Blood Pressure in Acute Stroke

To Treat or Not to Treat: That Is Still the Question

Philip M. Bath, DSc, FMedSci; Jason P. Appleton, MRCP(UK); Kailash Krishnan, MRCP(UK), PhD; Nikola Sprigg, FRCP, DM

One of the oldest questions in acute stroke management, and perhaps the most challenging since it has yet to be solved after more than half a century of published research, is how to manage high blood pressure (BP). The problem might be summed up as follows:

> To *treat*, or not to *treat*: that is the question:
> Whether 'tis nobler in the mind to suffer
> The slings and arrows of outrageous *pressure*,
> Or to take *drugs* against a sea of *blood*,
> And by opposing end them? To *live*: to *walk*;
> —With apologies to *Shakespeare*, *Hamlet Act III, Scene I*

To treat, or not to treat, high BP was debated >30 years ago in 1985,[1–3] and yet there is no definitive answer here in 2018. Part of the debate is driven by opposing arguments based on epidemiology and pathophysiology and part by the failure of every large trial to provide a definitive answer. There is considerable evidence that high BP is associated independently with a poor outcome after ischemic stroke (IS) whether defined by early recurrence or death, or late death and dependency.[4,5] Similarly, high BP is related to hematoma expansion[6] and functional outcome after intracerebral hemorrhage (ICH).[7] A straightforward conclusion of this epidemiological evidence is that high BP should be lowered. In contrast, pathophysiological concerns are based on the presence of dysfunctional cerebral autoregulation during acute stroke, and so lowering BP will reduce tissue perfusion, increase lesion size, and thereby worsen outcome.[8]

There are many causes of high BP in acute stroke, including prior hypertension, acute neuroendocrine stimulation (via the renin-angiotensin-aldosterone system [RAAS], sympathetic autonomic nervous, and corticotrophin-cortisol systems), the Cushing reflex (due to raised intracranial pressure), and stress associated with admission to hospital and concurrent pain (eg, due to urinary retention).[9] These factors offer multiple targets for treatment.

The principle of uncertainty (or clinical equipoise) has driven the completion of many medium- and large-sized trials in acute IS, hemorrhagic, or mixed stroke (Table 1). Although varying considerably in design, the trials each compared active or intensive lowering of BP with no or guideline-based lowering. Whereas some smaller trials involving a few hundreds of patients were negative (ie, treatment worsened outcome: BEST [β-Blocker Stroke Trial], Bridgers et al,[14] INWEST [Intravenous Nimodipine West European Stroke Trial][15,20]), larger trials (involving a thousand or more patients) have all been neutral (SCAST [Scandinavian Candesartan Acute Stroke Trial], INTERACT-2 [Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2], CATIS [China Antihypertensive Trial in Acute Ischemic Stroke], ENOS [Efficacy of Nitric Oxide in Stroke], ATACH-2 [Antihypertensive Treatment of Acute Cerebral Hemorrhage-2][12,13,16,21,22]). For the sake of this review, SCAST can be considered to be negative because the presence of 2 primary outcomes meant that the shift in modified Rankin Scale (mRS) in a negative direction (P=0.048) just missed statistical significance at P<0.025.[21] Equally, INTERACT-2 can be considered to be positive because although it was neutral on its primary dichotomous analysis of the mRS (P=0.06), intensive BP lowering was associated with a positive shift analysis (P=0.04) and improved quality of life (P=0.002).[12]

Without definitive positive trials, a conclusion at this stage could be that the epidemiological observations are epiphenomena and do not predict the effect of intervention, as has been seen in other areas of medicine such as vitamin supplementation,[25] and, therefore, that BP does not need to be lowered. However, an alternative hypothesis is that lowering BP may be a useful marker of efficacy but effects on outcome depend on which sort of stroke is being treated, how and when BP is lowered, and what other effects the treatment has. This review examines the hypothesis that it is how and when BP is first lowered, and in what stroke type, that is important rather than lowering BP per se. The review uses the results of published medium- and large-sized trials, as summarized in 2 Cochrane Collaboration systematic reviews[26,27] along with more recent studies.

Received February 20, 2018; final revision received April 24, 2018; accepted May 14, 2018.
From the Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, United Kingdom.
Presented in part at the International Stroke Conference, Los Angeles, CA, January 24–26, 2018.
The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.118.021254/-/DC1.
Correspondence to Philip M. Bath, DSc, FMedSci, Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, United Kingdom. E-mail philip.bath@nottingham.ac.uk
(*Stroke*. 2018;49:1784-1790. DOI: 10.1161/STROKEAHA.118.021254.)

Table 1. Medium and Large Randomized Controlled Trials of Blood Pressure Lowering in Acute Stroke

	Intervention/Class (Agent)	Size	OTR (h)	Result; Comment(s)
ICH				
(SCAST-ICH[10]	ARA [candesartan po]	274	<30	Negative)
INTERACT[11]	Intensity, multiple classes: a-AA (urapidil IV, phentolamine) 63%; loop diuretic (furosemide) 35%; NO donor (nitroglycerin) 13%	404	<6	Neutral
INTERACT-2[12]	Intensity, multiple classes: a-AA (urapidil IV) 32.5%; NO donor (nitroglycerin, nitroprusside) 27.0%; CCB (nicardipine) 16.2%; combined α-AA/β-RA (labetalol) 14.4%; diuretic (furosemide) 12.4%	2794	<6	Neutral; positive on ordinal analysis
ATACH-2[13]	CCB (nicardipine IV)	1000	<4.5	Neutral
INTERACT-3 bundle	Intensity, multiple classes (+glucose and temperature control, and reversal of anticoagulation)	≈8621	<6	Ongoing
ICH-ADAPT-2	Intensity using labetalol, hydralazine, enalapril	≈270	<6	Ongoing
IS				
Bridgers et al[14]	CCB (nimodipine IV)	204	<24	Negative tendency
INWEST[15]	CCB (nimodipine IV)			Negative
CATIS[16]	ACE (enalapril IV) then CCB then diuretic	4071	<24	Neutral
(SCAST-IS[17]	ARA [candesartan po]		<30	Neutral)
VENTURE[18]	ARA (valsartan po)	393	<48	Neutral
ENCHANTED-BP[19]	Intensity (mainly a-AA, urapidil IV)			Ongoing
Mixed				
BEST[20]	β-RA (atenolol, propranolol po)	302	<48	Negative
SCAST[21]	ARA (candesartan po)	2029	<30	Neutral; negative if recurrence coprimary ignored
ENOS[22]	NO donor (NTG td)	4011	<48	Neutral
(ENOS early[23]	NO donor [NTG td]	273	<6	Positive)
RIGHT-2[24]	NO donor (NTG td)	≈1105	<4	Ongoing
MR-ASAP	NO donor (NTG td)	≈1400	<3	Ongoing

The relevant subgroups of trials are shown in brackets. a-AA indicates α–receptor antagonist; ACE, angiotensin-converting enzyme; ARA, angiotensin receptor antagonist; ATACH, Antihypertensive Treatment of Acute Cerebral Hemorrhage; BEST, β-Blocker Stroke Trial; BP, blood pressure; CATIS, China Antihypertensive Trial in Acute Ischemic Stroke; CCB, calcium channel blocker; ENCHANTED-BP, Enhanced Control of Hypertension and Thrombolysis in Stroke Study; ENOS, Efficacy of Nitric Oxide in Stroke; ICH, intracerebral hemorrhage; ICH-ADAPT-2, Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial-2; INTERACT, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; INWEST, Intravenous Nimodipine West European Stroke Trial; IS, ischemic stroke; IV, intravenous; MR-ASAP, Multicenter Randomized Trial of Acute Stroke Treatment in the Ambulance With a Nitroglycerin Patch; NO, nitric oxide; NTG, nitroglycerin/glyceryl trinitrate; OTR, onset to randomization; RA, adrenoceptor antagonists; RIGHT-2, Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial-2; SCAST, Scandinavian Candesartan Acute Stroke Trial; td, transdermal and VENTURE, Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke.

INTERACT-3: URL: http://www.clinicaltrials.gov. Unique identifier: NCT03209258.

ICH-ADAPT: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02281838.

MR_ASAP: URL: http://www.isrctn.com. Unique identifier: ISRCTN99503308.

RIGHT-2: URL: http://right-2.ac.uk. Unique identifier: ISRCTN26986053.

Where relevant, reference to small mechanistic or pharmacodynamic trials is also made. It does not address whether antihypertensive drugs taken before stroke should be continued or stopped temporarily[28] or whether and how antihypertensive agents should be taken long term for secondary prevention.[29]

Antihypertensive therapy is rich with multiple evidence-based drug classes, and 7 classes have been tested in acute stroke (Tables 2 and 3). There are no medium- to large-sized trials involving centrally acting drugs, endothelin antagonists, or renin inhibitors.

Antihypertensive Drug Classes of Relevance in Acute Stroke

α–Adrenoceptor Antagonists

Stimulation of α1–adrenergic receptors increases smooth muscle contraction under catecholamine control. Antagonism of these receptors by drugs such as doxazosin and urapidil leads to vasorelaxation. A third of patients (32.5%) in the INTERACT-2 trial in ICH received an α–adrenoceptor antagonist (a-AA), typically urapidil (Table 1).[12] Treatment improved the mRS, and the results are compatible with the hypothesis

Table 2. Characteristics of Antihypertensive Drug Classes on Additional Mechanisms

Class	CBF	CO	HR	BPV	NP	Plt	WBC	RAAS	SANS	Outcome	Comments
a-AA			(↑)	↓		↓			↓	ICH ↑? IS?	Positive early after ICH? ENCHANTED-BP
ACE inhibitors	→			↑			↓	↓		IS →	Neutral after IS. Avoid in ICH?
ARA	→			↑	+[30]	↓	↓	↓		ICH ↓? IS →	SCAST-ICH: Negative—AT_2 receptor effects? SCAST-IS, VENTURE
β-RA		↓	↓	↑		↓[31]		↓		IS ↓	Enhance hypoperfusion?
CCB	→	(↓)	(↓)	↓	+[32]	↓		↑		IS →↓ ICH →	Neutral after IS,[33] with some negative trials
Diuretics				↓				↑			Onset slow (thiazide like)[34]
NO	→↑		(↑)	↓	+[35]	(↓)	(↓)			ICH ↑? IS ↑?	Positive early after IS and ICH? Supplement low vascular levels.[36,37] Enhance reperfusion? Spontaneous NO donors (eg, SNP), but not nitrates, have antiplatelet activity[38]

a-AA indicates α–receptor antagonists; ACE, angiotensin-converting enzyme; ARA, angiotensin receptor antagonists; BPV, blood pressure variability; β-RA, β–receptor antagonists; CBF, cerebral blood flow; CCB, calcium channel blockers; CO, cardiac output; HR, heart rate; ICH, intracerebral hemorrhage; IS, ischemic stroke; NO, nitric oxide donors; NP, neuroprotection; Plt, platelet function; RAAS, renin-angiotensin-aldosterone system; SANS, sympathetic autonomic nervous system; SNP sodium nitroprusside; and WBC, white blood cell effects.

that blocking noradrenaline and adrenaline may be beneficial. Nevertheless, the first and smaller INTERACT trial had a higher utilization of a-AA but was neutral.[11] The ENCHANTED-BP study (Enhanced Control of Hypertension and Thrombolysis in Stroke Study) is using a similar approach of testing intensity of BP lowering in patients with hyperacute IS,[19] and interim data suggest a high utilization of a-AA (C. Anderson, personal communication, results expected early 2019).

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) converts the inactive hormone angiotensin I to the active vasoconstrictor angiotensin II. Hence, ACE inhibitors such as enalapril cause vasorelaxation. The large CATIS trial in acute IS reported a neutral effect of intravenous enalapril on mRS (Table 1).[16] No large trials of ACE inhibitors for acute ICH have been reported.

Angiotensin Receptor Antagonists

The angiotensin II receptor-1 is activated by the vasoconstrictor angiotensin II. Antagonism of the receptor with drugs such as candesartan and valsartan leads to vasorelaxation. The large SCAST trial assessed oral candesartan, with doses rising over the treatment period, in patients with acute IS and hemorrhagic stroke (Table 1). Practically, the trial can be considered to be negative,[21] with all the harm occurring in patients with ICH and a neutral effect in IS.[10,17] The medium-sized VENTURE trial (Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke) of oral valsartan for acute IS was also neutral.[18] One interpretation is that elevated angiotensin II levels in acute ICH are important and their effects should not be blocked. Alternatively or additionally, blockade of the angiotensin II AT_1 receptor leaves the AT_2 receptor exposed, and agonism of this leads to inhibition of cell growth and neuronal regeneration.[39] The neutral findings of CATIS, SCAST, and VENTURE suggest that the RAAS is not a useful target in acute stroke.

β–Adrenoceptor Antagonists

Stimulation of β1–adrenergic receptors increases cardiac muscle contraction (inotropic effect) and heart rate (chronotropic effect) under catecholamine control. As a result, antagonism of these receptors by drugs such as atenolol and propranolol reduces cardiac output and heart rate. The BEST trial in acute mixed stroke found that these agents, when given orally, increased mortality at 1 month (Table 1).[20] Although BEST was not large and separate results for ICH and IS are not published, one interpretation that is plausible biologically

Table 3. Summary of Results Divided by Time From Onset-To-Treatment, Stroke Type, and Class of Antihypertensive Agent in Patients With Acute Stroke

Time	Stroke Type	a-AA	NO	Diuretic	ACE Inhibitors	ARA	CCB	β-RA
<6	ICH	+	+?	+?			0	
	IS	?	+?					
>6	ICH		0			–/0		…
	IS		0		0	0	…	…

Trial results: –, negative; 0, neutral; +, positive;?, ongoing trial(s). a-AA indicates α–receptor antagonist; ACE, angiotensin-converting enzyme; ARA, angiotensin receptor antagonist; β-RA, β–receptor antagonist; CCB, calcium channel blocker; IS, ischemic stroke; and NO, nitric oxide donor.

is that reducing cardiac output in acute stroke is potentially hazardous.

Some drugs have antagonist effects on both α and β receptors, such as labetalol (where β-antagonist effects dominate). Although some guidelines recommend using this agent in acute stroke,[40] there is limited evidence on the effect of labetalol on functional outcome after stroke to support this assertion, with just 14% of INTERACT-2 treated with labetalol.

Calcium Channel Blockers

The movement of calcium through L-type channels in cell membranes drives smooth muscle contraction. Hence blockade of these channels with dihydropyridine calcium channel blockers (CCBs), such as nicardipine and nimodipine, causes vasorelaxation. Numerous trials of CCBs have been performed in acute stroke, usually testing nimodipine as a putative neuroprotectant. Although nimodipine had no overall effect in IS,[32] 2 trials found that high-dose intravenous therapy was associated with a worse functional outcome.[14,15] The moderately large ATACH-2 trial assessed intravenous nicardipine in hyperacute ICH and was neutral leading to the trial being stopped early for futility (Table 1).[13] Since dihydropyridine CCBs have some antiplatelet activity,[41,42] their use in ICH (as recommended in guidelines, Table I in the online-only Data Supplement) might be considered questionable.

Diuretics

Of the multiple types of diuretics, loop diuretics (furosemide) have been used in acute stroke. They act by inhibiting the renal luminal Na-K-Cl cotransporter in the thick ascending limb of the loop of Henle. A small proportion of patients (12.4%) in the positive INTERACT-2 trial in ICH received a loop diuretic. A small trial of bendroflumethiazide, a thiazide diuretic, found that it had minimal BP effect over the first week of treatment in patients with acute stroke.[34]

Nitric Oxide Donors

Nitric oxide (NO) is a potent endogenous mixed arterial and venous vasodilator and has significant hypotensive effects. Vascular levels of NO are low after stroke[36,37] so it is plausible to supplement it. NO may be administered as a nitrate (such as nitroglycerin [NTG] also known as glyceryl trinitrate) or spontaneous NO donor (such as sodium nitroprusside). The large ENOS trial of transdermal NTG found that it did not alter mRS,[22] although hyperacute administration within 6 hours was associated with improved functional outcome in a predefined subgroup (Table 1).[23] NO donors (NTG, sodium nitroprusside) were used in 27% of patients with ICH in the positive hyperacute INTERACT-2 trial.[12] The ongoing RIGHT-2 trial (Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial-2) is assessing NTG administered by paramedics before hospital admission (with results expected in early 2019).

Stroke Type

Trials of BP lowering have been performed in ICH alone, IS alone, and mixed groups of patients (Table 1). Although probable efficacy was seen in the INTERACT-2 trial in ICH,[12] nicardipine was neutral in ATACH-2,[13] and candesartan (angiotensin receptor antagonists [ARA]) appeared to be harmful in the subgroup of SCAST patients with ICH.[10] Opposing results were also seen in trials of mixed groups of patients; although 2 studies of NTG were positive in both stroke types when given early,[23,43] β–adrenoceptor antagonists (β-RA) were negative in BEST.[20]

Timing

The trials varied considerably in their time window from onset to randomization, this ranging from <6 to <48 hours. The only evidence for benefit was seen in those studies where patients were randomized within 6 hours, as seen in INTERACT-2, RIGHT, and ENOS early.[12,23,43] This observation is comparable with the time dependency seen for thrombolysis and thrombectomy in IS[44,45] and raises the possibility that at least some effects of NTG may be related to reperfusion following vasodilation.[46] Trials recruiting beyond 6 hours were all neutral (CATIS, ENOS, VENTURE[16,18,22]) or negative (BEST, INWEST[15,20]). The subgroup of patients randomized after 24 hours into the CATIS trial appeared to have less death or major disability at 3 months, although this was not apparent at 14 days or hospital discharge, and so may reflect the play of chance.[16] An outlier is the neutral 1000-patient ATACH-2 trial that recruited patients within 4.5 hours of ICH onset and lowered BP with intravenous nicardipine; this result may be more related to use of a dihydropyridine CCB per se (as already discussed) rather than timing.

Trial Size

This review largely focuses on medium to large trials involving 100s to 1000s of participants and so of comparable sizes to trials of thrombectomy and intravenous thrombolysis, respectively. Even the largest completed trials involving >4000 participants (CATIS, ENOS) will not have been large enough to detect small but potentially clinically worthwhile effect sizes. The ongoing INTERACT-3 trial aims to recruit more than twice the number of participants of these already large trials. (Table 1).

Additional Effects of Antihypertensive Agents

The various antihypertensive drug classes exhibit multiple other (collateral) effects (Table 2), some of which might be considered advantageous (such as potential neuroprotection) and others a disadvantage (such as reducing cardiac output).

Cerebral Blood Flow/Perfusion

Many small studies have been performed that assessed cerebral blood flow (CBF) or CBF velocity after administration of ACE inhibitors, ARA, β-RA (labetalol), CCB, diuretic, or NO donor.[38,47–49] Although no difference in CBF was seen in randomized controlled trials, an increase in CBF was seen with CCBs in before-after studies. However, all these studies were small (median size 24 participants) and tended to be of low-medium quality. No CBF studies investigated β-RA or labetalol. There is an urgent need for large high-quality randomized trials using modern imaging techniques and assessing the effects of antihypertensives on CBF, especially those agents recommended in guidelines or that are widely used (labetalol, nicardipine, NTG, urapidil).

Cardiac Output

β-RA such as propranolol and atenolol reduce cardiac output which may then reduce CBF, a debateable aim when this is already reduced in the penumbral area of IS and in ischemic areas around hematoma. This sequence might explain increased deaths seen in the BEST trial.[20] Exploring the relationship between cardiac output and CBF is important because labetalol, which has significant β-RA activity, is recommended in guidelines and is widely used. Verapamil, a phenylalkylamine CCB, also has negative inotropic, chronotropic, and dromotropic effects, but this drug has not been assessed in IS.

BP Variability

High BP and many derivatives, including mean arterial pressure, pulse pressure, BP variability, peak systolic BP, and rate-pressure product, are each associated with early events and late poor outcome in both acute IS[5,50] and ICH.[51] Although all the antihypertensive drug classes discussed here lower BP (by definition), they have varying effects on variability[52]: whereas CCBs and nonloop diuretics reduce interindividual variance, ACE, ARA, and β-RA increase variability. Further, these differences seen in variability appear to explain, in part, differences seen in the effects of these drug classes on stroke.[52] NTG, a NO donor, also reduces variability.[53] Whether effects on variability explain the results of acute stroke BP trials remains unclear because neutral or negative results were seen with agents that both reduce (CCBs) or increase (ACE, ARA, and β-RA) variability.

Neuroprotection

Several antihypertensive drug classes (ARA, CCB, NO donors) have putative neuroprotective properties,[30,32,35] at least in animal models of stroke. The relevance of this is unclear because no large clinical trials of putative neuroprotectants have led to their introduction in clinical practice.

Antiplatelet

Multiple antihypertensive classes (ARA, β-RA, CCB, spontaneous NO donors such as sodium nitroprusside) exhibit antiplatelet activity. Intravenous CCBs are widely used for the hyperacute management of high BP after stroke in spite of neutral results in ICH (nicardipine in ATACH-2[13]) and some negative results in IS (nimodipine in Bridgers et al,[14] INWEST[15]). Although there are many hypotheses why INTERACT-2 and ATACH-2 gave different results in hyperacute ICH (Table II in the online-only Data Supplement),[54] a key potential explanation is that the mild antiplatelet effects of dihydropyridine CCBs (which includes nicardipine)[41,42] neutralized its BP effects in ATACH-2.

Anti-White Cell Effects

Nitric oxide and some NO donors (eg, sodium nitroprusside but not NTG), ACE inhibitors and ARA, have anti-white cell activity manifest through reduction of leukocyte migration, adhesion, and other functions.[55–58] In contrast, the effect of other antihypertensive classes on leukocyte activity is unclear. Accentuated white cell function occurs soon after stroke with neutrophils then monocytes invading the brain; 1 trial of an antileukocyte monoclonal in acute IS was negative with increased death and worse functional outcome.[59] Hence, there is a risk that antihypertensives with antileukocyte activity might be harmful; pharmacodynamics studies examining white cell function in acute stroke are urgently needed.

Inhibition of RAAS

ACE inhibitors, ARA, and β-RA exert some or all of their BP-lowering effect by attenuating the RAAS. Although acute stroke is associated with RAAS stimulation, attenuating this activity appears unhelpful because trials have found that ACE inhibitors and ARA were neutral in IS (CATIS, SCAST[16,17]), ARA was negative in ICH (SCAST[10]), and β-RA were negative in mixed stroke.[20]

Inhibition of the Sympathetic Autonomic Nervous System

Noradrenaline is a key vasoconstrictor, and levels are elevated in acute stroke.[60] Hence, blocking its effects will lower BP and might improve cerebral perfusion. No large pure a-AA trials have been performed, but they are frequently used in China (typically with urapidil) and a significant minority of patients took them in the INTERACT studies[11,12] and are on them in the ongoing ENCHANTED-BP trial.

The Future

The hypothesis presented here is that it is when and how BP is lowered, and in which type of stroke, that is important, not whether BP is lowered per se. Further, it is the additional effects of antihypertensives that may drive effects on outcome. This hypothesis is data driven and depends on the results of completed medium- and large-sized trials. In essence, intervention probably needs to be started within the ultra- and hyperacute phase of stroke (<6 hours) if a beneficial effect is to be seen, and efficacy may be localized to 1 or 2 classes, a-AA and NO donors. The evidence for a-AA is less clear because urapidil was used more in INTERACT, which showed no tendency to an effect on functional outcome, than the positive INTERACT-2 trial. Further, these results apply only to ICH. Although ENOS was neutral for treatment within 48 hours, NTG appeared to improve mRS in both IS and ICH if given within 6 hours in both ENOS and RIGHT.[61] If the observations for a-AA and NTG are true, then attenuating sympathetic activity and/or supplementing vascular NO[46] may be key mechanisms for facilitating efficacy when lowering BP.

However, the findings are soft and more trials are required, and the ongoing ENCHANTED-BP, ICH-ADAPT-2 (Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial-2), INTERACT-3, MR-ASAP (Multicenter Randomized Trial of Acute Stroke Treatment in the Ambulance With a Nitroglycerin Patch), and RIGHT-2 trials (Table 1) will help test these hypotheses. If none of these predictions deliver, then it is possible that BP is a bystander in very acute stroke and lowering it is unimportant. New studies are required to further assess the effects of the various antihypertensive classes on additional mechanisms as listed in Table 2, including parameters such as BP variability.[62] Imaging studies in IS need to assess effects of BP lowering on CBF, collateral circulation, penumbral size, influence of

intra and extracranial stenosis, and interaction with mechanical thrombectomy. Similarly, imaging studies in ICH need to assess induction of ischemia (as is being investigated in ICH-ADAPT-2) and effects on hematoma characteristics such as spot sign, edema, intraventricular hemorrhage, and proximal ischemia. Ongoing and future large trials will need to assess the role of lowering BP not just by stroke type but by severity and etiology; for example, BP lowering may have differential effects in stroke related to small vessel disease in comparison with large artery and cardioembolic stroke. Further, future trials may need to be much larger (as with the ongoing INTERACT-3 bundle trial, Table 1) and so able to detect small but clinically meaningful effect sizes.

In contrast to remaining questions about efficacy within 6 hours, no agents appear to be beneficial when given later than 6 hours; worse, some classes appear to be hazardous including ARA in ICH, intravenous CCB in IS, and β-RA in either stroke type. Guidelines that recommend the use of labetalol (with predominant β-RA activity) and CCB for lowering BP in acute stroke may need to be revised (Table I in the online-only Data Supplement).

Acknowledgments

This review builds on presentations by P.M. Bath at the European Stroke Conference (2013) and 2018 International Stroke Conference, Cerebrovascular Education and Discovery (CED) Talks.

Disclosures

P.M. Bath was chief investigator of ENOS; receives research grant funding from the British Heart Foundation as the Chief Investigator for the RIGHT-2 trial; has received modest honoraria for speaking at symposia sponsored by Nestle HealthScience; has received modest honoraria for consultancy for Phagenesis Ltd; has modest ownership interests in Platelet Solutions Ltd and DiaMedica Therapeutics Inc; is Stroke Association Professor of Stroke Medicine; and is an National Institute for Health Research Senior Investigator. J.P. Appleton is funded by the British Heart Foundation through the RIGHT-2 trial. The other authors report no conflicts.

References

1. Yatsu FM, Zivin J. Hypertension in acute ischemic strokes. Not to treat. *Arch Neurol*. 1985;42:999–1000.
2. Spence JD, Del Maestro RF. Hypertension in acute ischemic strokes. Treat. *Arch Neurol*. 1985;42:1000–1002.
3. Hachinski V. Hypertension in acute ischemic strokes. *Arch Neurol*. 1985;42:1002.
4. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315–1320.
5. Sprigg N, Gray LJ, Bath PM, Boysen G, De Deyn PP, Friis P, et al; TAIST Investigators. Relationship between outcome and baseline blood pressure and other haemodynamic measures in acute ischaemic stroke: data from the TAIST trial. *J Hypertens*. 2006;24:1413–1417. doi: 10.1097/01.hjh.0000234123.55895.12.
6. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke*. 2004;35:1364–1367. doi: 10.1161/01.STR.0000128795.38283.4b.
7. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24. doi: 10.1161/01.HYP.0000105052.65787.35.
8. Owens WB. Blood pressure control in acute cerebrovascular disease. *J Clin Hypertens (Greenwich)*. 2011;13:205–211. doi: 10.1111/j.1751-7176.2010.00394.x.
9. Carlberg B, Asplund K, Hägg E. Factors influencing admission blood pressure levels in patients with acute stroke. *Stroke*. 1991;22:527–530.
10. Jusufovic M, Sandset EC, Bath PM, Berge E; Scandinavian Candesartan Acute Stroke Trial Study Group. Blood pressure-lowering treatment with candesartan in patients with acute hemorrhagic stroke. *Stroke*. 2014;45:3440–3442. doi: 10.1161/STROKEAHA.114.006433.
11. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al; INTERACT Investigators. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol*. 2008;7:391–399. doi: 10.1016/S1474-4422(08)70069-3.
12. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al; INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355–2365. doi: 10.1056/NEJMoa1214609.
13. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. doi: 10.1056/NEJMoa1603460.
14. Bridgers SL, Koch G, Munera C, Karwon M, Kurtz NM. Intravenous nimodipine in acute stroke: interim analysis of randomized trials (abstract). *Stroke*. 1991;22:153.
15. Wahlgren NG, Macmahon DG, Dekeyser J, Indredavik B, Ryman T. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis*. 1994;4:204–210
16. Chen N, Yang M, Guo J, Zhou M, Zhu C, He L. Cerebrolysin for vascular dementia. *Cochrane Database Syst Rev*. 2013;1:CD008900
17. Jusufovic M, Sandset EC, Bath PM, Karlson BW, Berge E; Scandinavian Candesartan Acute Stroke Trial Study Group. Effects of blood pressure lowering in patients with acute ischemic stroke and carotid artery stenosis. *Int J Stroke*. 2015;10:354–359. doi: 10.1111/ijs.12418.
18. Oh MS, Yu KH, Hong KS, Kang DW, Park JM, Bae HJ, et al; Valsartan Efficacy oN modesT blood pressUre REduction in acute ischemic stroke (VENTURE) study group. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. *Int J Stroke*. 2015;10:745–751. doi: 10.1111/ijs.12446.
19. Huang Y, Sharma VK, Robinson T, Lindley RI, Chen X, Kim JS, et al; ENCHANTED Investigators. Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) Trial: an international multicenter 2×2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. *Int J Stroke*. 2015;10:778–788. doi: 10.1111/ijs.12486.
20. 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.
21. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, et al; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741–750. doi: 10.1016/S0140-6736(11)60104-9.
22. ENOS Trial Investigators. 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. doi: 10.1016/S0140-6736(14)61121-1.
23. Woodhouse L, Scutt P, Krishnan K, Berge E, Gommans J, Ntaios G, et al; ENOS Investigators. 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. doi: 10.1161/STROKEAHA.115.009647.
24. Appleton JP, Scutt P, Dixon M, Howard H, Haywood L, Havard D, et al; RIGHT-2 Investigators. Ambulance-delivered transdermal glyceryl trinitrate versus sham for ultra-acute stroke: rationale, design and protocol for the rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2 (right-2) trial (isrctn26986053). *Int J Stroke*. 2017:1747493017724627. doi: 10.1177/1747493017724627.
25. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al; HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293:1338–1347. doi: 10.1001/jama.293.11.1338.
26. Geeganage C, Bath PM. Vasoactive drugs for acute stroke. *Cochrane Database Syst Rev*. 2010;(7):CD002839.

27. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev*. 2014;(10):Cd000039. doi: 10.1002/14651858.
28. Woodhouse LJ, Manning L, Potter JF, Berge E, Sprigg N, Wardlaw J, et al; Blood Pressure in Acute Stroke Collaboration. Continuing or temporarily stopping prestroke antihypertensive medication in acute stroke: an individual patient data meta-analysis. *Hypertension*. 2017;69:933–941. doi: 10.1161/HYPERTENSIONAHA.116.07982.
29. Katsanos AH, Filippatou A, Manios E, Deftereos S, Parissis J, Frogoudaki A, et al. Blood pressure reduction and secondary stroke prevention: a systematic review and metaregression analysis of randomized clinical trials. *Hypertension*. 2017;69:171–179. doi: 10.1161/HYPERTENSIONAHA.116.08485.
30. Villapol S, Saavedra JM. Neuroprotective effects of angiotensin receptor blockers. *Am J Hypertens*. 2015;28:289–299. doi: 10.1093/ajh/hpu197.
31. Bonten TN, Plaizier CE, Snoep JJ, Stijnen T, Dekkers OM, van der Bom JG. Effect of β-blockers on platelet aggregation: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2014;78:940–949. doi: 10.1111/bcp.12404.
32. Zhang J, Yang J, Zhang C, Jiang X, Zhou H, Liu M. Calcium antagonists for acute ischemic stroke. *Cochrane Database Syst Rev*. 2012;(5):Cd001928. doi: 10.1002/14651858.
33. Horn J, de Haan RJ, Vermeulen M, Luiten PG, Limburg M. Nimodipine in animal model experiments of focal cerebral ischemia: a systematic review. *Stroke*. 2001;32:2433–2438.
34. Eames PJ, Robinson TG, Panerai RB, Potter JF. Bendrofluazide fails to reduce elevated blood pressure levels in the immediate post-stroke period. *Cerebrovasc Dis*. 2005;19:253–259. doi: 10.1159/000084089.
35. Willmot M, Gray L, Gibson C, Murphy S, Bath PM. A systematic review of nitric oxide donors and L-arginine in experimental stroke; effects on infarct size and cerebral blood flow. *Nitric Oxide*. 2005;12:141–149. doi: 10.1016/j.niox.2005.01.003.
36. Ferlito S, Gallina M, Pitari GM, Bianchi A. Nitric oxide plasma levels in patients with chronic and acute cerebrovascular disorders. *Panminerva Med*. 1998;40:51–54.
37. Rashid PA, Whitehurst A, Lawson N, Bath PM. Plasma nitric oxide (nitrate/nitrite) levels in acute stroke and their relationship with severity and outcome. *J Stroke Cerebrovasc Dis*. 2003;12:82–87. doi: 10.1053/jscd.2003.9.
38. Butterworth RJ, Cluckie A, Jackson SH, Buxton-Thomas M, Bath PM. Pathophysiological assessment of nitric oxide (given as sodium nitroprusside) in acute ischaemic stroke. *Cerebrovasc Dis*. 1998;8:158–165. doi: 10.1159/000015842.
39. de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev*. 2000;52:415–472.
40. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. 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. doi: 10.1161/STR.0b013e318284056a.
41. Johnson GJ, Leis LA, Francis GS. Disparate effects of the calcium-channel blockers, nifedipine and verapamil, on alpha 2-adrenergic receptors and thromboxane A2-induced aggregation of human platelets. *Circulation*. 1986;73:847–854.
42. Wigley FM, Wise RA, Malamet R, Scott TE. Nicardipine in the treatment of Raynaud's phenomenon. Dissociation of platelet activation from vasospasm. *Arthritis Rheum*. 1987;30:281–286.
43. Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, et al. 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*. 2013;44:3120–3128. doi: 10.1161/STROKEAHA.113.001301.
44. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5.
45. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647.
46. Bath PM. William M. Feinberg award for excellence in clinical stroke: high explosive treatment for ultra-acute stroke: hype of hope. *Stroke*. 2016;47:2423–2426. doi: 10.1161/STROKEAHA.116.013243.
47. Sare GM, Gray LJ, Bath PM. Effect of antihypertensive agents on cerebral blood flow and flow velocity in acute ischaemic stroke: systematic review of controlled studies. *J Hypertens*. 2008;26:1058–1064. doi: 10.1097/HJH.0b013e3282fbd240.
48. McCourt R, Gould B, Gioia L, Kate M, Coutts SB, Dowlatshahi D, et al; ICH ADAPT Investigators. Cerebral perfusion and blood pressure do not affect perihematoma edema growth in acute intracerebral hemorrhage. *Stroke*. 2014;45:1292–1298. doi: 10.1161/STROKEAHA.113.003194.
49. Kate M, Asdaghi N, Gioia L, Buck B, Jeerakathil T, Shuaib A, et al. Blood pressure lowering with transdermal glyceryl trinitrate is not associated with improvement in cerebral perfusion. *Int J Stroke*. 2015;10:226–226.
50. Geeganage C, Tracy M, England T, Sare G, Moulin T, Woimant F, et al; for TAIST Investigators. 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. doi: 10.1161/STROKEAHA.110.596163.
51. Chung PW, Kim JT, Sanossian N, Starkmann S, Hamilton S, Gornbein J, et al; FAST-MAG Investigators and Coordinators. Association between hyperacute stage blood pressure variability and outcome in patients with spontaneous intracerebral hemorrhage. *Stroke*. 2018;49:348–354. doi: 10.1161/STROKEAHA.117.017701.
52. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010;375:906–915. doi: 10.1016/S0140-6736(10)60235-8.
53. Appleton JP, Sprigg N, Bath PM. Therapeutic potential of transdermal glyceryl trinitrate in the management of acute stroke. *CNS Drugs*. 2017;31:1–9. doi: 10.1007/s40263-016-0387-7.
54. Butcher K, Selim M. Acute blood pressure management in intracerebral hemorrhage: equipoise resists an attack. *Stroke*. 2016;47:3065–3066. doi: 10.1161/STROKEAHA.116.015060.
55. Bath PM, Hassall DG, Gladwin AM, Palmer RM, Martin JF. Nitric oxide and prostacyclin. Divergence of inhibitory effects on monocyte chemotaxis and adhesion to endothelium in vitro. *Arterioscler Thromb*. 1991;11:254–260.
56. Bath PM. The effect of nitric oxide-donating vasodilators on monocyte chemotaxis and intracellular cGMP concentrations in vitro. *Eur J Clin Pharmacol*. 1993;45:53–58.
57. Lonn EM, Yusuf S, Jha P, Montague TJ, Teo KK, Benedict CR, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation*. 1994;90:2056–2069.
58. Dandona P, Kumar V, Aljada A, Ghanim H, Syed T, Hofmayer D, et al. Angiotensin II receptor blocker valsartan suppresses reactive oxygen species generation in leukocytes, nuclear factor-kappa B, in mononuclear cells of normal subjects: evidence of an antiinflammatory action. *J Clin Endocrinol Metab*. 2003;88:4496–4501. doi: 10.1210/jc.2002-021836.
59. Enlimomab Acute Stroke Trial Investigators. Use of anti-icam-1 therapy in ischemic stroke: results of the enlimomab acute stroke trial. *Neurology*. 2001;57:1428–1434. doi: 10.1212/WNL.57.8.1428.
60. Myers MG, Norris JW, Hachniski VC, Sole MJ. Plasma norepinephrine in stroke. *Stroke*. 1981;12:200–204.
61. Bath PM, Woodhouse L, Krishnan K, Anderson C, Berge E, Ford GA, et al. Effect of treatment delay, stroke type, and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on outcome after acute stroke: a systematic review and meta-analysis of individual patient from randomised trials. *Stroke Res Treat*. 2016;2016:9706720. doi: 10.1155/2016/9706720.
62. Webb AJS, Mazzucco S, Li L, Rothwell PM. Prognostic significance of blood pressure variability on beat-to-beat monitoring after transient ischemic attack and stroke. *Stroke*. 2018;49:62–67. doi: 10.1161/STROKEAHA.117.019107.

KEY WORDS: acute stroke ■ antihypertensive agent ■ blood pressure ■ hypertension ■ intracerebral hemorrhage ■ ischemic stroke

Blood Pressure in Acute Stroke: To Treat or Not to Treat: That Is Still the Question

Philip M. Bath, Jason P. Appleton, Kailash Krishnan and Nikola Sprigg

Stroke. 2018;49:1784-1790; originally published online June 12, 2018;
doi: 10.1161/STROKEAHA.118.021254
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

Cerebrovascular Education and Discovery (CED) 2018

Blood pressure in acute stroke: To treat or not to treat - that is still the question

Philip M Bath, DSc FMedSci; Jason P Appleton, MRCP(UK); Kailash Krishnan, MRCP(UK) PhD; Nikola Sprigg, FRCP DM

Stroke Trials Unit, Division of Clinical Neuroscience
University of Nottingham
City Hospital campus
Nottingham NG5 1PB

Contents

1. Guidelines in intracerebral haemorrhage

Views on the importance and effects of BP lowering have changed over the 33 years since the 1985 debate. Prior to the recent large trials, there was simply too little information to drive clinical decision-making. However, INTERACT-2 [1] led to changes in guidelines in both Europe and North America with these recommending that very early and intensive BP lowering was beneficial in ICH (Supplementary Table I).[2, 3]

Following the publication of ATACH-2,[8] uncertainty has returned and the most recent guidelines from North America (but not Europe) appear to actively dissuade lowering BP in ICH.[5, 6] INTERACT-2 and ATACH-2 differ profoundly in multiple respects (Supplementary Table II) and these are likely to explain the difference in trial outcomes (essentially positive vs definitely neutral).[9, 10] In particular, INTERACT-2 was more than twice the size of ATACH-2 and so able to detect a smaller treatment effect (Supplementary Table II). A reasonable interpretation is that ATACH-2 showed that there is no additional benefit with an aggressive blood pressure target as compared with the intensive target tested in INTERACT-2.[4] Further, nicardipine has mild antiplatelet effects so an additional explanation for the results of ATACH-2 is that the limitation of haematoma expansion related to BP reduction was counteracted by a tendency to increased haematoma expansion due to antiplatelet effects, hence leading to a null finding. Overall, the results of INTERACT-2 are more likely to be representative of the benefit of lowering BP hyper-acutely in ICH than those from ATACH-2; as such, recent guidelines suggesting that BP should not be lowered acutely in ICH (Supplementary Table I) seem inappropriate.[5, 6]

2. Guidelines in ischaemic stroke

Guidelines for patients with IS universally recommend that BP is lowered <185/110 mmHg in patients who can receive thrombolysis (Supplementary Table I), this reflecting the license for alteplase which in turn reflects the protocols of trials that

demonstrated the efficacy of alteplase in hyperacute IS. Most guidelines do not specify how BP should be lowered but the ASA guidelines [7] and common practice in the west is based on intravenous labetalol or nicardipine (or sodium nitroprusside in extreme situations). Increasingly, transdermal NTG is used initially due to its ease of use. In China, the a-AA urapidil is often used.

Although there is no trial evidence, most guidelines recommend that patients with IS who will not receive thrombolysis and have very severe hypertension (>220/120 mmHg) should have their BP lowered by 15%. Reflecting the neutral results of large trials such as CATIS, ENOS and SCAST-IS, guidelines recommend that BP should not be lowered in those patients with moderate-to-severe hypertension (Supplementary Table I).

3. Comparison of INTERACT-2 and ATACH-2 trials

INTERACT-2 and ATACH-2 differed considerably in multiple respects [9] in both design features and results. In respect of design, they differed in size (2794 vs 1000, and so were powered for different effect sizes), randomisation time-window (<6 vs <4.5 hours), use of pre-randomisation treatment (disallowed vs encouraged to lower systolic BP <180 mmHg), and the approach used to lower BP (target vs nicardipine). Their results also differ for baseline systolic BP (179 vs 200 mmHg), achieved early on treatment systolic BP in the active and control groups (150 vs 128 mmHg), and presence of serious adverse events (no increase vs increase in renal events) (Supplementary Table II).

Supplementary Table I. Published guidelines on the management of high blood pressure in acute stroke

	Year	Time (hours)	BP level (mmHg)	BP target (mmHg)	Action	How	Recommendation grade
ICH							
ESO [2]	2014	<6		<140	Lower	No agent recommended	-
ASA [3]	2015	<6	>220		Aggressive lowering	No agent recommended	IIb/C
		<6	150-220	140	Lower	No agent recommended	I/A - IIa/B
RCP [4]	2016	<6	>150	140	Lower urgently	No agent recommended	-
ACC [5]	2017	<6	>220		Lower	Iv agent, but not specified	IIa/C-EO
		<6	150-220	<140	Do not lower	-	III harm/A
HC [6]	2017	<24		<140	Do not lower	-	A
IS							
ASA [7]	2013	<3.0	>185/110	<185/110	Lower before alteplase	Iv labetalol, nicardipine (SNP)	I/B
		<24	180-230/105-120		Lower	Iv labetalol, nicardipine (SNP)	
		<24	>140		Do not lower	-	IIb/C
RCP [4]	2016	<4.5	>185/110	<185/110	Lower before alteplase	No agent recommended	-
ACC [5]	2017	<4.5	>185/100	<185/110	Lower before alteplase	No agent recommended	I/B-NR
		<72	>220/120	Reduce by 15%	Lower	No agent recommended	IIb/C-EO
		<72	<220/120	-	Do not lower	-	III No benefit/A
HC [6]	2017	<4.5	>185/100	<185/110	Lower before alteplase	No agent recommended	B
		<72	>220/120	Reduce by 15%	Lower	No agent recommended	D
		<72	<220/120	-	Do not lower	-	D

ACC: American College of Cardiology; ASA: American Stroke Association; BP: blood pressure; ESO: European Stroke Organisation; HC: Hypertension Canada; ICH: intracerebral haemorrhage; IS: ischaemic stroke; RCP: Royal College of Physicians (London); SNP: sodium nitroprusside

Supplementary Table II. Summary and comparison of INTERACT2 and ATACH2 trials evaluating acute BP management in acute intracerebral haemorrhage

Characteristic	INTERACT 2 [1]	ATACH 2 [8]
Trial design		
Intended size	2800	1280
Absolute risk effect /power	7% at 90% power	10% at 90% power
Relative risk reduction	14%	17%
Patients	≤6 hours	≤4.5 hours (originally <3 hours); GCS> 5; ICH volume <60 cm^3
BP eligibility	SBP >150 <220mmHg	SBP >180 mmHg
Exclusion	Investigator judgment, e.g. if likely death; GCS<5; planned surgery	Spontaneous reduction in SBP; cerebellar haemorrhage; planned surgery; large IVH or pontine haemorrhage
Randomisation		
Treatment group	Intensive with target <140 mmHg	Aggressive with target 110-139 mmHg
Control group	Guideline with target <180 mmHg	Standard with target 140-179 mmHg
Adjustment for imbalance between treatment groups	Large sample size; sensitivity analysis after adjusting for potential confounders	Post-randomisation adjusted for GCS score, IVH and haematoma volume
Intervention	Local protocols: urapidil, labetalol, metoprolol, nicardipine, hydralazine, diuretics	First line: Intravenous nicardipine Second line: labetalol, diltiazem, urapidil
Administration of other antihypertensives		
Before randomisation	Not allowed	Allowed
After randomisation	Allowed	Not allowed
Treatment duration	7 days	1 day
Management after 24 hours	SBP <140 mmHg in intensive group	Nil specific
Primary outcome	mRS 0-2 v 3-6 at 90 days	mRS 0-3 v 4-6 at 90 days
Anticipated treatment effect	ARR ≥7%	ARR ≥10%
Anticoagulant related ICH	INR correction: investigator judgement	INR correction: To <1.5 prior to randomisation
Surgical evacuation	Excluded if planned	Excluded if planned
SAE assessment	Investigator judgement	Review by independent committee
Assessment of care	Not addressed	Review by independent committee

Results		
Achieved size	2839	1000
Time to randomisation (hours)*	3.7 [2.8, 4.8] v 3.7 [2.9, 4.7]	3.0 (1.0) v 3.1 (0.9)
Randomisation $\leq$4 hours †	56.7% v 54.3% within 4 hours	71.4% vs 64.2% within 3 hours
Baseline SBP (mmHg)	179 (17)	201 (27)
Target SBP reached	33.4% at 1 hour	87.8% at 2 hours
First SBP after treatment	150 vs. 164 mmHg	128.9 vs. 141.1 mmHg
Initial difference in SBP between groups	14 mmHg	12 mmHg
SBP	At 6 hours: 139 v 153 (p<0.0001)	At 2 hours: 128.9 (16) v 141.1 (14.8)
SBP at 24 hours	146 mmHg	126 mmHg
Baseline ICH volume, median	11 ml	10 ml
Haematoma expansion at 24 hours¶	26.1% v 26.4% (p=0.90)	18.9% v 24.4% (p=0.08)
Day 90		
mRS, poor	mRS 3-6 52.0% v 55.6% (ARR 3.6% p=0.06) ‡	mRS 4-6 38.7% v 37.7% (p=0.72)
EQ-5D HUS	0.60 (0.39) v 0.55 (0.40) (p=0.002)	0.7 v 0.7 (p=0.29)
SAE's (including significant hypotension and renal failure)	23.3% v 23.6% (p=0.92)	Overall: 25.6% v 20.0% Renal events within 7 days: 9% v 4% (p=0.002)
Intensity of care		
Admission to intensive care unit	38.6% v 37.8% (p=0.67)	unknown
Intubation	7.0% v 6.6% (p=0.74)	unknown
Decision to withdraw care	5.4% v 3.3% (p=0.005)	unknown

ARR: absolute risk reduction; GCS: Glasgow Coma Scale; EQ-5D HUS: EuroQoL health related quality of life health utility score; ICH: intracerebral haemorrhage; IVH: intraventricular haemorrhage; SBP: systolic blood pressure; mRS: modified Rankin scale; SAE: serious adverse events

* Median [interquartile range] or mean (standard deviation)
† Hypothesized time for maximum rate of haematoma expansion
¶ Haemorrhage expansion was defined as the difference in volume from 24 hours to baseline in INTERACT 2 and increase of 33% or more from baseline to 24 hours in ATACH 2
‡ Significant with ordinal analysis

REFERENCES

1. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355-2365
2. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European stroke organisation (eso) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014;9:840-855
3. Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2015;46:2032-2060
4. Intercollegiate Stroke Working Party. National clinical guideline for stroke. *Royal College of Physicians*. 2016;5th Edition 2016
5. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 acc/aha/aapa/abc/acpm/ags/apha/ash/aspc/nma/pcna guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Hypertension*. 2017;71:e13-e115
6. Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. *Can J Cardiol*. 2017;33:557-576
7. Jauch EC, Saver JL, Adams Jr HP, Connors B, Demaerschalk BM, Khatri P, 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
8. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033-1043
9. Butcher K, Selim M. Acute blood pressure management in intracerebral hemorrhage: Equipoise resists an attack. *Stroke*. 2016;47:3065-3066
10. Anderson CS, Selim MH, Molina CA, Qureshi AI. Intensive blood pressure lowering in intracerebral hemorrhage. *Stroke*. 2017;48:2034-2037