions delivered within 2 hours of ICH onset in the IPD meta-analysis.10 However, as such subgroup analysis is prone to chance findings and confounding, further data on the effects of ultra-early BP lowering are required as is being undertaken in the Intensive Ambulance-delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial (INTERACT4, *ClinicalTrials.gov* Identifier: NCT03790800).31

## Target systolic BP level after ICH

RCTs of BP lowering interventions within 7 days of acute ICH have tested various strategies and BP targets with mixed results. In the aforementioned IPD meta-analysis of 16 RCTs, there was heterogeneity in the treatment effect according to BP lowering strategy: ICH patients with titration of treatment to a systolic BP target appeared to have better outcomes than patients treated with a fixed agent without a specified target.10 These data support the pooled IPD analysis of INTERACT2 and ATACH-II of potential benefits to systolic levels as low as 120-130 mmHg.25 However, a ‘one-size-fits-all’ approach to up-, down- or cross-titrate BP lowering to achieve an effective target, at the lowest dose, and without causing hypotension and other side effects, is often challenging in practice.7,28 Avoiding a rapid, large reduction in systolic BP may be important: emerging data suggests systolic reductions of greater than ~70 mmHg in 1 hour are associated with poor functional recovery after small-to-medium volume ICH, with a ‘sweet spot’ for better outcome exists for reductions of between ~30-45 mmHg over 1 hour.32 Concerns also remain regarding extreme reductions in systolic BP and increased risk of acute kidney injury.33 However, the possibility of reverse causality exists in these observational analyzes (i.e. patients with larger baseline ICH volumes with inherently poor prognosis may have presented with higher baseline BP and had larger reductions in their systolic BP) and further randomized data are required.

## **Evidence to support BP control after SAH**

*Acute phase*

Observations that high BP after aneurysmal SAH is related to poor outcome, and that treating high BP can reduce rebleeding, have existed from almost half a century.34 Moreover, the lack of any apparent benefit on clinical outcome from BP lowering on rebleeding has been explained by the treatment being offset by an increased risk of DCI,35 and subsequently little progress has been made in resolving this dichotomy. In a recent study that compared rebleeding between a hospital with a policy of aggressive BP lowering versus one with a more liberal approach, the trend was for rebleeding to be lower in the former, but this was not statistically significant.36 Nevertheless, given the relation between high BP and risk of rebleeding, and of rebleeding and poor outcome, guidelines recommend that high BP should be treated in the acute phase of SAH. The European Stroke Organization (ESO) guidelines, for example, recommend treatment if systolic BP exceeds 180 mmHg, starting with analgesics and nimodipine, and continuing as necessary to maintain a mean arterial pressure of >90 mmHg.20 The American Heart Association (AHA) / American Stroke Association (ASA) guidelines similarly recommend treatment with a titratable agent but according to a lower threshold of systolic BP <160 mmHg.21

An RCT is clearly required to provide the necessary evidence to define the balance of potential benefits and risks of BP lowering in the acute phase of SAH. However, since the risk of rebleeding in patients undergoing early aneurysm occlusion is around 10% to 15%, and strict BP control does not eliminate rebleeding, such an RCT would need to include several thousands of patients, making it an ambitious endeavour.37,38 Since emergency clipping, that is clipping within the initial hours after admission on a 24/7 basis, has a modest treatment effect, if at all, and its cost-effectiveness is uncertain due to the high burden on resources,39 a RCT of BP lowering should be a high priority, as it is a promising strategy to improve outcome that could be initiated during the transport of patients by ambulance to an appropriate facility.

*Subacute phase*

After aneurysm occlusion, the most important complication is DCI, which typically occurs between 4 to 12 days after SAH. Traditionally, DCI has been linked to vasospasm, and to such an extent that the terms are used synonymously. However, since not all patients with vasospasm develop DCI, and not all patients with DCI have vasospasm, vasospasm is neither a sufficient nor a necessary factor, for the development of DCI. Given the relation between vasospasm and DCI, and the observation that it is associated with hypovolemia, the combination of hemodilution, hypervolemia and hypertension, the so-called triple H therapy, has been the mainstay of medical prevention and treatment of DCI for decades. The rationale behind this treatment is to improve cerebral perfusion, but supporting RCT evidence has been lacking.40 A systematic review showed no evidence from controlled studies for a positive effect of triple-H or its separate components on cerebral blood flow (CBF) in SAH,41 but uncontrolled studies have suggested that hypertension is more effective than hemodilution or hypervolemia at increasing CBF.

# These findings led to the Hypertension Induction in the Management of AneurysmaL subArachnoid Haemorrhage with Secondary IschemiA (HIMALAIA) RCT to determine the effectiveness of induced hypertension in patients with symptoms of DCI after SAH. Unfortunately, the RCT was stopped prematurely after the first interim analysis, due to slow patient recruitment and futility of the treatment on CBF. Despite a higher mean arterial BP in the intervention group, there was no statistical difference in CBF between the intervention and control groups.42 Although the RCT lacked statistical power for reliable estimates due to early termination, there was no hint of improved functional outcome from the intervention,43 but rather of a trend towards more serious adverse events (odds ratio [OR] 2.1, 95% confidence interval [CI] 0.9-5.0). A systematic review performed to put the results into context identified no other controlled studies on the effect of induced hypertension. There were nine uncontrolled studies (totalling 187 patients), reporting on clinical improvement after instalment of induced hypertension, in some combined with hypervolemia, or in case of no response, with balloon angioplasty or intra-arterial treatment with vasodilators. Most studies reported clinical improvement in most patients but seven (285 patients) reported complications, the most serious being cardiac arrhythmia, pulmonary edema, hemorrhagic transformation, and intracranial bleeding in up to 50%, and death in up to 25%, of patients.43 Thus, despite the possibility of an initial clinical improvement with induced hypertension, there is uncertainty as to whether this treatment improves overall outcome, yet there is reasonable evidence that it increases the risk of serious complications. Other explanations for the lack of efficacy of induced hypertension is that it only benefits the subgroup of patients who develop DCI, or that the increase of BP is too little, too late, or too short. Thus, another RCT is clearly warranted, but again this will require a large international effort.

## **Agents for BP lowering**

The ideal agent for BP lowering is one that is well tolerated and easily titratable to achieve and maintain a desired BP target without excessive BP variability, and with minimal influence on cerebral vasodilation and hemostasis that might enhance ongoing hemorrhage. However, there are regional differences in the availability of intravenous BP lowering agents: nicardapine (calcium channel blocker) is favored in North America,44 whereas urapidil (α-adrenoreceptor blocker) is popular in China.45 Other agents include adrenoreceptor blockers (labetalol and metoprolol), other calcium channel blockers (nimodipine), nitrates, diuretics, renin-angiotensin system blockers, hydralazine and nitroprusside. Despite clevidipine monotherapy being shown to be effective, safe and associated with minimal hematoma expansion during rapid BP lowering in ICH,46 there has been less interest in this agent compared to nicardipine. There may be heterogeneity in the effects (and safety) of various BP lowering agents, according to those most frequently used in the treatment group of 16 RCTs in the IPD meta-analysis.10 Patients who received α- and β-adrenoreceptor blockers appeared to have better outcomes from active/intensive BP lowering, compared to patients who had renin-angiotensin system blockers, calcium channel blockers, nitrates and magnesium sulfate. These findings suggest that α- and β-adrenoreceptor blockers may benefit from blocking the autonomic response that has been shown to drive the hypertensive response from critical illness.11 However, further research is required to substantiate these findings.

Class I evidence exists for the use of nimodipine, an L-type calcium channel antagonist, in patients with SAH,47 which improves clinical outcome by reducing the risk of DCI. An important consideration, aside from its beneficial effect, are its BP lowering effects, of which significantly lowering diastolic BP (>20% from baseline) alone is associated with unfavorable outcome in acute ischemic stroke.48 Some authors, therefore, favor combining nimodipine with vasopressors in patients after aneurysm occlusion for SAH. Interestingly, the safety of nimodipine in ICH was shown in a small comparative study, where a reduction in ICP was seen during its administration but not afterwards.49

## **Emerging mechanistic concepts underlying BP lowering**

Improved understanding of systemic hemodynamics and cerebral autoregulation may provide insights to allow BP lowering strategies to be optimized in acute ICH,50 as well as other hypertensive emergencies, without compromising cerebral perfusion.51 In SAH, systolic BP peaks >150 mmHg are associated with increased risk of re-rupture of a cerebral aneurysm, which has a high (>50%) case fatality. A recent comprehensive review involving 95 patients over three ICH studies and 413 patients over eight SAH studies showed that impairment of dynamic cerebral autoregulation, mainly measured by transcranial doppler, is associated with poor outcome.50

Although ICH patients have a significant burden of cerebral small vessel disease, where cerebral blood flow and autoregulation are likely impaired, this does not appear to modify the effects of intensive BP lowering.52–54 Data from patients after symptomatic lacunar infarction (which is a component of cerebral small vessel disease) show impaired dynamic cerebral autoregulation globally (middle cerebral and posterior cerebral arteries) which is maintained consistently over the subsequent six months.55 Similarly, meta-analyses have demonstrated lower cerebral blood flow velocity (CBFV) and cerebral autoregulation ipsilaterally in acute ICH.56,57 Again moderate BP lowering does not appear to significantly influence these parameters58 but may reduce perihematomal edema.16

Yet, impaired cerebrovascular tone and resistance are implicated in acute ICH, systemic BP change may drive alterations in cerebral autoregulation, and thus tone, that triggers a vasoconstrictor cascade. Whilst this may be a protective mechanism, designed to maintain perfusion in the presence of a hematoma and potential penumbra, hemodynamic disturbance that arises from intensive BP lowering may compromise homeostatic mechanisms on cerebral blood flow in a damaged vascular network.

In the era of increasing magnetic resonance imaging (MRI) in acute ICH, ischemic complications after ICH are increasingly recognized but their etiology and prognosis remains uncertain. ICH patients with a high burden of white matter hyperintensities on MRI imaging do appear to have worse ICH-related outcomes.54 However, data are contradictory with regard to the severity of white matter hyperintensities, with mild grades being associating with risk of ischemic stroke and advanced grades with ICH. There are reassuring perfusion data during hypertensive states after acute ischemic stroke, with labetalol and sublingual GTN precipitating increased volumes of hypoperfused tissue,59 but again the etiology and prognosis of such lesions remains unclear. Whilst exploratory data have raised questions as to whether diffusion-weighted MRI hyperintense lesions are associated with BP lowering or indeed predict poor outcome,60 definitive data are lacking and specifically regarding the temporal relationship between BP change after ICH in relation to various vasoactive and perfusion altering factors on BP (pre- and post-lowering), carbon dioxide (CO2) level,61 and head position.62 Reassuringly, CBF appears to remain stable with acute BP lowering in ICH, which suggests that cerebral autoregulation is maintained in this state, albeit in those with mild-moderate sized hematomas. Importantly, the lack of foresight over various central and peripherally influencing hemodynamic factors, post-hoc analyses of RCTs have largely disregarded hemodynamic perturbations as the cause for adverse diffusion weighted MRI ischemic lesions in ICH.60

Spontaneous hyperventilation (defined as PaCO2 <35 mmHg and pH >7.45) occurs in SAH and ICH,61,63 where it is associated with DCI and poor neurological outcome in the former.63 In ICH, there is evidence that lower pCO2 (secondary spontaneous hyperventilation) is associated with increased risk of ischemic lesions in the context of BP reduction, and that hypocapnia alters CBF by widening the plateau on the autoregulatory curve. It appears, therefore, that hypocapnia is an important mediator of cerebral ischemia.

The phenomenon of cerebral ischemia being precipitated by uncontrolled ICP and low cerebral perfusion pressure (CPP) after SAH is well recognized. Thus, strategies to avoid increased ICP and support high CPP values where there is the potential for vasospasm may improve outcome after SAH.64 A focus on cerebral autoregulation after SAH has long preceded investigation in ICH,65 with non-invasive ultrasound based technologies being embedded into clinical practice to assess for vasospasm, determine CBF, and assess static and dynamic cerebral autoregulation.66 Several large studies have confirmed impaired cerebral autoregulation in SAH, with granularity over pathophysiology and response to interventions being particularly informative. Specifically, impaired autoregulation is related to reduce level of consciousness,67 despite there being no difference in autoregulation between those with and without symptomatic vasospasm.68

**BP lowering in the context of raised ICP**

Although elevated ICP can initially impair CBF and cerebrospinal fluid exchange, and later cause cerebral ischemia and herniation, our understanding of the relationship between BP and ICP in ICH is limited, as is the broader management of cerebral edema in general. Any deviation from a normal ICP (range 7-15 mmHg) and excessive variability, are associated with poor prognosis in ICH.69 Raised ICP is related to impaired dynamic cerebral autoregulation,70 but it is unclear whether larger hematomas cause high ICP, low compliance and impaired myogenic response, or is it solely that high ICP leads to lower cerebral perfusion pressure.71 To date, there have been no RCTs of the effects of ICP monitoring after ICH,7,72 and in SAH. One single center RCT suggests that tailoring treatment according to mean ICP wave amplitude (MWA) rather than absolute values results in better clinical outcome,73 while several small studies have shown variable changes in ICP from different BP lowering agents. Clearly, larger mechanistic studies are needed.74

Uncertainty remains as to whether BP lowering benefits the sickest patients after ICH: those with large hematomas (>50 mL) who are at high risk of cerebral hypoperfusion from both the treatment and high ICP, with consequently low CPP.24 RCTs have failed to include large numbers of such patients, and only smaller mechanistic studies have shown low CPP without attention to interventions such as BP lowering. The international Third, Intensive Care Bundle With Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT3, *ClinicalTrials.gov* Identifier: NCT03209258) endeavours to provide further evidence for goal-directed care bundle including early intensive BP lowering in a broad range of patients with acute ICH, using a multicenter, stepped wedge cluster randomized design.75

In SAH, much of our understanding of thresholds and approaches to care have been extrapolated from patients with traumatic brain injury, the distinction clearly is around bleeding risks and relationship to ICH change, an RCT in this area is a high priority.76

**Summary**

This focused update has outlined the current evidence, knowledge gaps, and emerging concepts on systemic hemodynamics, cerebral autoregulation and perfusion. We summarize several clinical research priorities in ICH and SAH (Box). Specifically, the emergence of PaCO2 change as an important modifier of response to intervention (BP lowering) and prognostic marker may allow ultra-acute data on systemic and cerebral hemodynamics in ICH to be obtained, particularly pre- and post-BP agent delivery. Given the overlap in clinical questions, pathophysiology and complications across these two subtypes of hemorrhagic stroke, we call for greater international and cross-disciplinary capacity-building collaborations between ICH and SAH researchers. There is potential value in further IPD meta-analyses of RCT data to understand differences in ICH associated with SAH, and vice versa, but also in using novel platform registries with nested RCTs that can address multiple research questions within a common infrastructure. Although less ideal for assessing effectiveness, the use of propensity-score matching and artificial intelligence methodologies of large prospective cohort datasets can allow an assessment of all aspects of patient management. Lastly, by considering the pathophysiological overlap between ICH and SAH, we may better understand the potential benefits of pharmacological agents in both contexts rather than isolation (e.g. is there a role for nimodipine in ICH?).

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**Figure Legend**

**Figure:** *Spot the difference*: similarities between cerebral small vessel disease-related intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (SAH)

Footnote: BP denotes blood pressure

**Box:** Clinical priorities for evaluating blood pressure lowering in intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (SAH)

**Figure**



# Box:

**Clinical priorities in ICH**

* Determine safety of ultra-acute pre-hospital BP lowering and determine acceptable agents
* Discern complex interplay between ICH and BP lowering, pre-existing cerebral small vessel disease and new white matter ischemic lesions
* Determine the directionality of carbon dioxide change post-ICH and clinical outcome
* Understand the effects of BP lowering on ICP in ICH

**Clinical priorities in SAH**

* Randomized data on BP lowering in SAH until point of aneurysm occlusion is needed
* Characterize differences in response to management and outcome of SAH with and without ICH
* Investigate the benefits of BP control in the sub-acute phase post SAH

**Recommended approaches**

* International cross-disciplinary capacity-building collaborations between ICH and SAH researchers
* Individual patient data meta-analyses of trial data to understand differences in ICH associated with SAH and vice versa
* Platform ICH registries with nested clinical trials
* Consider pathophysiological overlap between ICH and SAH and potential benefits of pharmacological agents in both contexts rather than isolation

# References

1. Qureshi A, Ezzeddine M, Nasar A, Suri M, Kirmani J, Hussein H, Divani A, Reddi A. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med.* 2007;25:32–38.

2. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:2315–2321.

3. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28:2370–2375.

4. Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. *Stroke*. 2001;32:1176–1180.

5. Zhang Y, Reilly KH, Tong W, Xu T, Chen J, Bazzano LA, Qiao D, Ju Z, Chen CS, He J. Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. *J. Hypertens.* 2008;26:1446–52.

6. Faust K, Horn P, Schneider UC, Vajkoczy P. Blood pressure changes after aneurysmal subarachnoid hemorrhage and their relationship to cerebral vasospasm and clinical outcome. *Clin. Neurol. Neurosurg.* 2014;125:6–40.

7. Sandset EC, Anderson CS, Bath PM, Christensen H, Fischer U, Gąsecki D, Lal A, Manning LS, Sacco S, Steiner T, et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *Eur. Stroke J.* 2021;6:48–89.

8. Mensing LA, Vergouwen MDI, Laban KG, Ruigrok YM, Velthuis BK, Algra A, Rinkel GJE. Perimesencephalic hemorrhage: a review of epidemiology, risk factors, presumed cause, clinical course, and outcome. *Stroke*. 2018;49:1363–70.

9. Rinkel GJE, Wijdicks EFM, Vermeulen M, Hasan D, Brouwers PJAM, van Gijn J. The clinical course of perimesencephalic nonaneurysmal subarachnoid hemorrhage. *Ann. Neurol.* 1991;29:463–8.

10. Moullaali TJ, Wang X, Sandset EC, Woodhouse LJ, Law ZK, Arima H, Butcher KS, Chalmers J, Delcourt C, Edwards L, et al. Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *J. Neurol. Neurosurg. Psychiatry*. 2021;jnnp-2021-327195.

11. Wang X, Sandset EC, Moullaali TJ, Chen G, Song L, Carcel C, Delcourt C, Woodward M, Robinson T, Chalmers J, et al. Determinants of the high admission blood pressure in mild-to-moderate acute intracerebral hemorrhage. *J. Hypertens.* 2019;37:1463–1466.

12. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet. Neurol.* 2018;17:885–894.

13. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175–1181.

14. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score. *Stroke*. 2001;32:891–897.

15. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. 2018;392:1257–1268.

16. Leasure AC, Qureshi AI, Murthy SB, Kamel H, Goldstein JN, Walsh KB, Woo D, Shi FD, Huttner HB, Ziai WC, et al. Intensive blood pressure reduction and perihematomal edema expansion in deep intracerebral hemorrhage. *Stroke*. 2019;50:2016–2022.

17. Manning LS, Robinson TG. New insights into blood pressure control for intracerebral haemorrhage. *Front. Neurol. Neurosci.* 2015;37:35–50.

18. Leasure AC, Qureshi AI, Murthy SB, Kamel H, Goldstein JN, Woo D, Ziai WC, Hanley DF, Al-Shahi Salman R, Matouk CC, et al. Association of intensive blood pressure reduction with risk of hematoma expansion in patients with deep intracerebral hemorrhage. *JAMA Neurol.* 2019;76:949–955.

19. Stienen MN, Germans M, Burkhardt JK, Neidert MC, Fung C, Bervini D, Zumofen D, Roethlisberger M, Marbacher S, Maduri R, et al. Predictors of in-hospital death after aneurysmal subarachnoid hemorrhage: analysis of a nationwide database (Swiss SOS [Swiss Study on Aneurysmal Subarachnoid Hemorrhage]). *Stroke*. 2018;49:333–340.

20. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc. Dis.* 2013;35:93–112.

21. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–37.

22. Vlak MHM, Rinkel GJE, Greebe P, Van Der Bom JG, Algra A. Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study. *Stroke*. 2011;42:1878–82.

23. MacLeod MR, White PM. Not tonight, darling, I might get a headache. *Stroke*. 2011;42:1807–1808.

24. Anderson CS, Selim MH, Molina CA, Qureshi AI. Intensive blood pressure lowering in intracerebral hemorrhage. *Stroke*. 2017;48:2034–2037.

25. Moullaali TJ, Wang X, Martin RH, Shipes VB, Robinson TG, Chalmers J, Suarez JI, Qureshi AI, Palesch YY, Anderson CS. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol.* 2019;18:857–864.

26. Samarasekera N, Fonville A, Lerpiniere C, Farrall AJ, Wardlaw JM, White PM, Smith C, Al-Shahi Salman R, Addison A, Ahmad K, et al. Influence of intracerebral hemorrhage location on incidence, characteristics, and outcome:population-based study. *Stroke*. 2015;46:361–368.

27. Sidhartha JM, Purma AR, Reddy LVPK, Sagar NK, Teja MP, Subbaiah MV, Purushothaman M. Risk factors for medical complications of acute hemorrhagic stroke. *J. Acute Dis.* 2015;4:222–225.

28. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke*. 2015;46:2032–2060.

29. Li Q, Warren AD, Qureshi AI, Morotti A, Falcone GJ, Sheth KN, Shoamanesh A, Dowlatshahi D, Viswanathan A, Goldstein JN. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. *Ann. Neurol.* 2020;88:388–395.

30. Bath PM, Woodhouse LJ, Krishnan K, Appleton JP, Anderson CS, Berge E, Cala L, Dixon M, England TJ, Godolphin PJ, et al. Prehospital transdermal glyceryl trinitrate for ultra-acute intracerebral hemorrhage: data from the RIGHT-2 trial. *Stroke*. 2019;50:3064–3071.

31. Song L, Chen C, Chen X, Guo Y, Liu F, Lin Y, Billot L, Li Q, Liu H, Si L, et al. INTEnsive ambulance-delivered blood pressure Reduction in hyper-ACute stroke Trial (INTERACT4): study protocol for a randomized controlled trial. *Trials*. 2021;in press.

32. Wang X, Di Tanna GL, Moullaali TJ, Martin RH, Shipes VB, Robinson TG, Chalmers J, Suarez JI, Qureshi AI, Palesch YY, et al. J-shape relation of blood pressure reduction and outcome in acute intracerebral hemorrhage: a pooled analysis of INTERACT2 and ATACH-II individual participant data. *Int. J. stroke*. 2021;in press (accepted November 2021).

33. Uniken Venema S, Van den Berg S, Nederkoorn P, Van Der Worp B. Multicentre randomised trial of acute stroke treatment in the ambulance with a nitroglycerin patch (MR ASAP). *Eur. Stroke J.* [Internet]. 2021;6:514–543. Available from: https://doi.org/10.1177/23969873211044666

34. Torner JC, Kassell NF, Wallace RB, Adams HP. Preoperative prognostic factors for rebleeding and survival in aneurysm patients receiving antifibrinolytic therapy: report of the cooperative aneurysm study. *Neurosurgery*. 1981;9:506–513.

35. Wijdicks EFM, Vermeulen M, Murray GD, Hijdra A, van Gijn J. The effects of treating hypertension following aneurysmal subarachnoid hemorrhage. *Clin. Neurol. Neurosurg.* 1990;92:111–117.

36. Calviere L, Gathier C, Rafk M, Koopman I, Rousseau V, Albucher J, Geeraerts T, Rinkel G, Olivot J, Vergouwen M. Rebleeding rate in two comprehensive stroke units using different blood pressure management. *Int. J. Stroke*. 2018;12:54–55.

37. Oheda M, Inamasu J, Moriya S, Kumai T, Kawazoe Y, Nakae S, Kato Y, Hirose Y. Early rebleeding in patients with subarachnoid haemorrhage under intensive blood pressure management. *J. Clin. Neurosci.* 2015;22:1338–42.

38. Post R, Germans MR, Tjerkstra MA, Vergouwen MDI, Jellema K, Koot RW, Kruyt ND, Willems PWA, Wolfs JFC, de Beer FC, et al. Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial. *Lancet*. 2021;397:112–118.

39. Tack RWP, Vergouwen MDI, van der Schaaf I, van der Zwan A, Rinkel GJE, Lindgren AE. Preventable poor outcome from rebleeding by emergency aneurysm occlusion in patients with aneurysmal subarachnoid haemorrhage. *Eur. Stroke J.* 2019;4:240–6.

40. Rinkel GJ, Feigin VL, Algra A, van Gijn J. Circulatory volume expansion therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst. Rev.* 2004;4:CD000483.

41. Dankbaar JW, Slooter AJC, Rinkel GJE, Schaaf ICVD. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: A systematic review. *Crit. Care*. 2010;14:R23.

42. Gathier CS, Dankbaar JW, Van Der Jagt M, Verweij BH, Oldenbeuving AW, Rinkel GJE, Van Den Bergh WM, Slooter AJC. Effects of induced hypertension on cerebral perfusion in delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a randomized clinical trial. *Stroke*. 2015;46:3277–81.

43. Gathier CS, Van Den Bergh WM, Van Der Jagt M, Verweij BH, Dankbaar JW, Müller MC, Oldenbeuving AW, Rinkel GJE, Slooter AJC. Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage a randomized clinical trial. *Stroke*. 2018;49:76–83.

44. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N. Engl. J. Med.* 2016;375:1033–43.

45. Anderson C, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med.* 2013;368:2355–2365.

46. Graffagnino C, Bergese S, Love J, Schneider D, Lazaridis C, Lapointe M, Lee K, Lynch G, Hu MY, Williams GC. Clevidipine rapidly and safely reduces blood pressure in acute intracerebral hemorrhage: the ACCELERATE trial. *Cerebrovasc. Dis.* 2013;36:173–80.

47. Bederson JB, Connolly ES, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE, Harbaugh RE, Patel AB, Rosenwasser RH. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009;40:994–1025.

48. Ahmed N, Näsman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. *Stroke*. 2000;31:1250–5.

49. Li Y, Fang W, Tao L, Li M, Yang Y, Gao Y, Ge S, Gao L, Zhang B, Li Z, et al. Efficacy and safety of intravenous nimodipine administration for treatment of hypertension in patients with intracerebral hemorrhage. *Neuropsychiatr. Dis. Treat.* 2015;19:1231–8.

50. Nogueira RC, Aries M, Minhas JS, H Petersen N, Xiong L, Kainerstorfer JM, Castro P. Review of studies on dynamic cerebral autoregulation in the acute phase of stroke and the relationship with clinical outcome. *J. Cereb. blood flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* 2021;271678X211045222.

51. Robinson TG, Minhas JS, Miller J. Review of major trials of acute blood pressure management in stroke. *J. Cereb. Blood Flow Metab.* 2021;271678X211004310.

52. Sato S, Delcourt C, Heeley E, Arima H, Zhang S, Al-Shahi Salman R, Stapf C, Woo D, Flaherty ML, Vagal A, et al. Significance of cerebral small-vessel disease in acute intracerebral hemorrhage. *Stroke*. 2016;47:701–7.

53. Shoamanesh A, Morotti A, Romero JM, Oliveira-Filho J, Schlunk F, Jessel MJ, Ayres AM, Vashkevich A, Schwab K, Afzal MR, et al. Cerebral microbleeds and the effect of intensive blood pressure reduction on hematoma expansion and functional outcomes a secondary analysis of the ATACH-2 randomized clinical trial. *JAMA Neurol.* 2018;75:850–859.

54. Morotti A, Shoamanesh A, Oliveira-Filho J, Schlunk F, Romero JM, Jessel M, Ayres A, Vashkevich A, Schwab K, Cassarly C, et al. White matter hyperintensities and blood pressure lowering in acute intracerebral hemorrhage: a secondary analysis of the ATACH-2 trial. *Neurocrit. Care*. 2020;32:180–186.

55. Guo ZN, Xing Y, Wang S, Ma H, Liu J, Yang Y. Characteristics of dynamic cerebral autoregulation in cerebral small vessel disease: diffuse and sustained. *Sci. Rep.* 2015;5:15269.

56. Minhas JS, Panerai RB, Ghaly G, Divall P, Robinson TG. Cerebral autoregulation in hemorrhagic stroke: a systematic review and meta-analysis of transcranial doppler ultrasonography studies. *J. Clin. Ultrasound*. 2018;47:14–21.

57. Minhas JS, Panerai RB, Swienton D, Robinson TG. Feasibility of improving cerebral autoregulation in acute intracerebral hemorrhage (BREATHE-ICH) study: results from an experimental interventional study. *Int. J. Stroke*. 2020;15:627–637.

58. Butcher KS, Jeerakathil T, Hill M, Demchuk AM, Dowlatshahi D, Coutts SB, Gould B, McCourt R, Asdaghi N, Findlay JM, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial. *Stroke*. 2013;44:620–626.

59. Kate M, Asdaghi N, Gioia LC, Buck B, Majumdar SR, Jeerakathil T, Shuaib A, Emery D, Beaulieu C, Butcher K. Blood pressure reduction in hypertensive acute ischemic stroke patients does not affect cerebral blood flow. *J. Cereb. Blood Flow Metab.* 2019;39:1878–1887.

60. Shoamanesh A, Cassarly C, Morotti A, Romero JM, Oliveira-Filho J, Schlunk F, Jessel M, Butcher K, Gioia L, Ayres A, et al. Intensive blood pressure lowering and DWI lesions in intracerebral hemorrhage: exploratory analysis of the ATACH-2 randomized trial. *Neurocrit. Care*. 2021;10.1007/s12028-021-01254-9.

61. Hextrum S, Minhas JS, Liotta EM, Sorond FA, Naidech AM, Maas MB. Hypocapnia, ischemic lesions, and outcomes after intracerebral hemorrhage. *J. Neurol. Sci.* 2020;418:117139.

62. Minhas JS, Wang X, Lavados PM, Moullaali TJ, Arima H, Billot L, Hackett ML, Olavarria V V, Middleton S, Pontes-Neto O. Head positioning and blood pressure variability in acute ischaemic and haemorrhagic stroke: a post-hoc analysis of the HeadPoST study. *J. Hum. Hypertens.* 2019;33:411–418.

63. Williamson CA, Sheehan KM, Tipirneni R, Roark CD, Pandey AS, Thompson BG, Rajajee V. The association between spontaneous hyperventilation, delayed cerebral ischemia, and poor neurological outcome in patients with subarachnoid hemorrhage. *Neurocrit. Care*. 2015;23:330–338.

64. Svedung Wettervik T, Howells T, Lewén A, Ronne-Engström E, Enblad P. Temporal Dynamics of ICP, CPP, PRx, and CPPopt in high-grade aneurysmal subarachnoid hemorrhage and the relation to clinical outcome. *Neurocrit. Care*. 2021;34:390–402.

65. Heilbrun MP, Olesen J, Lassen NA. Regional cerebral blood flow studies in subarachnoid hemorrhage. *J. Neurosurg.* 1972;37:36–44.

66. Lidington D, Wan H, Bolz SS. Cerebral autoregulation in subarachnoid hemorrhage. *Front. Neurol.* 2021;12:688362.

67. Tenjin H, Hirakawa K, Mizukawa N, Yano I, Ohta T, Uchibori M, Hino A, Carter LP. Dysautoregulation in patients with ruptured aneurysms: Cerebral blood flow measurements obtained during surgery by a temperature-controlled thermoelectrical method. *Neurosurgery*. 1988;23:705–9.

68. Cossu M, Gennaro S, Balestrero M, Rossi A. Autoregulation of cortical blood flow during surgery for ruptured intracranial aneurysms. *J. Neurosurg. Sci.* 1999;43:99–105.

69. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J. Neurol. Neurosurg. Psychiatry*. 2004;75:813–821.

70. Panerai RB, Hudson V, Fan L, Mahony P, Yeoman PM, Hope T, Evans DH. Assessment of dynamic cerebral autoregulation based on spontaneous fluctuations in arterial blood pressure and intracranial pressure. *Physiol. Meas.* 2002;23:59–72.

71. Nakagawa K, Serrador JM, LaRose SL, Sorond FA. Dynamic cerebral autoregulation after intracerebral hemorrhage: a case-control study. *BMC Neurol.* 2011;11:108.

72. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, Forsting M, Harnof S, Klijn CJM, Krieger D, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int. J. Stroke*. 2014;9:840–855.

73. Eide PK, Bentsen G, Sorteberg AG, Marthinsen PB, Stubhaug A, Sorteberg W. A randomized and blinded single-center trial comparing the effect of intracranial pressure and intracranial pressure wave amplitude-guided intensive care management on early clinical state and 12-month outcome in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2011;69:1105–1115.

74. Kadicheeni M, Robinson TG, Divall P, Parry-Jones AR, Minhas JS. Therapeutic variation in lowering blood pressure: effects on intracranial pressure in acute intracerebral haemorrhage. *High Blood Press. Cardiovasc. Prev.* 2021;28:115–128.

75. Song L, Hu X, Ma L, Chen X, Ouyang M, Billot L, Li Q, Munoz-Venturelli P, Abanto C, Pontes-Neto O, et al. INTEnsive care bundle with blood pressure Reduction in Acute Cerebral Hemorrhage trial (INTERACT3): study protocol for a pragmatic stepped-wedge cluster-randomized controlled trial. *Trials*. 2021;in press.

76. Alotaibi NM, Wang JZ, Pasarikovski CR, Guha D, Al-Mufti F, Mamdani M, Saposnik G, Schweizer TA, Loch Macdonald R. Management of raised intracranial pressure in aneurysmal subarachnoid hemorrhage: time for a consensus? *Neurosurg. Focus*. 2017;43:E13.