Published in final edited form as:

Stroke. 2022 April ; 53(4): 1074–1084. doi:10.1161/STROKEAHA.121.036143.

BLOOD PRESSURE MANAGEMENT FOR ISCHEMIC STROKE IN THE FIRST 24 HOURS

Philip M Bath, DSc FMedSci[1,2], **Lili Song, MD PhD**[3,4], **Gisele S Silva, MD PhD**[5], **Eva Mistry, MBBS MSCI**[6], **Nils Petersen, MD MSc**[7], **Georgios Tsivgoulis, MD PhD**[8], **Mikael Mazighi, MD PhD**[9], **Oh Young Bang, MD PhD**[10], **Else Charlotte Sandset, MD PhD**[11,12]

[1.]Stroke Trials Unit, Mental Health and Clinical Neuroscience, University of Nottingham, Nottingham NG7 2UH UK

[2.]Stroke, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH UK

[3.]The George Institute China at Peking University Health Science Center, Beijing, PR China

[4.]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

[5.]Neurology, Federal University of São Paulo (UNIFESP) and Hospital Israelita Albert Einstein, São Paulo Brazil

[6.]Department of Neurology and Rehabilitation Medicine, University of Cincinnati, 260 Stetson St, Suite 2310, Cincinnati, OH 45219 USA

[7.]Department of Neurology, Divisions of Vascular Neurology and Neurocritical Care, Yale School of Medicine, New Haven, USA

[8.]Second Department of Neurology, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[9.]Department of Neurology, Lariboisiere hospital, and interventional Neuroradiology, Fondation Rothschild hospital, University of Paris, INSERM 1148, FHU Neurovasc, Paris, France

[10.]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

[11.]Stroke Unit, Department of Neurology, Oslo University Hospital, Oslo, Norway

[12.]The Norwegian Air Ambulance Foundation, Oslo, Norway

Abstract

High blood pressure (BP) is common after ischemic stroke and associated with a poor functional outcome and increased mortality. The conundrum then arises on whether to lower BP to improve outcome or whether this will worsen cerebral perfusion due to aberrant cerebral autoregulation. A number of large trials of BP-lowering have failed to change outcome whether treatment was started prehospital in the community or hospital. Hence, nuances on how to manage high BP

Corresponding author: Professor Philip Bath, Stroke Trials Unit, University of Nottingham, South floor, D floor, Queen's Medical Centre, Nottingham NG7 2UH, UK, philip.bath@nottingham.ac.uk.

are likely, including whether different interventions are needed for different causes, the type and timing of the drug, how quickly BP is lowered, and the collateral effects of the drug, including on cerebral perfusion and platelets. Specific scenarios are also important, including when to lower BP before, during, and after intravenous thrombolysis and endovascular therapy/thrombectomy, when it may be necessary to raise BP and when antihypertensive drugs taken before stroke should be restarted. This narrative review addresses these and other questions. Although further large trials are ongoing, it is increasingly likely that there is no simple answer. Different subgroups of patients may need to have their BP lowered (e.g. prior to or after thrombolysis), left alone, or elevated.

INTRODUCTION

Managing blood pressure (BP) in the acute phase of ischemic stroke is an important problem in stroke care, with high BP present in 70% of patients. Typical decisions relate to patients needing reperfusion. Guidelines recommend that high BP exceeding 185/110 mmHg be lowered before thrombolysis [1, 2] but without specifying what drug(s) to use and what target BP should be lowered. Outside of thrombolysis, there is even less certainty. Although the management of BP in acute stroke has been debated since 1985,[3–5] there has been little advance in our knowledge over the last 35 years despite the completion of numerous randomized-controlled clinical trials (RCTs), almost all of which were neutral or negative for effect on functional outcome. As a result, the management of BP in acute ischemic stroke remains controversial.[6, 7]

Simply lowering BP does not seem to alter outcome in the acute phase of ischemic stroke, and clearly, some nuances need to be considered. First, the causes of high BP are multitudinous and vary between patients.[8] High BP in the acute stroke setting can be proactive and/or reactive to the stroke. In this respect, treating hypertension that contributed to the stroke may make more sense than lowering BP that increased in response to the stroke, as occurs with increasing intracranial pressure. Second, antihypertensive drug classes vary in their targets and hormonal and collateral effects, so administering one class may be more appropriate than using another. For example, targeting the renin-angiotensin-aldosterone system (RAAS) may be unhelpful if hypertension is related to sympathetic stimulation. Equally, using ß-blockers may be inappropriate in low cardiac output states. Third, timing may be critical; for example, lowering BP in the ultra-acute period may be hazardous whilst collaterals have not opened adequately, and cerebral perfusion depends on BP. The following review addresses these and other questions in more detail. Where possible, we focus on the results of RCTs rather than observational studies, which inevitably suffer from indication and other forms of bias. Trials of BP lowering have focused on two strategies, either using a specific drug or comparing intensive versus guideline BP targets (Figure 1). We describe these by following the ABCD approach to lowering BP [9] and adding other drug classes and target trials. Additional information is given in the Supplement. This is a narrative review and there are no data for sharing.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Patients admitted with stroke have consistently higher BP levels than patients hospitalized for other causes. Up to 75% of acute stroke patients have BP >140/90 mmHg at the time of hospital admission.[10]

Elevated BP in the acute phase may, in part, result from previous arterial hypertension but also from physiological responses to brain injury in addition to the stress of acute hospitalization. The hypertensive response is likely multifactorial and influenced by the underlying etiology.[7] Data from the prehospital setting suggest that patients with small vessel disease have higher BP than those with a cardioembolic etiology. The higher blood pressure observed in small vessel disease may represent the rightward shift in the autoregulatory curve due to long-standing hypertension rather than the effect of the infarct itself. Similar observations have been seen in patients with deep versus lobar intracerebral haemorrhage.[11] A more dynamic movement in blood pressure to ensure cerebral perfusion in large vessel occlusion stroke is supported by the drop in BP observed after recanalization of a large vessel occlusion, most commonly caused by cardiac emboli.[12] Many factors contribute to the hypertensive response, such as excessive sympathetic and renin-angiotensin-aldosterone system activity, increased cortisol and inflammatory cytokines, pain and stress associated with acute hospitalization, baroreceptor dysfunction, and in some patients, increased intracranial pressure (Cushing's reflex).[8] The sympathetic and parasympathetic systems are predominantly lateralized in the left and right cerebral hemispheres, respectively. The prefrontal and insular cortex are involved in autonomic control with connections to the brainstem nuclei, mainly the solitary tract and the ventrolateral medulla. The amygdala, cingulate gyrus, and hypothalamus are also involved in BP control.[13] Thus, direct damage to inhibitory modulatory centers or even indirect effects of reduced parasympathetic activity, resulting in a reduction in the sensitivity of baroreceptors, may be mechanisms specifically related to stroke that explain the acute stroke-related hypertensive response.[14]

A spontaneous drop in BP is observed in two-thirds of patients over the first week after hospital admission [7, 15] with a significant reduction occurring within 10 hours of the first measurement.[16] This fall in BP may result from the patient's adaptation to the hospital environment and normalization of cerebral autoregulation following recanalization of large vessel occlusion.[17] Cerebral autoregulation is a mechanism by which cerebral blood flow is maintained constant over a range of cerebral perfusion pressure between 60 - 150 mmHg and depends on myogenic, neurogenic, and metabolic mechanisms.[18] Autoregulation is usually impaired in acute stroke and can result in a linear relationship of cerebral blood flow and cerebral perfusion pressure that depends on mean arterial pressure. Hence, sudden drops in BP can reduce cerebral blood flow and thus increase the volume of ischemic damage.[19] In contrast, increases in BP lead to a progressive contraction of arterioles up to the upper limit of autoregulation, after which passive vasodilation, increased cerebral blood flow, and damage to the blood-brain barrier leads to cerebral edema.[20] In chronically hypertensive patients, the cerebral autoregulation curve may be moved to the right by vessel stiffening and the presence of luminal narrowing.[21] In patients with acute ischemic stroke, autoregulation in the ischemic region and the peri-ischemic region are usually altered.[22] Dysfunction of the

autoregulation curve can occur even in the contralateral hemisphere due to vasodilation in response to ischemia and activation of the collateral network. A transcranial Doppler study to assess cerebral vasoreactivity in the acute phase of ischemic stroke suggests that a flow stealing phenomenon from the affected to the unaffected hemisphere (also referred to as the reversed Robin Hood syndrome [23]) may sometimes occur.

U-shaped associations between high and low BP and poor short- and long-term outcomes have been demonstrated in different cohorts globally.[24–27] These outcomes are partly mediated by increased early recurrence, death from cerebral edema in patients with high BP, and increased ischemic cardiac events in patients with low BP. Although hypotension is uncommon in stroke patients, low BP levels can be associated with sepsis, arrhythmias, heart failure, acute myocardial infarction, aortic dissection, and hypovolemia. In addition to systolic BP, mean arterial pressure, pulse pressure, and systolic pressure variability are also associated with neurological deterioration, recurrent stroke, and death.[28] The relationship between BP levels and post-stroke clinical outcomes was evaluated in a systematic review of 18 studies and showed that patients with high admission BP had a 1.5 to 5 times greater chance of death and long-term dependence.[29]

Reperfused but previously ischemic/oligemic brain is likely to be most susceptible to failure of cerebral autoregulation. Animal studies have shown that blood-brain barrier disruption is more significant in rat models with transient middle cerebral artery occlusion followed by reperfusion than rat models with permanent cerebral artery occlusion.[30] Rat studies have also shown that reperfused arteries (after transient ischemia) significantly lose their myogenic tone, resulting in an inability to vasoconstrict in response to increased systemic pressure.[31] This can lead to significant hyperemia in brain tissue with existing blood-brain barrier disruption, resulting in hemorrhagic complications and inflammatory consequences. Lastly, cerebral arteries that are transiently occluded and then reperfused have less myogenic tone and cerebral autoregulatory capabilities.[32] Thus, hemodynamic changes may be significant not only immediately after reperfusion but for several hours after.

PREHOSPITAL TRIALS IN PATIENTS WITH SUSPECTED STROKE

Treatment for acute stroke should be initiated as early as possible after symptom onset. BP management is an accessible, easy-to-administer, and low-cost intervention. Without access to imaging, treatments started in the prehospital setting must be safe in both ischemic stroke and intracerebral hemorrhage. Several randomized trials have explored the feasibility, effect on BP, safety, and efficacy of antihypertensive therapy administered in the ambulance in patients with suspected acute stroke; many of these studies recruited patients with hypertension as defined by the World Health Organization, i.e. systolic BP >140 mmHg.

ACE-I trials

The UK-based Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST) feasibility trial [33] recruited 14 patients with suspected stroke within three hours of symptom onset and systolic BP >160mmHg. Participants were randomized to sublingual lisinopril (5 mg), or placebo and treatment started in the ambulance. As compared to placebo, lisinopril was associated with a lower BP at hospital arrival, 171 (30)/91 (23) mmHg versus 177

(20)/97 (16) mmHg, and 4 hours after admission, 143 (47)/74 (23) mmHg versus 159 (35)/79 (24) mmHg. No information on long-term outcomes was collected.

NO donor trials

The UK-based Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke trial (RIGHT) [34] tested the feasibility and role of paramedics in performing an ambulance-based trial in patients with ultra-acute suspected stroke. RIGHT randomized 41 patients with Face Arm Speech Time (FAST) score of 2 or 3, within 4 hours of symptom onset and systolic BP ≥140 mmHg to receive either transdermal glyceryl trinitrate (GTN, nitroglycerin) or none. The primary outcome of systolic BP at two hours post-randomization was reduced significantly by 18 mmHg in the GTN group. GTN treatment was associated with improved functional outcome with a shift to independence at 90 days assessed using the modified Rankin scale (mRS) (p=0.04). There was no difference in death (16% versus 37.5%, p=0.15) or serious adverse events (SAEs) (56% versus 63%, p=0.75).

The larger Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT-2) [35] followed RIGHT and randomized 1149 patients in the UK with suspected acute stroke (FAST score of 2 or 3) and systolic BP ≥120 mmHg to GTN or sham. The BP level of >120 mmHg was chosen since the trialists had moved to the hypothesis that GTN might aid collateral reperfusion and not just lower BP. Prehospital administration of GTN did not alter functional outcome (mRS) at 90 days in either patients with confirmed stroke or transient ischemic attack (adjusted commons odds ratio for poor functional outcome, acOR 1.25, 95% CI 0.97-1.60; p=0.083) or in all participants (acOR 1.04, 95% CI 0.84-1.29; p=0.69). There were no differences in secondary outcomes, death, or SAEs between the two groups. Although GTN was associated with a worse outcome in ICH,[36] mRS at 90 days was better with GTN in mimics and did not differ in participants with ischemic stroke (acOR 1.13, 95% CI 0.86-1.48; n=706) (P Bath, personal communication). A meta-analysis of participants treated early in ENOS [37] (which is discussed in hospital-based trials section) and in RIGHT [34] and RIGHT-2 [35] found no difference in the outcomes of death at 90 days (OR 0.52, 95% CI 0.16–1.72; p=0.28, I^2=86%) or functional outcome (OR 0.80, 95% CI 0.59–1.10; p=0.17, I^2=16%).[35]

Guidelines

Based on the existing published evidence, the ESO guideline on BP management in acute ischemic stroke and intracerebral hemorrhage recommended against routine BP lowering in the prehospital setting in patients with suspected stroke (quality of evidence: moderate; strength of recommendation: weak).[2] The current situation is unsatisfactory, and further trials are needed urgently, especially since drugs such as GTN and labetalol are widely used in hospitals during the first few hours after stroke onset. Further, guidelines are firm in recommending lowering BP below 185/110 mmHg before thrombolysis [38, 39] and so lowering BP in the ambulance could reduce the time in hospital to initiate reperfusion therapy, as suggested in RIGHT.[34]

HOSPITAL-BASED TRIALS IN PATIENTS WITH ISCHEMIC OR MIXED STROKE

There are still many gaps in defining ideal BP management in patients with acute ischemic stroke. A Cochrane review including 26 clinical trials with more than 17,000 participants suggested insufficient evidence for lowering BP in the acute phase of ischemic stroke. Most of the data in this review evaluated studies with wide variability in time to onset of antihypertensive medications, with only four studies administering medications within six hours. The included studies evaluated the use of ACE-I, angiotensin receptor antagonists, alpha-2 adrenergic agonists, calcium channel blockers, diuretics, nitric oxide donors, and target-driven BP lowering.[40]

ARB trials

The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study randomized 339 patients with ischemic stroke and BP ≥180/105 mmHg to receive seven days of oral candesartan or placebo within 36 hours of symptom onset. Twelve-month mortality and cardiovascular outcomes (secondary outcome) were reduced in patients receiving candesartan, although there was no difference in functional outcomes at three months.[41] A *post hoc* analysis of the PRoFESS study (Prevention Regimen for Effectively Avoiding Second Strokes) evaluated the effect of adding telmisartan versus placebo to conventional antihypertensive therapy in 1360 patients with acute ischemic stroke recruited within 72 hours of the ictus. Telmisartan was safe and associated with reduced BP by 6–7/2-4 mmHg but no difference in functional outcome, death, stroke recurrence, or recurrence of cardiovascular events. Patients included in the PRoFESS study had lower BP levels than patients evaluated in the ACCESS study, were recruited later and treated for a more extended period.[42, 43]

The SCAST study (Scandinavian Candesartan Acute Stroke Trial) recruited 2029 patients with ischemic or hemorrhagic stroke within 30 hours of symptom onset who had systolic BP greater than ≥140 mm Hg. Patients received candesartan or placebo for seven days. BP fell in the studied groups, but there was a greater reduction in the group treated with candesartan. The study evaluated co-primary outcomes of cardiovascular recurrence and stroke functional outcome. Although recurrence was neutral, functional outcome measured using the modified Rankin scale was non-significantly worse in patients receiving candesartan,[44] a finding that appeared to be localized to participants with ICH.[45] Neutral and negative results of angiotensin receptor antagonists suggest harmful effects of this class of medication on cerebral perfusion, increasing ischemic injury.

Beta-blocker trials

The BEST study evaluated the use of ß-blockers (atenolol or propranolol) at low doses and showed increased mortality in patients treated within the first 48 hours of symptom onset. The negative inotropic effect of ß-blockers may be associated with worsening cerebral perfusion, although there are no physiological data to support this hypothesis.[46]

CCB trials

An analysis of the INWEST study (Nimodipine West European Stroke Trial) showed a significant correlation between reduced diastolic BP with nimodipine and worsening neurological examination. Patients with a reduction in diastolic pressure greater than 20% had a higher risk of dependence and disability.[12] A subsequent systematic review evaluated the use of calcium channel blockers in acute stroke. It showed that higher doses, administration within 12 hours of symptom onset, and the intravenous route were associated with worse outcomes.[13] A comparable trial in the US found similar results.[47] The harmful effects of calcium channel blockers in the acute phase of stroke may be mediated by reductions in regional cerebral flow.

Diuretic trials

There are limited data on the use of diuretics in the acute phase of stroke. A small study evaluated the use of Bendroflumethiazide, a thiazide diuretic, in 37 patients with ischemic stroke within 96 hours of symptom onset. There was no difference in BP levels over seven days of treatment, and there was also no difference in cerebral blood flow measurements.[48]

NO donor trials

The ENOS study included 4011 patients with ischemic or hemorrhagic stroke within 48 hours of symptom onset who were randomized to receive transdermal glyceryl trinitrate (GTN) patches 5 mg versus placebo for seven days. Additionally, patients using antihypertensive drugs before the stroke were randomized to continue or to stop their medications. GTN significantly reduced BP as compared to placebo and was safe but did not alter functional outcome.[49] However, a pre-specified subgroup analysis in patients treated within the first six hours of symptom onset showed a benefit on the modified Rankin scale, mortality, cognitive improvement, mood and quality of life, in both ischemic stroke and intracranial hemorrhage.[37]

Mixed drug class trials

Clonidine (α_2-adrenoreceptor agonist), nicardipine, and captopril versus placebo were tested in a small randomized controlled trial in patients with middle cerebral artery occlusion within 72 hours of symptom onset. There was a drop in BP in both groups but no difference in clinical outcomes.[50]

The CHHIPS trial (Controlling Hypertension and Hypotension Immediately Post-Stroke) included 179 patients with ischemic or hemorrhagic stroke within 36 hours of symptom onset with systolic BP >160 mm Hg. Three groups of patients received oral labetalol (50mg), lisinopril (50mg), or placebo; dysphagic patients received intravenous labetalol, sublingual lisinopril, or placebo. The dose of medication was progressively increased until a pressure between 145-155 mmHg or a reduction of 15 mmHg was achieved at four and eight hours after randomization. There was no difference in the functional outcome assessed using the modified Rankin scale at 14 days.[51]

Target BP trials

The CATIS study (China Antihypertensive Trial in Acute Ischaemic Stroke) enrolled 4071 hypertensive patients (systolic BP 140–220 mm Hg) within 48 hours of symptom onset. Patients were randomized to receive a 10-25% BP reduction within the first 24 hours of symptom onset, maintain a BP <140/90 mm Hg within seven days, or receive no antihypertensive medications. The study did not use any specific BP control regimen but suggested using intravenous angiotensin-converting enzyme inhibitors as first-line therapy and oral calcium channel blockers as a second option. Mean systolic BP dropped by 13% within 24 hours of randomization in the treatment group versus 7% in the control group.[52] Patients had mild strokes with a mean NIHSS of 4, and 66% of patients in the control group were independent within two weeks. In addition, the study excluded patients with carotid disease as an etiology and patients treated with intravenous thrombolysis. The primary functional outcome was neutral, which may have reflected, in part, the inclusion of mostly mild strokes.

ACUTE BP MANAGEMENT IN THE SETTING OF REPERFUSION TREATMENT

The optimal hemodynamics following acute stroke has perplexed clinicians for decades, and BP management in patients undergoing acute stroke reperfusion treatments remains an important unresolved issue. Because of failure of autoregulation, the acutely injured brain is particularly susceptible to changes in perfusion pressure.[53] Small fluctuations in systemic BP can lead to significant hyper- or hypoperfusion, which can be detrimental to already injured brain tissue. These risks may be heightened during reperfusion due to hemorrhagic complications, blood-brain barrier disruption and reperfusion-induced vascular injury. Thus, BP management in patients undergoing reperfusion therapies requires a careful balance of these opposing risks.

Thrombolysis

The current American Heart Association/American Stroke Association (AHA/ASA) acute stroke management guidelines and recent European Stroke Organization recommendations on acute stroke BP management support BP lowering below 185/110mmHg before initiating intravenous thrombolysis.[1, 2] This recommendation is based on the NINDS tPA trial, which excluded patients with BP >185/110 mmHg from receiving tPA.[54] In addition, several observational studies have suggested that elevated SBP prior to thrombolytic administration is associated with higher odds of symptomatic intracerebral hemorrhage.[55, 56] However, aggressive BP lowering before reperfusion therapy may exacerbate cerebral hypoperfusion and cause further ischemic core growth. The optimal BP levels below which thrombolytics are safe remain an area of speculation without strong supporting data, as discussed in the Supplement.

The current AHA/ASA and ESO guidelines recommend maintaining BP <180/105 mm Hg for 24 hours post-intravenous thrombolytic administration.[1, 57] In patients treated with intravenous thrombolysis, hypertension usually resolves after recanalization.[58] Higher BP post tPA and BP protocol violations have been associated with an increased risk of

intracerebral hemorrhage and a lower incidence of functional independence.[55, 59, 60] Several randomized trials have tested the efficacy of BP lowering post-tPA administration without success. The recent phase III randomized-controlled ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) trial found a lower rate of intracerebral hemorrhage in patients randomized to the intensive BP lowering arm (target SBP 130-140 mm Hg after tPA) when compared to patients treated with guideline-recommended SBP goal of less than 180mm Hg.[61] However, there was no difference in the primary outcome of global disability at 90-days. Thus, the current consensus is to adhere to the current guideline-recommended BP goals.

In the SITS-ISTR registry, an association between symptomatic intracranial hemorrhage and BP was observed, with a four times greater risk with systolic BP above 170 mmHg when compared to patients with BP between 141–150 mm Hg.[6, 62]

Endovascular therapy

Periprocedural BP management for patients undergoing EVT remains a question of great debate. The current AHA/ASA and ESO guidelines recommend maintaining BP below 185/110 mmHg for patients who undergo EVT with or without intravenous thrombolysis.[1, 57] This recommendation is primarily based on the pivotal trial protocols requiring this BP goal for patients undergoing EVT, as many patients were also treated with intravenous thrombolysis. The management of BP can be divided into pre-, peri- and post-procedure.

Pre-EVT—Elevated pre-EVT BP has been associated with larger final infarct volumes and worse functional outcomes and may be related to poor collaterals or a more proximal vessel occlusion. However, optimal targets remain unknown, and few studies have evaluated pre-EVT BP management.[26, 63] One study has found that large drops or increases in pre-EVT mean arterial BP are associated with worse patient outcomes.[64] These findings suggest that BP reductions before EVT could exacerbate ischemia, while BP increase may indicate failure of compensatory mechanisms to maintain blood flow to the ischemic tissue.

Peri-EVT—Similarly, observational studies have shown that drops in intraprocedural BP or reductions below critical thresholds are associated with worse outcomes, regardless of the type of procedural anesthesia.[65–68] A recent *post hoc* analysis of three randomized-controlled clinical trials identified mean arterial pressure (MAP) reductions below 70 mm Hg or reductions >20% from baseline as critical thresholds for an increased risk of a worse functional outcome.[69]

BP is one of the most dynamic variables, and ideal targets likely differ during acute stroke management. When dividing intraprocedural BP management into two phases according to the time of recanalization, pre-recanalization decreases in BP were associated with larger infarct volumes and worse functional outcomes supporting this phasic breakdown of BP management according to recanalization.[70]

Post-EVT—Observational studies have consistently demonstrated that elevated post-EVT BP is associated with hemorrhagic complications and worse functional outcomes independent of successful reperfusion of the affected vessel following EVT.[71–74] These

observations have been confirmed by a large meta-analysis.[75] In addition, another large prospective observational study showed that post-EVT systolic BP of 160 mmHg best dichotomized patients with good vs. bad functional outcomes at 90-days (higher BP was associated with worse outcomes).[76] A recent analysis of the time-varying behavior of BP after thrombectomy showed that patients have distinct systolic BP trajectories after thrombectomy that differ in their relation to functional outcome and sICH.[77] Observational studies are discussed in the Supplement.

A recent phase II randomized-controlled clinical trial, BPTARGET, did not find a difference in the primary outcome of any radiographic intraparenchymal hemorrhage between patients allocated to lower 100-129 mm Hg vs. higher 130-185 mmHg post-EVT BP arms.[78] However, the mean BP difference between the groups was small (mean SBP 128 vs. 138 mmHg), and only 50% of patients in the intense treatment group achieved the BP goal of 100-129 at 3 hours. Furthermore, the time within the target SBP range was only between 60-70% in both groups. Several ongoing randomized-controlled clinical trials in this space are expected to clarify post-EVT BP management.

INDUCED HYPERTENSION

Since cerebral autoregulation is disturbed during stroke,[79] it may be appropriate to increase BP perfusion. During vessel occlusion, a substantial pressure differential is created between the occluded and patent vessels, this increasing cerebral blood flow (CBF) and luminal shear stress in collateral vessels in a BP-dependent manner.

Trials

Three randomized controlled trials of induced hypertension have been conducted.[80,81,82] However, no large trials have been reported. The first trial was a small US study evaluating the effects of phenylephrine-induced hypertension in patients with acute ischemic stroke and large diffusion-perfusion mismatch (n=17);[80] NIHSS score, cognitive score, and volume of hypoperfused tissue improved significantly within the first three days in treated patients.

A Korean multicenter trial, the Safety and Efficacy of Therapeutic Induced Hypertension in Acute Non-Cardioembolic Ischemic Stroke (SETIN-HYPERTENSION), showed that among patients with non-cardioembolic stroke ineligible for revascularization therapy and those with progressive stroke (n=153), phenylephrine-induced hypertension was safe and resulted in early neurologic improvement during the first seven days and long-term functional independence at 90 days.[82] This trial included patients with intracranial atherosclerosis and small vessel occlusion as well as those with large vessel occlusion.

A single-center trial of the early Manipulation of Arterial BP in Acute ischemic Stroke (MAPAS) randomized patients unsuitable for thrombolytic therapy (n=218) into three BP groups, and if needed, norepinephrine or fluids were used to achieve targets.[81] Good outcome defined as an mRS score of 0–2 at 90 days was not different among the three BP ranges, but the odds of having a good outcome was greater in patients with intermediate target BP (161–180 mmHg) whilst symptomatic intracerebral hemorrhage occurred more frequently in those with the highest targets (181–200 mmHg). MAPAS included patients

with spontaneously elevated BP [81] which may reflect a neuroendocrine response to physiologic stress or chronic hypertension.

Many questions remain when considering induced hypertension, and patient selection is key,[82] as is further discussed in the Supplement.

Guidelines

Current guidelines recommend that induced hypertension should be performed with close neurological and cardiac monitoring and in the setting of clinical trials. The ASA guidelines recommended that in exceptional cases with carotid occlusion or systemic hypotension producing neurological sequelae, vasopressors might improve CBF.[83,84] The 2021 ESO guidelines suggested against the routine use of vasopressors to increase BP in patients with acute ischemic stroke not treated with reperfusion therapies who experience clinical deterioration.[2] Expert consensus suggested discontinuing existing BP-lowering therapy, administering intravenous fluids, and introducing non-pharmacological procedures before using vasopressor agents to increase BP.[2]

SUMMARY

In summary, the management of high BP in acute ischemic stroke remains unclear. Unlike for ICH, no medium-sized or large trials in ischemic stroke have been positive, and several have been negative (as opposed to neutral). Although further large trials are ongoing, we have to prepare ourselves for the result that changing BP may have no overall benefit. However, specific subgroups of patients may need to have BP lowered (e.g. prior to or after thrombolysis), left alone, or elevated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

PMB is Stroke Association Professor of Stroke Medicine and an Emeritus NIHR Senior Investigator.

SOURCES OF FUNDING

This project received no specific funding.

DISCLOSURES

PMB: Was a member of the Working Group of the European Stroke Organisation Guidelines on Blood Pressure Management in Acute Ischaemic Stroke and Intracerebral Haemorrhage. He receives funding from Nottingham University Hospitals Trust Charity (CI ENOS-2) and British Heart Foundation (CI - artificial intelligence project including acute stroke trials) and has received honoraria for consultancy with DiaMedica, Moleac and Phagenesis (unrelated to this review).

LS: receives internal funding from The George Institute and funding from Takeda China as co-PI of an ongoing prehospital blood pressure management trial (INTERACT4).

GSS receives funding from the Brazilian Ministry of Health for the Optimal Blood Pressure for the prevenTIon of Major vAscuLar Events in Stroke Patients (OPTIMAL Stroke trial)

EAM: receives funding from the NIH/NINDS as PI of an ongoing randomized trial on blood pressure management after endovascular therapy (BEST-II).

NHP: receives funding from the NIH/NINDS as PI of a study on autoregulation-guided blood pressure management after stroke.

GT: Was a co-chair of the Working Group of the European Stroke Organisation Guidelines on Blood Pressure Management in Acute Ischaemic Stroke and Intracerebral Haemorrhage.

MM: PI of the BP -TARGET trial.

ECS: Was chair of the Working Group of the European Stroke Organisation Guidelines on Blood Pressure Management in Acute Ischaemic Stroke and Intracerebral Haemorrhage.

ABBREVIATIONS

ACE-I	angiotensin-converting enzyme-inhibitor
ARB	angiotensin receptor antagonist/blocker trials
BP	blood pressure
CCB	calcium channel blocker
EVT	endovascular therapy
ESO	European Stroke Organization
GTN	glyceryl trinitrate
NO	nitric oxide
RAAS	renin-angiotensin-aldosterone system
RCTs	randomized-controlled clinical trials
tPA	Tissue plasminogen activator

REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2019;50:e344–e418 [PubMed: 31662037]
2. Sandset E, Anderson C, Bath P, Christensen H, Fischer U, Gasecki D, Lal A, Manning L, Sacco S, Steiner T, et al. European stroke organisation (eso) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. European Stroke Journal. 2021;6:XLVIII–LXXXIX [PubMed: 34780578]
3. Yatsu FM, Zivin J. Hypertension in acute ischaemic strokes - not to treat. Arch.Neurol 1985;42:999–1000 [PubMed: 4038107]
4. Spence JD, Del Maestro RF. Hypertension in acute ischaemic strokes - treat. Arch.Neurol 1985;42:1000–1002 [PubMed: 4038094]
5. Hachinski V. Hypertension in acute ischaemic strokes. Arch.Neurol 1985;42:1002 [PubMed: 4038095]
6. Qureshi AI. Acute hypertensive response in patients with stroke: Pathophysiology and management. Circulation. 2008;118:176–187 [PubMed: 18606927]

7. Bath PM, Appleton JP, Krishnan K, Sprigg N. Blood pressure in acute stroke: To treat or not to treat: That is still the question. Stroke. 2018;49:1784–1790 [PubMed: 29895536]
8. Carlberg B, Asplund K, Hagg E. Factors influencing admission blood pressure levels in patients with acute stroke. Stroke. 1991;4:527–530
9. Dickerson JEC, Hingorani AD, Ashby MJ, Plamer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. Lancet. 1999;353:2008–2013 [PubMed: 10376615]
10. Leonardi-Bee J, Bath P, Phillips S, Sandercock P. Why is blood pressure in acute ischaemic stroke associated with a poor outcome? Data from the international stroke trial. Cerebrovascular Diseases. 2001;11 (suppl 4):72 (abstract)
11. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, Mehta Z, Rothwell PM. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: A population-based study. Lancet Neurology. 2014;13:374–384 [PubMed: 24582530]
12. Gioia LC, Zewude RT, Kate MP, Liss K, Rowe BH, Buck B, Jeerakathil T, Butcher K. Prehospital systolic blood pressure is higher in acute stroke compared with stroke mimics. Neurology. 2016;86:2146–2153 [PubMed: 27194383]
13. Samuels MA. The brain-heart connection. Circulation. 2007;116:77–84 [PubMed: 17606855]
14. Aiyagari V, Gorelick PB. Management of blood pressure for acute and recurrent stroke. Stroke. 2009;40:2251–2256 [PubMed: 19390077]
15. Qureshi AI, Ezzeddine MA, Nasar A, Suri MFK, Kirmani JF, Hussein HM, Divani AA, Reddi AS. Prevalence of elevated blood pressure in 563 704 adult patients with stroke presenting to the ed in the united states. American Journal of Emergency Medicine. 2007;25:32–38 [PubMed: 17157679]
16. Aslanyan S, Fazekan F, Weir CJ, Horner S, Lees KR, for the GAIN International Steering Committee and Investigators. Effect of blood pressure during the acute period of ischemic stroke on stroke outcome. A tertiary analysis of the gain international trial. Stroke. 2003;34:2420–2425 [PubMed: 14500934]
17. Britton M, Carlsson A, de Faire U. Blood pressure course in patients with acute stroke and matched controls. Stroke. 1986;17:861–864 [PubMed: 3764955]
18. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke. 1989;20:45–52 [PubMed: 2492126]
19. Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. Cerebrovascular Diseases. 2003;16:69–75 [PubMed: 12766365]
20. McManus M, Liebeskind DS. Blood pressure in acute ischemic stroke. J Clin Neurol. 2016;12:137–146 [PubMed: 26833984]
21. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug induced hypotension. Circulation. 1976;53:720–727 [PubMed: 815061]
22. Symon L, Held K, Dorsch NW. A study of regional autoregulation in the cerebral circulation to increased perfusion pressure in normocapnia and hypercapnia. Stroke. 1973;4:139–147 [PubMed: 4633923]
23. Alexandrov AV, Sharma VK, Lao AY, Tsivgoulis G, Malkoff MD, Alexandrov AW. Reversed robin hood syndrome in acute ischemic stroke patients. Stroke. 2007;38:3045–3048 [PubMed: 17916768]
24. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the international stroke trial. Stroke. 2002;33:1315–1320 [PubMed: 11988609]
25. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, Konstantopoulou P, Mavrikakis M. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med. 2004;255:257–265 [PubMed: 14746563]
26. Mulder M, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lycklama ANG, Emmer BJ, van der Worp HB, et al. Baseline blood pressure effect on the benefit and safety of intra-arterial treatment in mr clean (multicenter randomized clinical trial of endovascular treatment of acute ischemic stroke in the netherlands). Stroke. 2017;48:1869–1876 [PubMed: 28432266]

27. Maier B, Gory B, Taylor G, Labreuche J, Blanc R, Obadia M, Abrivard M, Smajda S, Desilles JP, Redjem H, et al. Mortality and disability according to baseline blood pressure in acute ischemic stroke patients treated by thrombectomy: A collaborative pooled analysis. J Am Heart Assoc. 2017;6
28. Geeganage C, Tracy M, England T, Sare G, Moulin T, Woimant F, Christensen H, De Deyn PP, Leys D, O'Neill D, et al. Relationship between baseline blood pressure parameters (including mean pressure, pulse pressure, and variability) and early outcome after stroke: Data from the tinzaparin in acute ischaemic stroke trial (taist). Stroke. 2011;42:491–493 [PubMed: 21183747]
29. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: A systematic review. Hypertension. 2004;43:18–24 [PubMed: 14662649]
30. Yang GY, Betz AL. Reperfusion-induced injury to the blood-brain barrier after middle cerebral artery occlusion in rats. Stroke. 1994;25:1658–1664; discussion 1664-1655 [PubMed: 8042219]
31. Cipolla MJ, McCall AL, Lessov N, Porter JM. Reperfusion decreases myogenic reactivity and alters middle cerebral artery function after focal cerebral ischemia in rats. Stroke. 1997;28:176–180 [PubMed: 8996508]
32. Cipolla MJ, Curry AB. Middle cerebral artery function after stroke: The threshold duration of reperfusion for myogenic activity. Stroke. 2002;33:2094–2099 [PubMed: 12154269]
33. Shaw L, Price C, McLure S, Howel D, McColl E, Younger P, Ford GA. Paramedic initiated lisinopril for acute stroke treatment (pil-fast): Results from the pilot randomised controlled trial. Emergency medicine journal : EMJ. 2014;31:994–999 [PubMed: 24078198]
34. Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, Siriwardena AN, Bath PM. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: The rapid intervention with glyceryl trinitrate in hypertensive stroke trial (right, isrctn66434824). Stroke; a journal of cerebral circulation. 2013;44:3120–3128
35. Investigators R-. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (right-2): An ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. Lancet. 2019;393:1009–1020 [PubMed: 30738649]
36. 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 [PubMed: 31587658]
37. Woodhouse L, Scutt P, Krishnan K, Berge E, Gommans J, Ntaios G, Wardlaw J, Sprigg N, Bath PM. Effect of hyperacute administration (within 6 hours) of transdermal glyceryl trinitrate, a nitric oxide donor, on outcome after stroke: Subgroup analysis of the efficacy of nitric oxide in stroke (enos) trial. Stroke. 2015;46:3194–3201 [PubMed: 26463698]
38. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke; a journal of cerebral circulation. 2018;49:e46–e110
39. Kobayashi A, Czlonkowska A, Ford GA, Fonseca AC, Luijckx GJ, Korv J, de la Ossa NP, Price C, Russell D, Tsiskaridze A, et al. European academy of neurology and european stroke organization consensus statement and practical guidance for pre-hospital management of stroke. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2018;25:425–433
40. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014:Cd000039
41. Schrader J, Luders S, Kulschewski A, Berger J, Zidek W, Treib J, Einhaupl K, Diener HC, Dominiak P, Grp AS. The access study - evaluation of acute candesartan cilexetil therapy in stroke survivors. Stroke. 2003;34:1699–1703 [PubMed: 12817109]
42. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med. 2008;359:1225–1237 [PubMed: 18753639]

43. Bath PM, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, Diener C, Invest P. Effect of telmisartan on functional outcome, recurrence and blood pressure in patients with acute ischaemic stroke: A profess substudy. Stroke. 2009;40:E128–E128
44. Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S, Murray GD, Richter PS, Roine RO, Terent A, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (scast): A randomised, placebo-controlled, double-blind trial. Lancet. 2011;377:741–750 [PubMed: 21316752]
45. Jusufovic M, Sandset E, Bath P, Berge E. Blood pressure lowering treatment with candesartan in patients with acute hemorrhagic stroke. Stroke. 2014;45:3440–3442 [PubMed: 25256183]
46. Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR. Low dose beta blockade in acute stroke ("best" trial): An evaluation. Br Med J (Clin Res Ed). 1988;296:737–741
47. Bridges SL, Koch G, Munera C, Karwon M, Kurtz NM. Intravenous nimodipine in acute stroke: Interim analysis of randomised trials. Stroke. 1991;22:153
48. Eames PJ, Robinson TG, Panerai RB, Potter JF. Bendrofluazide fails to reduce elevated blood pressure levels in the immediate post-stroke period. Cerebrovascular Diseases. 2005;19:253–259 [PubMed: 15731556]
49. Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, Sprigg N, Berge E, Beridze M, Caso V, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (enos): A partial-factorial randomised controlled trial. Lancet. 2015;385:617–628 [PubMed: 25465108]
50. Lisk DR, Grotta JC, Lamki LM, Tran HD, Taylor JW, Molony DA, Barron BJ. Should hypertension be treated after acute stroke? A randomised controlled trial using single photon emission computed tomography. Archives Neurology. 1993;50:855–862
51. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C. Controlling hypertension and hypotension immediately post-stroke (chhips): A randomised, placebo-controlled, double-blind pilot trial. Lancet Neurology. 2009;8:48–56 [PubMed: 19058760]
52. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, Tong W, Liu C, Xu T, Ju Z, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The catis randomized clinical trial. JAMA. 2013;311:479–489
53. Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke. Am J Hypertens. 2012;25:946–950 [PubMed: 22573015]
54. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–1587 [PubMed: 7477192]
55. Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikilidou M, Schellinger PD, Alexandrov AW, et al. Association of elevated blood pressure levels with outcomes in acute ischemic stroke patients treated with intravenous thrombolysis: A systematic review and meta-analysis. J Stroke. 2019;21:78–90 [PubMed: 30732443]
56. Teng RSY, Tan BYQ, Miny S, Syn NL, Ho AFW, Ngiam NJH, Yeo LLL, Choong AM, Sharma VK. Effect of pretreatment blood pressure on outcomes in thrombolysed acute ischemic stroke patients: A systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2019;28:906–919 [PubMed: 30612890]
57. Sandset EC, Anderson CS, Bath PM, Christensen H, Fischer U, Gąsecki D, Lai 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. European Stroke Journal. 2021;6:XLVIII–LXXXIX [PubMed: 34780578]
58. Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikilidou M, Schellinger PD, Alexandrov AW, et al. Association of elevated blood pressure levels with outcomes in acute ischemic stroke patients treated with intravenous thrombolysis: A systematic review and meta-analysis. Journal of stroke. 2019;21:78–90 [PubMed: 30732443]
59. Butcher K, Christensen S, Parsons M, De Silva DA, Ebinger M, Levi C, Jeerakathil T, Campbell BC, Barber PA, Bladin C, et al. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. Stroke. 2010;41:72–77 [PubMed: 19926841]
60. Tsivgoulis G, Katsanos AH, Mandava P, Kohrmann M, Soinne L, Barreto AD, Sharma VK, Mikulik R, Muir KW, Rothlisberger T, et al. Blood pressure excursions in acute ischemic

stroke patients treated with intravenous thrombolysis. J Hypertens. 2021;39:266–272 [PubMed: 32956103]

61. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, Li Q, Billot L, Delcourt C, Bath PM, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (enchanted): An international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet. 2019;393:877–888 [PubMed: 30739745]
62. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford G, Kaste M, Lees K, Toni D, Investigators S, Investigators S. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis retrospective analysis from safe implementation of thrombolysis in stroke-international stroke thrombolysis register (sitsistr). Stroke. 2009;40:2442–2449 [PubMed: 19461022]
63. Goyal N, Tsivgoulis G, Iftikhar S, Khorchid Y, Fawad Ishfaq M, Doss VT, Zand R, Chang J, Alsherbini K, Choudhri A, et al. Admission systolic blood pressure and outcomes in large vessel occlusion strokes treated with endovascular treatment. J Neurointerv Surg. 2017;9:451–454 [PubMed: 27117174]
64. Mistry EA, Dakay K, Petersen NH, Jayaraman M, McTaggart R, Furie K, Mistry A, Mehta T, Arora N, De Los Rios La Rosa F, et al. Pre-endovascular therapy change in blood pressure is associated with outcomes in patients with stroke. J Neurol Neurosurg Psychiatry. 2020;91:438–439 [PubMed: 32029540]
65. Lowhagen Henden P, Rentzos A, Karlsson JE, Rosengren L, Sundeman H, Reinsfelt B, Ricksten SE. Hypotension during endovascular treatment of ischemic stroke is a risk factor for poor neurological outcome. Stroke. 2015;46:2678–2680 [PubMed: 26173727]
66. Samuels N, van de Graaf RA, van den Berg CAL, Nieboer D, Eralp I, Treurniet KM, Emmer BJ, Immink RV, Majoie C, van Zwam WH, et al. Blood pressure during endovascular treatment under conscious sedation or local anesthesia. Neurology. 2021;96:e171–e181 [PubMed: 33028664]
67. Treurniet KM, Berkhemer OA, Immink RV, Lingsma HF, Ward-van der Stam VMC, Hollmann MW, Vuyk J, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, et al. A decrease in blood pressure is associated with unfavorable outcome in patients undergoing thrombectomy under general anesthesia. J Neurointerv Surg. 2018;10:107–111 [PubMed: 28404769]
68. Whalin MK, Halenda KM, Haussen DC, Rebello LC, Frankel MR, Gershon RY, Nogueira RG. Even small decreases in blood pressure during conscious sedation affect clinical outcome after stroke thrombectomy: An analysis of hemodynamic thresholds. AJNR Am J Neuroradiol. 2017;38:294–298 [PubMed: 27811133]
69. Rasmussen M, Schonenberger S, Henden PL, Valentin JB, Espelund US, Sorensen LH, Juul N, Uhlmann L, Johnsen SP, Rentzos A, et al. Blood pressure thresholds and neurologic outcomes after endovascular therapy for acute ischemic stroke: An analysis of individual patient data from 3 randomized clinical trials. JAMA Neurol. 2020;77:622–631 [PubMed: 31985746]
70. Petersen NH, Ortega-Gutierrez S, Wang A, Lopez GV, Strander S, Kodali S, Silverman A, Zheng-Lin B, Dandapat S, Sansing LH, et al. Decreases in blood pressure during thrombectomy are associated with larger infarct volumes and worse functional outcome. Stroke. 2019;50:1797–1804 [PubMed: 31159701]
71. Goyal N, Tsivgoulis G, Pandhi A, Chang JJ, Dillard K, Ishfaq MF, Nearing K, Choudhri AF, Hoit D, Alexandrov AW, et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. Neurology. 2017;89:540–547 [PubMed: 28687721]
72. Matusevicius M, Cooray C, Bottai M, Mazya M, Tsivgoulis G, Nunes AP, Moreira T, Ollikainen J, Tassi R, Strbian D, et al. Blood pressure after endovascular thrombectomy: Modeling for outcomes based on recanalization status. Stroke. 2020;51:519–525 [PubMed: 31822252]
73. Mistry EA, Mistry AM, Nakawah MO, Khattar NK, Fortuny EM, Cruz AS, Froehler MT, Chitale RV, James RF, Fusco MR, et al. Systolic blood pressure within 24 hours after thrombectomy for acute ischemic stroke correlates with outcome. J Am Heart Assoc. 2017;6
74. Anadani M, Arthur AS, Alawieh A, Orabi Y, Alexandrov A, Goyal N, Psychogios MN, Maier I, Kim JT, Keyrouz SG, et al. Blood pressure reduction and outcome after endovascular therapy with successful reperfusion: A multicenter study. J Neurointerv Surg. 2020;12:932–936 [PubMed: 31806668]

75. Malhotra K, Goyal N, Katsanos AH, Filippatou A, Mistry EA, Khatri P, Anadani M, Spiotta AM, Sandset EC, Sarraj A, et al. Association of blood pressure with outcomes in acute stroke thrombectomy. Hypertension. 2020;75:730–739 [PubMed: 31928111]
76. Mistry EA, Sucharew H, Mistry AM, Mehta T, Arora N, Starosciak AK, De Los Rios La Rosa F, Siegler JE 3rd, Barnhill NR, Patel K, et al. Blood pressure after endovascular therapy for ischemic stroke (best): A multicenter prospective cohort study. Stroke. 2019;50:3449–3455 [PubMed: 31587660]
77. Petersen NH, Kodali S, Meng C, Li F, Nguyen CK, Peshwe KU, Strander S, Silverman A, Kimmel A, Wang A, et al. Blood pressure trajectory groups and outcome after endovascular thrombectomy: A multicenter study. Stroke. 2021:STROKEAHA121034408
78. Mazighi M, Richard S, Lapergue B, Sibon I, Gory B, Berge J, Consoli A, Labreuche J, Olivot JM, Broderick J, et al. Safety and efficacy of intensive blood pressure lowering after successful endovascular therapy in acute ischaemic stroke (bp-target): A multicentre, open-label, randomised controlled trial. Lancet Neurol. 2021;20:265–274 [PubMed: 33647246]
79. Meyer JS, Shimazu K, Fukuuchi Y, Ohuchi T, Okamoto S, Koto A, Ericsson AD. Impaired neurogenic cerebrovascular control and dysautoregulation after stroke. Stroke. 1973;4:169–186 [PubMed: 4702305]
80. Hillis AE, Ulatowski JA, Barker PB, Torbey M, Ziai W, Beauchamp NJ, Oh S, Wityk RJ. A pilot randomized trial of induced blood pressure elevation: Effects on function and focal perfusion in acute and subacute stroke. Cerebrovascular diseases (Basel, Switzerland). 2003;16:236–246 [PubMed: 12865611]
81. Nasi LA, Martins SCO, Gus M, Weiss G, de Almeida AG, Brondani R, Rebello LC, DalPizzol A, Fuchs FD, Valenca MJM, et al. Early manipulation of arterial blood pressure in acute ischemic stroke (mapas): Results of a randomized controlled trial. Neurocritical care. 2019;30:372–379 [PubMed: 30460598]
82. Bang OY, Chung JW, Kim SK, Kim SJ, Lee MJ, Hwang J, Seo WK, Ha YS, Sung SM, Kim EG, et al. Therapeutic-induced hypertension in patients with noncardioembolic acute stroke. Neurology. 2019;93:e1955–e1963 [PubMed: 31645472]
83. Adams HP Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, et al. Guidelines for the early management of adults with ischemic stroke: A guideline from the american heart association/american stroke association stroke council, clinical cardiology council, cardiovascular radiology and intervention council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups: The american academy of neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007;38:1655–1711 [PubMed: 17431204]
84. Jauch EC, Saver JL, Adams HP Jr., Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr., Qureshi AI, Rosenfield K, et al. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2013;44:870–947 [PubMed: 23370205]

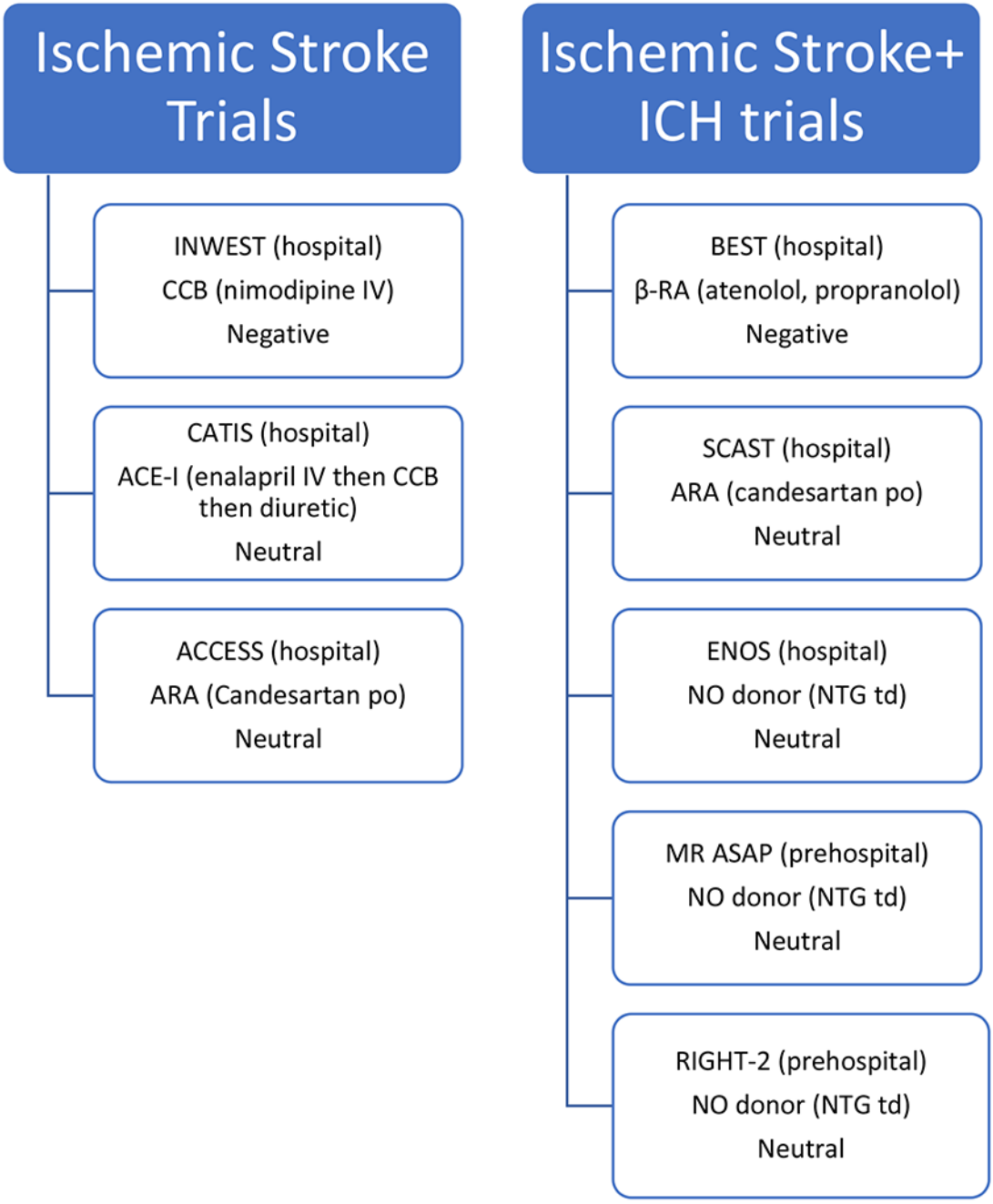

Figure 1:
Relevant Randomized Controlled Trials of Blood Pressure Lowering in Acute Stroke