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

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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:

"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 more than 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 ischaemic stroke whether defined by early recurrence or death, or late death and dependency.[4, 5] Similarly, high BP is related to haematoma expansion [6] and functional outcome after intracerebral haemorrhage (ICH).[7] A straight-forward 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, 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 (e.g. due to urinary retention).[9] These factors offer multiple targets for treatment.

The principle of uncertainty (or clinical equipoise) has driven the completion of a number of medium and large sized trials in acute ischaemic, haemorrhagic, 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. Whilst some smaller trials involving a few hundreds of patients were negative (i.e. treatment worsened outcome: BEST, Bridgers, INWEST [14, 15, 20]), larger trials (involving a thousand or more patients) have all been neutral (SCAST, INTERACT-2, CATIS, ENOS, ATACH-2 [12, 13, 16, 21, 22]). For the sake of this review, SCAST can be considered to be negative since the presence of two primary outcomes meant that the shift in 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 since 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 summarised in two Cochrane Collaboration systematic reviews [26, 27] along with more recent studies. 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 seven classes have been tested in acute stroke (Tables 2, 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

Alpha adrenoceptor antagonists (a-AA)

Stimulation of alpha1-adrenegric receptors increases smooth muscle contraction under catecholamine control. Antagonism of these receptors by drugs such as doxazosin and urapidil leads to vasorelaxation. 32.5% of patients in the INTERACT-2 trial in ICH received an a-AA, typically urapidil (Table 1).[12] Treatment improved the mRS and the results are compatible with the hypothesis that blocking noradrenaline and adrenaline may be beneficial. Nevertheless, the first and smaller INTERACT trial had a higher utilisation of a-AA but was neutral.[11] The ENCHANTED-BP trial is using a similar approach of testing intensity of BP lowering in patients with hyperacute ischaemic stroke,[19] and interim data suggest a high utilisation of a-AA (personal communication: C Anderson, results expected early 2019).

Angiotensin converting enzyme inhibitors (ACE-I)

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

Angiotensin receptor antagonists (ARA)

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 ischaemic and haemorrhagic 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 ischaemic stroke.[10, 17] The medium-sized VENTURE trial 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.[30] The neutral findings of CATIS, SCAST and VENTURE suggest that the renin-angiotensin-aldosterone system (RAAS) is not a useful target in acute stroke.

Beta adrenoceptor antagonists (ß-RA)

Stimulation of beta-$_1$-adrenegric 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 one month (Table 1).[20] Although BEST was not large and separate results for ICH and ischaemic stroke are not published, one interpretation that is plausible biologically is that reducing cardiac output in acute stroke is potentially hazardous.

Some drugs have antagonist effects on both alpha and beta receptors, such as labetalol (where beta-antagonist effects dominate). Whilst some guidelines recommend using this agent in acute stroke,[31] 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 (CCB)

The movement of calcium through L-type channels in cell membranes drives smooth muscle contraction. Hence blockade of these channels with dihydopyridine 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 ischaemic stroke,[32] two 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 dihydopyridine CCBs have some antiplatelet activity,[33, 34] their use in ICH (as recommended in guidelines, Supplementary Table I) 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. 12.4% of patients 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 blood pressure effect over the first week of treatment in patients with acute stroke.[35]

Nitric oxide donors (NO donor)

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, SNP). 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 pre-defined subgroup (Table 1).[23] NO donors (NTG, SNP) were used in 27% of patients with ICH in the positive hyper-acute INTERACT-2 trial.[12] The ongoing RIGHT-2 trial 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, ischaemic stroke alone, and mixed groups of patients (Table 1). Whilst probable efficacy was seen in the INTERACT-2 trial in ICH,[12] nicardipine was neutral in ATACH-2,[13] and candesartan (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; whilst two studies of NTG were positive in both stroke types when given early,[23, 38] ß-RA were negative in BEST.[20]

Timing

The trials varied considerably in their time-window from onset-to-randomisation, this ranging from less than 6 to less than 48 hours. The only evidence for benefit was seen in those studies where patients were randomised within 6 hours, as seen in INTERACT-2, RIGHT and ENOS-early.[12, 23, 38] This observation is comparable with the time-dependency seen for thrombolysis and thrombectomy in ischaemic stroke,[39, 40] and raises the possibility that at least some effects of NTG may be related to reperfusion following vasodilation.[41] Trials recruiting beyond 6 hours were all neutral (CATIS, ENOS, VENTURE [16, 18, 22]) or negative (BEST, INWEST [15, 20]). The subgroup of patients randomised 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 dihydopyridine CCB *per se* (as already discussed) rather than timing.

Trial size

This review largely focusses 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 more than 4000 participants (CATIS, ENOS) will not have been large enough to detect small but potentially clinically worthwhile effect sizes. The ongoing INTERACT-3 trial is more-then-twice the size 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 (CBF)/perfusion

A number of small studies have been performed that assessed CBF or cerebral blood flow velocity following administration of an ACE-I, ARA, ß-RA (labetalol), CCB, diuretic, or NO donor.[46-49] Whilst no difference in CBF was seen in randomised 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 ß-RA or labetalol. There is an urgent need for large high quality randomised 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

ß-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

ischaemic stroke and in ischaemic areas around haematoma. This sequence might explain increased deaths seen in the BEST trial.[20] Exploring the relationship between cardiac output and CBF is important since labetalol, which has significant ß-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 ischaemic stroke.

Blood pressure variability

High BP and a number of 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] whilst CCBs and non-loop diuretics reduce inter-individual variance, ACE, ARA and ß-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 since neutral or negative results were seen with agents that both reduce (CCBs) or increase (ACE, ARA and ß-RA) variability.

Neuroprotection

Several antihypertensive drug classes (ARA, CCB, NO donors) have putative neuroprotective properties,[32, 42, 45] at least in animal models of stroke. The relevance of this is unclear since no large clinical trials of putative neuroprotectants have led to their introduction in clinical practice.

Antiplatelet

Multiple antihypertensive classes (ARA, ß-RA, CCB, spontaneous NO donors such as SNP) 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, INWEST [14, 15]). Although there are many hypotheses why INTERACT-2 and ATACH-2 gave different results in hyper-acute ICH (Supplementary Table II),[54] a key potential explanation is that the mild antiplatelet effects of dihydopyridine CCBs (which includes nicardipine) [33, 34] neutralised its BP effects in ATACH-2.

Anti-white cell effects

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

Inhibition of renin-angiotensin-aldosterone system (RAAS)

ACE-I, ARA and ß-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 since trials have found that ACE-I and ARA were neutral in IS (CATIS, SCAST [16, 17]), ARA was negative in ICH (SCAST [10]), and ß-RA were negative in mixed stroke.[20]

Inhibition of the sympathetic autonomic nervous system (SANS)

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 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 hyper-acute phase of stroke (<6 hours) if a beneficial effect is to be seen, and efficacy may be localised to one or two classes, a-AA and NO donors. The evidence for a-AA is less clear since 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. Whilst 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 observation for a-AA and NTG are true, then attenuating sympathetic activity and/or supplementing vascular NO [41] 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, INTERACT-3, MR-ASAP 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 extra-cranial stenosis, and interaction with mechanical thrombectomy. Similarly, imaging studies in ICH need to assess induction of ischaemia (as is being investigated in ICH-ADAPT-2) and effects on haematoma characteristics such as spot sign, oedema, intraventricular haemorrhage, and proximal ischaemia. Ongoing and future large trials will need to assess the role of lowering BP not just by stroke type, but by severity and aetiology; 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 ischaemic stroke, and ß-RA in either stroke type. Guidelines that recommend the use of labetalol (with predominant ß-RA activity) and CCB for lowering BP in acute stroke may need to be revised (Supplementary Table I).

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Table 1. Medium and large randomised controlled trials of blood pressure lowering in acute stroke. Where relevant, subgroups of trials are shown in brackets

	Intervention/Class (agent)	**Size**	**OTR (hours)**	**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 alpha-AA/ß-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 [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]	ß-RA (atenolol, propranolol po)	302	<48	Negative
SCAST [21]	ARA (candesartan po)	2029	<30	Neutral; negative if recurrence co-primary ignored
ENOS [22]	NO donor (NTG td)	4096	<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

ARA: angiotensin receptor antagonist; a-AA: alpha-receptor antagonist; CCB: calcium channel blocker; ICH: intracerebral haemorrhage; IS: ischaemic stroke; iv: intravenous; NO: nitric oxide; NTG: nitroglycerin/glyceryl trinitrate; OTR: onset to randomisation; td: transdermal

INTERACT-3: https://clinicaltrials.gov/ct2/show/NCT03209258

ICH-ADAPT: https://clinicaltrials.gov/ct2/show/NCT02281838

MR_ASAP: https://www.isrctn.com/ISRCTN99503308

RIGHT-2: http://right-2.ac.uk

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-I	⇨			⇧			⇩	⇩		IS ⇨	Neutral after IS. Avoid in ICH?
ARA	⇨			⇧	+ 42	⇩	⇩	⇩		ICH ⇩? IS ⇨	SCAST-ICH: Negative – AT_2 receptor effects? SCAST-IS, VENTURE
ß-RA		⇩	⇩	⇧		⇩ 43		⇩		IS ⇩	Enhance hypoperfusion?
CCB	⇨	(⇩)	(⇩)	⇩	+ 32	⇩		⇧		IS ⇨⇩ ICH ⇨	Neutral after IS,[44] with some negative trials
Diuretics				⇩				⇧			Onset slow (thiazide-like) [35]
NO	⇨⇧		(⇧)	⇩	+ 45	(⇩)	(⇩)			ICH ⇧? IS ⇧?	Positive early after IS and ICH? Supplement low vascular levels.[36, 37] Enhance reperfusion? Spontaneous NO donors (e.g. SNP), but not nitrates, have antiplatelet activity [46]

ACE-I; angiotensin converting enzyme-inhibitors; ARA: angiotensin receptor antagonists; A-AA: alpha-receptor antagonists; BPV: blood pressure variability; ß-RA: beta-receptor antagonists; CBF: cerebral blood flow; CCB: calcium channel blockers; CO: cardiac output; ICH: intracerebral haemorrhage; IS: ischaemic stroke; NO: nitric oxide donors; Plt: Platelet function; RAAS: renin-angiotensin-aldosterone system; SANS: sympathetic autonomic nervous system; SNP: sodium nitroprusside; UK: unknown

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-I	ARA	CCB	ß-RA
<6	ICH	+	+?	+?			0	
	IS	?	+?					
>6	ICH		0			–/0		-
	IS		0		0	0	-	-

Trial results: -: negative; 0: neutral; +: positive; ?: ongoing trial(s)

a-AA: alpha-receptor antagonist; ACE-I: angiotensin converting enzyme-inhibitors; ARA: angiotensin receptor antagonist; ß-RA: beta-receptor antagonist; CCB: calcium channel blocker; NO: nitric oxide donor;