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Review Article

Hypertension in Acute Intracerebral Haemorrhage and Ischaemic Stroke: When and When not to Treat.

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Abstract

The most common forms of hypertensive crisis in developed countries are pulmonary oedema/heart failure, acute coronary syndrome, acute intracerebral haemorrhage and acute ischaemic stroke. Hypertension can be both cause and consequence of stroke and is associated with poor functional outcome and increased mortality. It does not necessarily follow that lowering of blood pressure acutely will confer benefit, so the question that arises is when and when not to treat? Current recommendations are to consider patients with acute spontaneous intracerebral haemorrhage with a SBP of 150-220 mmHg for urgent treatment within 6 hours of symptom onset, using a locally agreed protocol for BP lowering, aiming to achieve a systolic BP between 130-139 mmHg within one hour and sustained for at least 7 days. By contrast the only certainty for BP lowering after acute ischaemic stroke is a BP target <185/110mmHg for thrombolysis. The many randomised trials in acute ischaemic stroke are inconclusive about stopping or continuing antihypertensive drugs, or specific BP targets, in almost all other settings.

Keywords: acute intracerebral haemorrhage; acute ischaemic stroke; hypertension; treatment

Introduction

The management of hypertensive crisis has been the subject of many recent reviews [1-3]. These have tended to draw on recommendations of the AHA [4], ESC [5-6] and NICE [7] and are based on expert opinion rather than randomised treatment trials, given the lack of the latter in this particular field of medicine. In this review, we will examine in more detail the evidence relating to the management of one particular hypertensive crisis, namely that of hypertension in acute stroke. To our knowledge, acute stroke is the only hypertensive crisis that has been subjected to randomised trials. Our review will concentrate on three large randomised trials in stroke due to intracerebral haemorrhage (ICH) [8-10], and one recently published large trial in acute ischaemic stroke [11]. For additional analyses of these and several smaller trials, see the reviews by [12-13].

Literature Review

Intracerebral haemorrhage

INTERACT-2 (Investigators in the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) was a randomised controlled trial in 2,839 patients with ICH and elevated systolic BP (SBP) 150–220 mm Hg who were allocated to receive intensive (target SBP <140 mm Hg within 1 hour, with lower limit of 130 mm Hg for treatment cessation) or guideline recommended BP lowering treatment (target SBP <180 mm Hg) [8]. Physicians could choose which drugs to use. An intravenous agent, commonly urapidil, nicardipine, labetalol or nitroglycerin, was prescribed in 90.1% of those allocated to intensive treatment and in 42.9% of controls. The primary outcome of death or disability (modified Rankin scores 3-6) at 90 days was observed in 52.0% of the participants in the intensive treatment group and in 55.6% receiving standard treatment (odds ratio with intensive treatment, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06). A prespecified ordinal analysis showed significantly lower modified Rankin scores (ie less disability) with intensive treatment (odds ratio 0.87; 95% CI, 0.77 to 1.00; P=0.04). Participants in the intensive treatment group also had significantly better health-related quality of life at 90 days, as assessed by the EQ-5D questionnaire, than did those in the standard therapy group (P=0.002) [8].

INTERACT-3 was a randomized controlled trial in 7036 patients, with ICH and SBP 140mmHg or greater, who were allocated to early intensive BP reduction as part of a bundle of hyperacute care incorporating protocols for hyperglycaemia, pyrexia and abnormal anticoagulation, or to usual care [10]. Target systolic blood pressure in the care bundle group was less than 140 mm Hg within one hour of the initiation of treatment, with a systolic blood pressure of 130 mm Hg being the threshold for the cessation of treatment. An intravenous agent, commonly urapidil, sodium nitroprusside, labetalol or nicardipine, was prescribed in 78.9% of those allocated to intensive treatment and to 70.9% of controls. The primary outcome was functional recovery measured by the modified Rankin scale at 6 months. The likelihood of a poor functional outcome was lower in the care bundle group (odds ratio

0·86; 95% CI 0·76 to 0·97; p=0·015) [10]. There was no significant difference in the combined end point of death or disability (modified Rankin scores 3–6) at 6 months (odds ratio 0·89; 95% CI 0·78–1·02; p=0·10).

ATACH-2 (Antihypertensive Treatment of Acute Cerebral Haemorrhage) randomised 1000 patients with acute ICH and hypertension to the same two systolic BP targets as INTERACT-2 (ie, <140 or <180 mmHg), though intravenous nicardipine had to be used as first-line medication [9]. The BP target was to be maintained for 24 hours. The primary outcome of death or major disability (modified Rankin scores 4-6) at 3 months was observed in 38.7% of the participants in the intensive-treatment group and in 37.7% in the standard-treatment group (relative risk, 1.04; 95% confidence interval, 0.85 to 1.27) after adjusting for age, initial GCS score, and presence or absence of intraventricular haemorrhage. There were no significant differences in disability or quality of life scores at 3 months [9]. Of note, an ATACH-2 subgroup analysis has since shown that in 'fast-bleeding' patients (defined as an ICH volume/onset to computed tomography time >5 ml/hr) who received treatment within 2 hours after symptom onset, intensive BP lowering was associated with improved functional independence (odds ratio 1.98, 95% CI 1.06–3.69; p = 0.031) [11].

In summary, three large randomised trials of antihypertensive therapy in patients with ICH have shown no reduction in a combined end-point of death or disability. Two reported small but significant improvements in disability and quality of life scores, while the third didn't. Although target systolic BP was the same, there were differences in trial design and execution. INTERACT-2 and ATACH-2 were trials purely of early BP reduction whereas INTERACT-3 tested a package of hyperacute care of which early BP reduction was but one component. BP lowering had to start within 6 hours of presentation in both INTERACT trials and within 4.5 hours in ATACH-2. The choice of drug and the route of administration in INTERACT-2 and INTERACT-3 were at the discretion of the trial physician while all patients in ATACH-2 were to receive intravenous nicardipine as first line therapy. BP reduction was faster and more pronounced in ATACH-2 (average SBP over the first 24 hours was 120-130 mmHg in ATACH-2 compared to 135-145 mmHg in INTERACT-2 and INTERACT-3). It is conceivable therefore that this degree of reduction may have been excessive in ATACH-2 [15], though it has recently been suggested that a subgroup of 'fast bleeding' patients who receive intravenous antihypertensive therapy within two hours may benefit [11]. Importantly, all three trials excluded patients who had an underlying structural cause eg tumour, arteriovenous malformation or aneurysm; or Glasgow Coma Scale below 6; or early neurosurgery to evacuate the haematoma; or a massive haematoma with a poor expected prognosis [8-10].

Acute ischaemic stroke

CATIS-2 (China Antihypertensive Trial in acute Ischaemic Stroke) was a multicentre, randomised open label trial of early versus delayed antihypertensive treatment in 4810 patients with acute ischaemic stroke and elevated SBP 140-220mmHg [11]. Patients were allocated to receive antihypertensive treatment within 24-48 hours of stroke onset (target 10-20% SBP reduction within 24 hours and SBP <140/90mmHg within 7 days) or to discontinue antihypertensive medications for seven days if they were already on treatment, and then receive treatment from day 8 (target SBP <140/90mmHg). The most frequently used antihypertensive medications were oral calcium channel blockers, followed by ACE inhibitors, angiotensin receptor blockers and diuretics. Just under 25% of patients in the early treatment group received an intravenous drug. Mean SBP was 139mmHg and 151mmHg respectively in the early and delayed treatment groups on day seven. The primary outcome of death or disability (modified Rankin scores 3-6) at 90 days was observed in 12.0% of the early and 10.5% of the delayed treatment groups (odds ratio with early treatment 1.18; 95%CI 0.98 to 1.41; P=0.08). There were no differences in disability scores, a secondary outcome, at 90 days [11].

Discussion

Intracerebral haemorrhage

We have summarised current recommendations for control of hypertension in acute ICH in Table 1 [7, 16-18]. There is a general consensus that patients in whom treatment can be started within 6 hours of symptom onset and whose SBP lies between 150 and 220mmHg, will benefit from blood pressure lowering. There are slight differences in recommended blood pressure targets (Table 1).

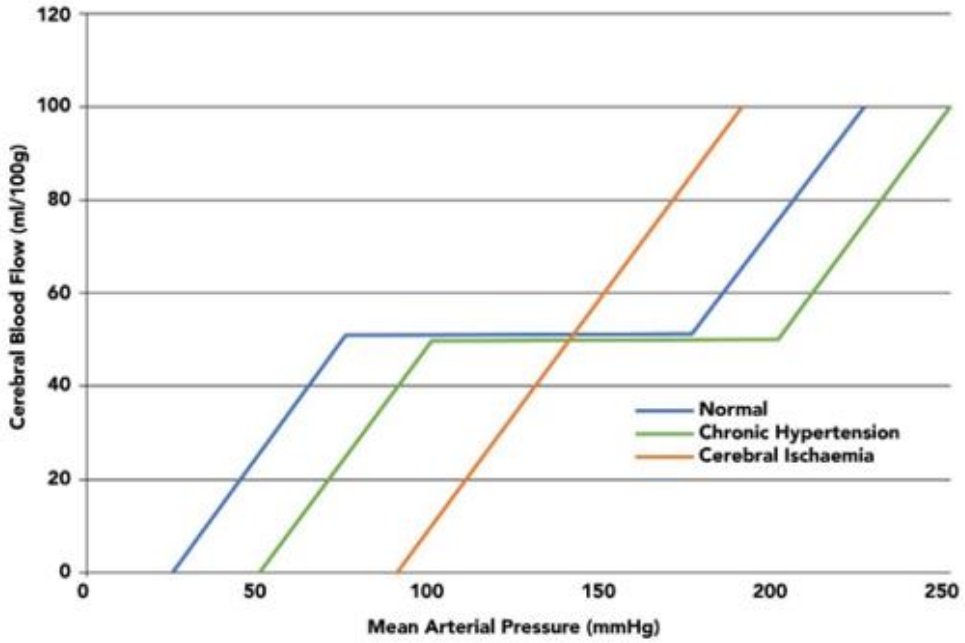
Expert Working Group	Recommendation
NICE 2022	to consider rapid blood pressure lowering for people with acute intracerebral haemorrhage who do not have any of the exclusions and who present within 6 hours of symptom onset and have a systolic blood pressure of between 150 and 220 mmHg, aiming to reach SBP of 140 mmHg or lower, while ensuring that the magnitude drop does not exceed 60 mmHg within 1 hour of starting treatment.
AHA/ASA Guideline 2022	to consider that in patients with spontaneous ICH of mild to moderate severity presenting with SBP between 150- and 220-mm Hg, acute lowering of SBP to a target of 140 mmHg with the goal of maintaining in the range of 130 to 150 mm Hg is safe and may be reasonable for improving functional outcomes.
National Clinical Guideline for Stroke 2023	to consider patients with acute spontaneous intracerebral haemorrhage with a SBP of 150-220 mmHg for urgent treatment within 6 hours of symptom onset, using a locally agreed protocol for BP lowering, aiming to achieve a systolic BP between 130-139 mmHg within one hour and sustained for at least 7 days.
British and Irish Hypertension Society 2023	to balance the risks of rapid and excessive BP reduction against the risk of ICH extension; personalise the BP target and pace of reduction based on background history and ongoing response; generally, consider SBP 140-180 or DBP 90–110 mmHg as appropriate targets; and if BP is severely elevated >220/120 mmHg, consider a smooth reduction in MAP no more than 20–25% over several hours (SBP should be kept ≥140 mmHg, preferably around 140–160 mmHg).

Table 1: Recommendations for BP reduction in acute ICH

Acute ischaemic stroke

CATIS-2 is the latest study to have concluded that early treatment of hypertension in ischaemic stroke does not confer benefit, and may possibly be harmful (CATIS-2). The only certainty for BP lowering after acute ischaemic stroke is a BP target <185/110mmHg for thrombolysis [19-20]. In almost all other settings, the many RCTs are inconclusive about stopping or continuing antihypertensive drugs, or specific BP targets [12]. Underpinning these findings is the phenomenon of cerebral autoregulation, by which cerebral blood flow is held constant across a wide range of mean

arterial pressure from around 50-150mmHg [21]. The autoregulatory curve is reset upwards in patients who have been hypertensive for some time and becomes pressure dependent in acute stroke, which exposes them to the risk of cerebral hypoperfusion if BP is lowered too quickly (Figure 1) [21].



Schematic cerebral auto regulatory curve showing the relation between cerebral blood flow and mean arterial pressure. This is shifted to the right in chronic hypertension. Cerebral blood flow becomes pressure dependent for a time after acute stroke.[21]

There are a few exceptions to the general rule that it is best not to lower BP too quickly in acute ischaemic stroke (apart from the recommendation to lower BP for thrombolysis above). If BP is >220/120mmHg in the acute phase then it is considered reasonable to lower MAP by no more than 15% over 24 hours to maintain perfusion of the penumbra [18-19], Early treatment of hypertension is also indicated in acute ischaemic stroke if this is associated with one or more hypertensive emergencies, namely hypertensive encephalopathy, hypertensive nephropathy, hypertensive heart failure, aortic dissection or pre-eclampsia/eclampsia [7,19]

Choice of Medication

Although the AHA [4] and the ESC [5] provide dosing schedules for no fewer than 12 intravenous antihypertensives, we feel it is unlikely that clinicians will have experience of more than a few of these, given that hypertensive emergencies are uncommon and the indications for their intravenous use infrequent [3]. Labetalol, nitroglycerin and nicardipine have all been used intravenously for control of hypertension acutely in intracerebral haemorrhage (Table 2). Of note, intravenous nicardipine is not stocked in all UK hospitals [3]. There remains uncertainty about the best time to start antihypertensive therapy in ischaemic stroke. The National Clinical Guideline for Stroke states that antihypertensive medication should generally be initiated prior to the transfer of care out of hospital or at 2 weeks, whichever is the soonest, or at the first clinic visit for people not admitted [7], by which time oral calcium channel blocker, ACE inhibitor or angiotensin receptor blocker would all be acceptable choices.

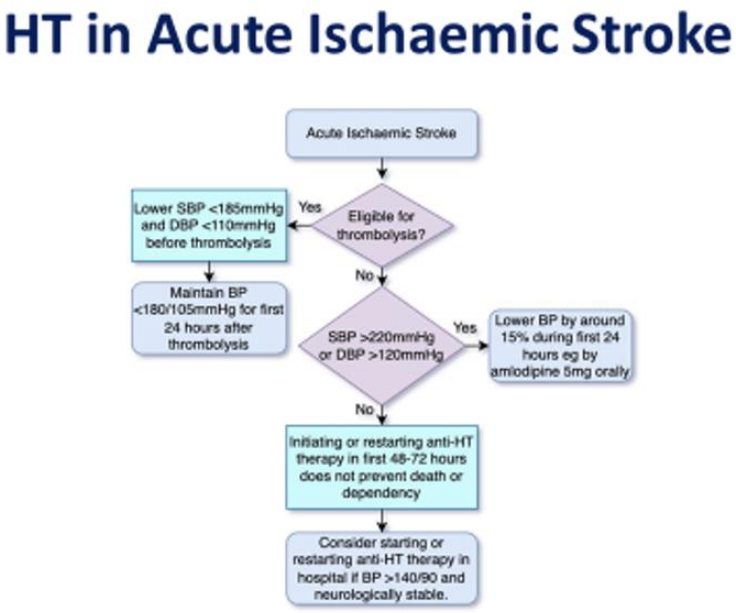
IV Labetalol	• To reconstitute, dilute 200mg in 200ml 5% dextrose to give concentration 1mg/ml • Infuse at 2mg/min until satisfactory response achieved. This will usually be by time 2mg/kg has been given. • Then either stop infusion or continue at a lower rate to maintain desired level of pressure. • Alternatively give 20mg IV bolus every 10 min to a maximum of 300mg if required • Onset of action for Labetalol is 5-15 min, duration 4-6 hours. • Avoid in systolic heart failure, second or third degree AV block, asthma and in phaeochromocytoma (insufficient alpha blockade)
IV Nitroglycerin	• Prepare the infusion by drawing up a 50ml syringe of ready mixed glyceryl trinitrate (50mg in 50ml) • Start infusion at 1mg/hour • Dose range is 1-10mg/hour to achieve and maintain desired level of pressure. • Onset of action for IV nitrate is 3-5 min, duration 3-5 min. • Avoid if volume deplete • Tolerance can limit usefulness • As with all infusion solutions, any unused portion should be discarded after 24 hours

IV Nicardipine	• Dilute each ampoule (25 mg/10 ml) with 240 ml normal saline to make 250 ml of IV solution. The final concentration should be 0.1 mg/ml. • Initiate therapy at 5 mg/hour as a continuous IV infusion. • After 15 minutes, dose can be increased in steps of 0.5–1 mg every 15 minutes, adjusted according to response, maximum rate 15 mg/hour, • Reduce dose gradually when target blood pressure achieved; maintenance 2–4 mg/hour. • The onset of action is 1 to 2 minutes, the mean duration of action after an intravenous bolus dose is around 25 minutes. • Nicardipine should be used cautiously in patients with impaired renal or hepatic function • If a peripheral vein is used, the infusion site should be changed every 12 hours.

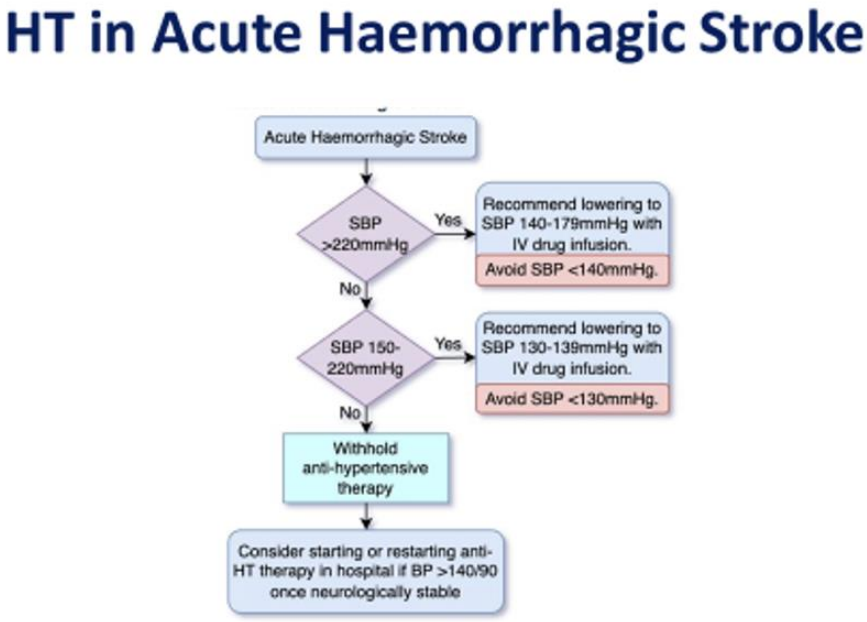
How to use IV Labetalol, IV Nitroglycerin and IV Nicardipine

Conclusion

Current recommendations for the management of hypertension in acute stroke reflect the need for a tailored approach. The evidence in favour of treating hypertension acutely in intracerebral haemorrhage is not as strong as we would wish, but is probably strong enough to consider those with a SBP of 150-220 mmHg for urgent treatment within 6 hours of symptom onset, using a locally agreed protocol for BP lowering, aiming to achieve a systolic BP between 130-139 mmHg within one hour and sustained for at least 7 days [7] (Figure 2). By contrast the only certainty for BP lowering after acute ischaemic stroke is a BP target <185/110mmHg for thrombolysis. The many randomised trials in acute ischaemic stroke are inconclusive about stopping or continuing antihypertensive drugs, or specific BP targets, in almost all other settings (Figure3).



Flowchart for treatment of hypertension in acute ischaemic stroke



Flowchart for treatment of hypertension in acute haemorrhagic stroke

References

1. Peixoto AJ. Acute severe hypertension. *N Engl J Med* 2019, 381:1843–1852.
2. Astarita A, Covella M, Vallelonga F, et al (2020). Hypertensive emergencies and urgencies in emergency departments: a systematic review and meta-analysis. *J Hypertens* 2020; 38:1203–1210.
3. Jolly H, Freel EM, Isles C (2023). Management of hypertensive emergencies and urgencies: narrative review. *Postgraduate Medical Journal* 2023; 99: 119–126.
4. Whelton PK, Carey RM, Aronow WS, et al (2018). 2017 guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *Hypertension* 2018; 71: 1269–324
5. Williams B, Mancia G, Spiering W et al (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens.* 2018; 36: 1953-2041.
6. van den Born B-JH, Lip GYH, Brguljan-Hitij J, et al (2019). ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother* 2019; 5: 37–46.
7. NICE guideline (NG128). Stroke and transient ischaemic attack in over 16s: diagnosis and initial management.
8. Anderson CD, Heeley E, Huang Y et al (2013) . For the INTERACT2 Investigators. Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage. *N Engl J Med* 2013; 368: 2355-2365.
9. Qureshi AI, Palesch YY, Barsan WD et al (2016) for the 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.
10. Ma L, Hu X, Song L et al (2023) for the INTERACT3 Investigators. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. *Lancet* 2023; 402: 27-40.
11. Liu L, Xie X, Pan Y et al (2023). For the CATIS-2 Investigators. Early versus delayed antihypertensive treatment in patients with acute ischaemic stroke: multicentre, open label, randomised, controlled trial. *BMJ*. 2023; 383.e076448.
12. Bath PM, Song S; Silva GS et al (2022). Blood Pressure Management for Ischemic Stroke in the First 24 Hours. *Stroke* 2022; 53: 1074–1084.
13. Moullaali TJ, Wang X, Sandset EC, et al (2022). Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *J Neurol Neurosurg Psychiatry* 2022; 93: 6–13.
14. Li Q, Morotti A, Warren A (2024). Intensive Blood Pressure Reduction is Associated with Reduced Hematoma Growth in Fast Bleeding Intracerebral Hemorrhage. *Ann Neurol* 2024; 95: 129–136.
15. Rabinstein AA (2018). Optimal Blood Pressure After Intracerebral Hemorrhage Still a Moving Target. *Stroke* 2018; 49: 275-276.
16. National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4.
17. Steven M. Greenberg SM, Ziai WC, Cordonnier C et al (2022). on behalf of the American Heart Association/American Stroke Association. 2022 Guideline for the Management of Patients with Spontaneous Intracerebral Haemorrhage: A Guideline from the American Heart Association/American Stroke Association. *Stroke; e282-e361*
18. Killarney S, Glover M, Kabila V et al (2023). Management of hypertensive crisis: British and Irish Hypertension Society Position document. *Journal of Human Hypertension* 2023; 37: 863–879.
19. Powers WJ, Rabinstein AA, Ackerson T et al (2019). 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.

20. Sandset E, Anderson C, Bath P et al (2021). European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *Eur Stroke J. 6: XLV111-LXXX1X*

21. Manning L, Robinson TG, Anderson CS (2014). Control of blood pressure in hypertensive neurological emergencies. *Curr Hypertens Rep*; 16: 436.

DOI: 10.31579/2690-8794/211