Question 19 evidence tables

Question 19: Does intensive blood pressure reduction and the duration of blood pressure lowering compared to standard treatment improve outcomes in patients with acute intracerebral haemorrhage?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

GTN = glyceryl trinitrate, MMSE = mini mental state examination, BP = blood pressure, TICS = telephone interview cognitive status, ICP = intracranial pressure, and CPP = cerebral perfusion pressure, GCS = general cognition score, IV = intravenous, PHER = perihaematomal oedema, AKI = acute kidney injury, RAAS = renin-angiotensin-aldosterone system, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
135	H. Arima et al. (2015). Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. *Neurology,* 84:5 464-71	Setting: Patients participating in the INTERACT-2 trial, an RCT at 144 sites in 21 countries. 69% of the patients were recruited in China. Design: Post-hoc secondary analysis of INTERACT-2 to examine: 1. Evidence of heterogeneity by 5 baseline SBP subgroups 2. Associations between achieved BP and mRS at 90 days. Subjects: 2839 patients in INTERACT2, key inclusions being < 6 h since onset, SBP 150-220.	The INTERACT2 intervention was to lower SBP to 130-140 within 1 h of starting treatment. This is relevant for the subgroup analysis but not for the observational analysis of achieved BP and outcome.	The primary outcome is mRS at 90 days.	There was no heterogeneity of treatment effect by 5 subgroups defined by baseline SBP of <160, 160–169, 170–179, 180–189, and >190 mm Hg (p mogeneity=0.790). Analyses of achieved BP showed linear increases in the risk of physical dysfunction for achieved SBP above 130 mmHg for both hyperacute (1–24 hours) and acute (2–7 days) phases while modest increases were also observed for achieved SBP below 130 mm Hg	**+** This is an exploratory, post-hoc secondary analysis of a high-quality RCT. It includes a post hoc subgroup analysis and an observational analysis.
135	H. Arima et al. (2015). Optimal achieved blood pressure in	Setting: Multicentre in secondary care.	Intervention: Target systolic BP <140mmHg within 1h, with lower	Functional outcome (modified Rankin scale) score at 90 days.	Analysis of the randomized comparisons showed that intensive BP lowering	**+**

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	acute intracerebral hemorrhage: INTERACT2. *Neurology,* 84:5 464-71	Design: One parallel group RCT, with treatment effect analysed in sub-groups by baseline systolic BP and associations between achieved BP after randomisation and outcome. Subjects: 2,794 adults within 6h of intracerebral haemorrhage onset and systolic BP 150-220 mm Hg.	limit of 130mmHg for treatment cessation. Comparator: Target systolic BP <180 mm Hg).		produced comparable benefits on mRS at 90 days in 5 subgroups defined by baseline SBP of <160, 160–169, 170–179, 180–189, and >=190 mm Hg (p homogeneity 0.790). Analyses of achieved BP showed linear increases in the mRS for achieved SBP above 130 mm Hg for both hyperacute (1–24 hours) and acute (2–7 days) phases while modest increases were also observed for achieved SBP below 130 mm Hg.	Good internal validity. Open treatment allocation.
136	P. M. W. Bath et al. (2015). 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. *The Lancet,* 385:9968 617-628	International multi-centre, randomised, placebo controlled, patient masked, outcome assessor-masked, parallel group design. Trial ran 2001-2013, 79% enrolled in 2008 or later. 173 sites in 23 countries over 5 continents. Both ischemic (n=3342) and haemorrhagic strokes (n=629) included. Mean NIHSS equivalent 11.2 (5.7) Mean age 70 years, 75% had pre-morbid mRS 0, median time to treatment 26 hours, UK 64%, Europe 16%, Asia 14%. Mean baseline BP 167/90.	Patients had SBP 140-200 mm Hg, treated within 48 hours of stroke onset. Randomly assigned to 7 days of transdermal GTN or no GTN for 7 days. In a factorial design, the subset of patients already on BP meds were randomly assigned to continue usual BP meds or stop same for 7 days.	Primary outcome mRS at 90 days. Secondary outcomes Barthel Index (ADLs), modified telephone MMSE (cognition), health-related QOL (EQ-5D and mood. Safety outcomes were all-cause mortality, cause specific case fatality, early neurological deterioration, recurrent stroke by day 7, hypotension episodes and serious adverse events.	After 1st dose of GTN, BP was 7/3.5 mm Hg lower in the GTN group. BP no different at day 3. Common OR for worse outcome with GTN 1.01 (0.91-1.13, p=0.83). Functional outcome did not differ across the 6 different treatment groups. Examination across pre-specified sub-groups gave significant interactions with GTN in women and when treatment given within 6 hours of stroke onset. No interaction between treatment and stroke type or continuing or stopping pre-stroke BP meds.	++ Mean time to randomisation 26 hours, BP 7.0/3.5 mm Hg lower in GTN arm may have been insufficient, GTN given in single-blind design, GTN had acceptable safety. No statistical adjustments made for multiplicity of testing.

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					GTN had no effect on mortality. GTN had no effect on secondary outcomes. GTN patients more likely to have headache or hypotension. SAE no different between groups at day 7 and 90. No difference in distribution of mRS at 90 days in continue vs stop BP meds OR 1.05 (0.90-1.12, p=0.55). Similar findings across all pre-specified sub-groups.	
136	P. M. W. Bath et al. (2015). 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. *The Lancet,* 385:9968 617-628	Hospital-based multicentre, partial-factorial randomised controlled trial in the UK, n=4011, "acute ischaemic or haemorrhagic stroke" with BP 140-220mmHg.	7 days of transdermal glyceryl trinitrate (5 mg per day), started within 48 h of stroke onset.	Function, assessed with the mRS at 90 days by observers masked to treatment assignment.	Mean blood pressure was 167 (SD 19) mm Hg/90 (13) mm Hg at baseline (median 26 h [16–37] after stroke onset), and was significantly reduced on day 1 in 2000 patients allocated to glyceryl trinitrate compared with 2011 controls (difference –7 0 [95% CI –8 5 to –5 6] mm Hg/–3 5 [–4 4 to –2 6] mm Hg; both p<00001) – this is about half that achieved in INTERACT2. Functional outcome at day 90 did not diff er in either treatment comparison—the adjusted common odds ratio (OR) for worse outcome with glyceryl trinitrate versus no	**+** (for indirectness; not the population we are interested in)

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					glyceryl trinitrate was 1.01 (95% CI 0 91–1 13; p=0 83), and with continue versus stop antihypertensive drugs OR was 1.05 (0 90–1 22; p=0.55). The results were similar for ICH and ischaemic stroke for the primary outcome (OR 1.03 for ICH, OR 0.96 for ischaemic stroke) with no significant interaction (P=0.83).	
137	T. Carandini et al. (2018). Intensive versus standard lowering of blood pressure in the acute phase of intracranial haemorrhage: a systematic review and meta-analysis. *Internal and emergency medicine,* 13:1 95-105	Setting: Multicentre in secondary care. Design: SR and MA of parallel group RCTs. Subjects: 6 RCTs including 4,385 adults (63% men, mean age 62y) with intracerebral haemorrhage and elevated blood pressure (BP).	Intervention: intensive BP reduction (i.e., systolic BP less than 140 mmHg or mean BP less than 110 mmHg) Comparator: standard BP reduction (i.e., systolic BP less than 180 mmHg).	Death or disability (mRS 3-5) assessed by the Modified Rankin Scale (mRS) at 90 days.	No differences were detected between the two treatment groups in 3-month mortality (RR = 0.99, 95% CI 0.83–1.17), disability (RR = 0.96, 95% CI 0.89–1.03) and combined death and disability (RR = 0.97, 95% CI 0.90–1.03).	**+** All relevant RCTs included. RCTs pooled had different interventions and comparators. Not IPDMA.
137	T. Carandini et al. (2018). Intensive versus standard lowering of blood pressure in the acute phase of intracranial haemorrhage: a systematic review and meta-analysis. *Internal and emergency medicine,* 13:1 95-105	SR and MA, 6 studies Subjects n=4385 5/6 multi-centre Published 2008-2016 Mean age 62, 63% male Target BP < 140 n=4 Target BP < 150 n=2 Within 6 hours n=4 Within 24-36 hours n=2	Intensive SBP lowering to target of < 140 or MAP < 110 vs standard BP lowering to < 180 mm Hg.	Primary outcomes – death, disability (mRS 3-5) or composite of death or disability at 3 months. Secondary outcomes – early neurological deterioration, substantial hematoma increase and non-fatal serious adverse events at 3 months.	Primary outcomes – Mortality RR 0.99 (0.83-1.17) Disability RR 0.96 (0.89-1.03) Composite RR 0.97 (0.90-1.03) Secondary outcomes – Early neuro deterioration RR 1.03 (0.88-1.19) Substantial haematoma enlargement RR 0.85 (0.70-1.03). Non-fatal serious adverse events at 3 months RR 1.07(0.90-1.28).	**+** Excluded studies not listed, likelihood of publication bias not assessed, time to treatment of included studies 4.5-36 hours, duration of BP treatment intervention 24 hours to 7 days, ordinal shift analysis not possible.

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					No significant differences on primary or secondary endpoints. For endpoints, trend to better outcomes with intensive BP seen. Clinical significance in terms of clinical importance assessed by transforming relative effects (RR) in absolute effects by calculating the absolute risk reduction/1000 patients treated for upper (worst scenario) and lower (best scenario) limits of the confidence intervals of the RR in intensively treated patients. At best, 49/1000 would have better outcome at 3 months vs 13/1000patients would have a worse clinical outcome if intensively treated. For increased hematoma volume, 76/1000 treated would have better outcome vs 7/1000 having a worse outcome (i.e. haematoma enlargement).	
138	D. Chambergo-Michilot et al. (2021). Evidence-based appraisal of blood pressure reduction in spontaneous	Scoping review and overview of reviews examining Clinical Practice Guidelines (CPG n=3), SRs (n=8) and RCTs (n=7).	CPGs published 2014-19 with recommendations on BP management in acute ICH. Quality assessed using	CPG recommended for use if AGREE II score > 60% in most domains. SR quality assessed by A Measurement Tool to	CPG: n=3 8 recommendations, only 2 Grade A. 2 of 3 CPGs recommended aggressive BP lowering if SBP 200-220.	**+** Variable quality of CPGs and SRs notable.

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	intracerebral hemorrhage: A scoping review and overview. *Clinical Neurology and Neurosurgery,* 202: 106497		Appraisal of Guidelines Research and Evaluation II (AGREE II, 6 domains, 23 items). SRs and RCTs compared efficacy and safety of intensive vs standard BP reduction in ICH patients.	assess Systematic Reviews v2 (AMSTAR 2). RCT quality graded using Risk of Bias Tool v 2.	All CPGs report intensive BP lowering to be safe. For overall quality and rigour, 2 of 3 CPGs had AGREE II scores > 60%. CPGs low score on editorial independence. SRs: n=8 None used GRADE method to evaluate certainty of evidence. 2 supported intensive BP reduction, 1 concluded that evidence insufficient, 4 concluded that intensive BP reduction safe but not effective. All SRs had critically low confidence. Intensive BP reduction associated with non-significant reduction in ICH growth. 3 of 8 had optimal quality scores (AMSTAR 2 $\geq$ 11). 1 CPG found a significant risk of renal adverse events with intensive BP reduction. RCT: n=7, 4 open label, 1 included only basal ganglia ICH, 5 included patients within 8 hours of onset. The largest study (INTERACT-2 n=2389)) found a trend to favourable	RCTs did not include large ICH or ICH cases with low GCS.

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					effect on disability or death (OR 0.87, 0.75-1.01), functional outcome (OR 0.87, 0.77-1.00) abd QOL in favour of the intensive. ATACH-2 (n=1000) found no differences in outcomes. Current evidence confined to small to medium sized ICH. Different BP reduction strategies used, avoid abrupt, uneven or large reductions in SBP. Further RCTs needed.	
138	D. Chambergo-Michilot et al. (2021). Evidence-based appraisal of blood pressure reduction in spontaneous intracerebral hemorrhage: A scoping review and overview. *Clinical Neurology and Neurosurgery,* 202: 106497	"scoping review and overview of reviews of the literature" – seems to mainly summarise guidelines.	Not uniform – all trials of BP lowering in ICH	Not standardised.	"guidelines support the use of intensive BP reduction; however, most recent SRs partially supported or did not support it due to the association with renal events. It seems the range goal between 140 and 180 mmHg could be safe and equally effective than intensive reduction."	**N/A**
139	M. Kadicheeni et al. (2021). Therapeutic Variation in Lowering Blood Pressure: Effects on Intracranial Pressure in Acute Intracerebral Haemorrhage. *High Blood Pressure and*	Setting: Multicentre in secondary care. Design: SR of mostly studies (15 before-and-after studies and 3 RCTs) of BP and intracranial pressure (ICP) after ICH. Subjects: 18 studies including between 1 and 385 adults (9 included intracerebral	BP reduction.	Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) at varying times.	Quantitative meta-analysis was not possible.	- Mostly not RCTs. Only 2/18 were high quality at low risk of bias.

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	Cardiovascular Prevention, 28:2 115-128	haemorrhage alone and the other 9 also included patients with other brain injuries), mean age 43-70 years.				
139	M. Kadicheeni et al. (2021). Therapeutic Variation in Lowering Blood Pressure: Effects on Intracranial Pressure in Acute Intracerebral Haemorrhage. *High Blood Pressure and Cardiovascular Prevention,* 28:2 115-128	Systematic review of ICH with BP and ICP or surrogate measures. 18 studies	BP lowering agents	Nil	BP lowering agents had a varying effect on ICP.	**+** Acceptable quality. SR investigating effects of BP lowering on ICP in acute ICH. Findings not of relevance to this question.
140	S. Kan et al. (2020). A clinical study on the association of clinical outcome and acute systolic blood pressure in cerebral hemorrhage patients. *International journal of clinical pharmacology and therapeutics,* 58:3 146-154	Setting: Single centre study at the Critical Care Center of General Hospital, Shanghai Jiaotong University, Shanghai, China Design: This is somewhat unclear. States "The patients were randomly assigned to receive different blood pressure lowering treatments" but this is not further described. Analysis is by achieved BP so may be best considered an observational study. Subjects: 3145 patients with ICH enrolled from Jul 2014 to June 2018. 1500 randomly assigned to 'intensive treatment of BP reduction' and 1645 to 'guideline-recommended therapy'.	The intervention is not described, simply referred to as 'intensive'. Analyses describe the intensive group along by BP bands and not a comparison to the 'guideline recommended' group.	Multiple outcomes are studied, no primary outcome is defined. Outcomes include mRS at 90 days, haematoma enlargement (> 6 ml increase within 24 h), 'gradual impact on the renal and cardiac systems during the first week', and death up to 90 days.	The analysis was conducted by dividing the intensive group in to 5 categories based on 'the distribution of the hourly average' (< 120 mmHg, 120-129, 130,139, 140-150, >150). 120-129 was then used as a reference category in a multifactorial model to study associations with outcomes. Although authors state 140-150 is associated with a greater odds of mRS 4-6 this is actually not significant (1.59[0.98 to 2.61]). Haematoma enlargement is more likely with 140-150 and > 150 and cardiorenal AEs are less likely in the same groups. Absolute reduction from baseline is also analysed with	**-** Appears to be an RCT and described as such but intervention, concealment and collection of outcomes is not clearly described, and analysis is not by allocated group. Some useful observations if considered an observational study but non-contributory regarding the intervention randomised – that is 'intensive BP lowering'.

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					> 95 mmHg associated with higher odds of cardiorenal AEs and > 60 mmHg associated with lower odds of haematoma expansion. The odds of death are lower with > 95 mmHg reduction.	
140	S. Kan et al. (2020). A clinical study on the association of clinical outcome and acute systolic blood pressure in cerebral hemorrhage patients. *International journal of clinical pharmacology and therapeutics,* 58:3 146-154	Critical Care Center of General Hospital, Shanghai Jiaotong University, Shanghai, China. Not clear how many participants, probably 3145. The abstract says "1,500 patients diagnosed with cerebral hemorrhage were randomized and assessed for their neurological symptoms and diagnosed with CT scan. Then it says "1,500 (42%) patients received intensive treatment, while 1,645(58%) patients were assigned the guideline recommended therapy." It appears that there was randomisation to the intervention but not control.	Intensive BP treatment. Not clear if it was truly randomised. In the results it says patients were stratified by BP and that "The patients were randomly assigned to receive different blood pressure lowering treatments."	Function (mRS 4-6) at 90 days.	"The 140 – 150 mmHg group observed an elevated risk compared to the 120 – 130 mmHg group in the modified Rankin scale ((OR = 1.59; 95% CI (0.98 – 2.61))."	- Inadequately and inconsistently described.
141	K. Krishnan et al. (2016). Glyceryl trinitrate for acute intracerebral hemorrhage: Results from the Efficacy of Nitric Oxide in Stroke (ENOS) trial, a subgroup analysis. *Stroke,* 47:1 44-52	Prespecified subgroup analysis from ENOS Trial. Included 629 participants with ICH presenting within 48 hours of symptom onset with sys BP>=140.61 participants were treated in < 6 hours. 54% enrolled from UK.	Treatment: GTN patch 5 mg daily for 1 week Control: no GTN.	mRS at 90 days Secondary outcomes: Barthel index, MMSE, TICS, EQ53, mood. Safety: mortality, early neurological deterioration, recurrent stroke at day 7, symptomatic hypertension/ hypotension and SAEs.	No difference in mRS (OR 1.04; 0.78-1.37, P=0.84) overall in larger cohort (n=629). In subgroup treated < 6 hours (n=61, 29 GTN/32 no GTN) GTN improved functional outcome with shift in 90-day mRS (OR 0.22, 0.07-0.69, P=0.001), better quality of life and cognition scores. GTN group had a trend toward	- Overall numbers treated < 6 hours small (n=61) Volume of ICH in GTN group smaller than in non GTN-treated group.

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					reduction in death (adj HR 0.19, 0.03-1.01, P=0.051)No difference in SAEs between GTN and no GTN.	
141	K. Krishnan et al. (2016). Glyceryl trinitrate for acute intracerebral hemorrhage: Results from the Efficacy of Nitric Oxide in Stroke (ENOS) trial, a subgroup analysis. *Stroke,* 47:1 44-52	Secondary analysis of ENOS including those with ICH only. N=629.	GTN 5mg patch vs no GTN patch daily for 7 days.	mRS at day 90.	Overall, no effect of GTN vs no GTN on mRS at day 90. In those randomised within 6hours, GTN was associated with improved clinical outcomes.	**+** Acceptable quality. Secondary analysis of ENOS RCT; no difference overall but in <6hours GTN improved clinical outcomes. This is not an intensity trial and therefore falls outside this PICO question.
142	Z. K. Law et al. (2021). Outcomes in antiplatelet-associated intracerebral hemorrhage in the tich-2 randomized controlled trial. *Journal of the American Heart Association,* 10:5 01-Dec	Secondary analysis of TICH-2 RCT in those on antiplatelets at randomisation.	Tranexamic acid vs placebo.	mRS at day 90 Haematoma expansion.	Antiplatelet therapy is independently associated with haematoma expansion and unfavourable functional outcome.	**++** Not relevant to this PICO.
143	A. C. Leasure et al. (2019). Intensive Blood Pressure Reduction and Perihematomal Edema Expansion in Deep Intracerebral Hemorrhage. *Stroke,* 50:8 2016-2022	Exploratory analysis of the ATACH-2 randomized trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage-2).	Investigated whether perihaematomal oedema expansion rate (PHER) was reduced by intensive BP reduction.	Poor outcome (3-month modified Rankin Scale score 4–6).	Intensive BP reduction was associated with decreased 24-hour PHER in deep ICH. PHER was not independently associated with outcome in all deep ICH but was associated with poor outcome in basal ganglia ICH.	**+** Secondary analysis of RCT.

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143	A. C. Leasure et al. (2019). Intensive Blood Pressure Reduction and Perihematomal Edema Expansion in Deep Intracerebral Hemorrhage. *Stroke,* 50:8 2016-2022	Randomised, multi-centre, 2 group, open label trial. Subjects recruited within 4.5 hours of symptom onset. BP was at least 180 mm Hg or higher, GCS was 5 or more, ICH volume was < 60 cc. 110 centres in 6 countries 56.2% Asian. 8532 patients screened, 1000 recruited, mean age 61.9 years, females 38.0%, mean baseline BP 200.6/27.0 mm Hg. Median NIHSS 11, large majority of ICH in thalamus and basal ganglia.	To reduce and maintain minimum hourly SBP in the range of 140-179 mm Hg versus 110-139 mm Hg during the 24 hours post randomisation with aim to reach target BP within 2 hours of randomisation. IV nicardipine 5-15 mg/hour was 1st line agent 2nd line agent IV labetolol or if not available IV diltiazem or urapidil.	Pre-specified exploratory analysis in supratentorial, deep ICH (n=870) to determine association between intensive BP reduction and perihematomal edema perihaematomal oedema expansion rate (PHER) at 24 hours. If PHER was associated with poor outcomes (mRS 4-6) If ICH location (thalamus or basal ganglia) modifies these associations. PHER calculated using baseline and 24 hour CT scans and expressed as ml/hour.	Enrolment of the main trial was stopped because of futility at a pre-specified interim analysis. Available CT imaging data n=780 (90%) Mean age 62 years, 63% male, thalamus 43%, basal ganglia 57%. Overall, median PHER was reduced in the intensive BP arm (0.01 cc/hr) vs standard BP arm (0.02 cc/hr, p=0.009). This finding remained significant on multivariable adjustment for all patients but not when examined for only thalamic or basal ganglia ICH alone PHER was not associated with poor outcomes in multivariable analysis. PHER was associated with poor outcomes in basal ganglia ICH (adjusted OR 1.42, 1.05-1.97, p=0.03) but not in the thalamus (adjusted OR 1.02, 0.74-1.4, p=0.89).	**++** Exploratory analysis so findings are only hypothesis generating. Likely insufficient power in ICH location analyses.
144	I. Lobanova et al. (2020). Outcomes of Intensive Systolic Blood Pressure Reduction in Patients with Intracerebral	Setting: Multicentre in secondary care. Design: One parallel group RCT, post hoc sub-group analysis. Subjects: 999 adults with intracerebral haemorrhage and	Intervention: intensive BP reduction with intravenous nicardipine (goal 110–139 mm Hg) within	Neurological deterioration and hematoma expansion within 24 hours and death or severe disability at 90 days, plus kidney adverse events and serious	Outcomes were worse with intensive vs standard BP lowering among 228 participants with initial systolic BP ≥220mmHg, but there was no significant	**+** Good internal validity, but not blinded.

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	Hemorrhage and Excessively High Initial Systolic Blood Pressure: Post Hoc Analysis of a Randomized Clinical Trial. *JAMA Neurology,* 77:11 1355-1365	systolic BP ≥180 mm Hg (62% men, mean age 62y).	4.5h of symptom onset. Comparator: standard BP reduction with intravenous nicardipine (goal 140–179 mm Hg) within 4.5h of symptom onset.	adverse events until day 7 or hospital discharge.	interaction between treatment group and initial systolic BP.	
144	I. Lobanova et al. (2020). Outcomes of Intensive Systolic Blood Pressure Reduction in Patients with Intracerebral Hemorrhage and Excessively High Initial Systolic Blood Pressure: Post Hoc Analysis of a Randomized Clinical Trial. *JAMA Neurology,* 77:11 1355-1365	Post hoc analysis of ATACH-2 evaluating the effects of intensive blood pressure lowering following ICH in patients with Systolic BP > 220 mmHg randomised < 4.5 hours on onset.	Intravenous nicardipine titrated to intensive target (110-139 mmHg) and standard target (140-179 mmHg). Intensive BP maintained for 24 hours.	Primary outcome; death and dependency mRS 4-6. Neurological deterioration (GCS > loss of 2 points, NIHSS > 4 points). Haematoma expansion at 24 hours. Hypotension < 72 hours < 90/60 mmHg. Kidney Adverse events.	228 patients had SBP > 220 mmHg and comparisons made between intensive versus standard targets. Death/Disability Intensive (39%) v Standard (38.4%): NS Haematoma expansion (13.8%: intensive vs 15.8% Standard): NS Kidney adverse events (13.6% Intensive vs 4.2% Stanadard) (Significant)** Neurological deterioration (15.5% vs Standard 6.8%): Significant**	**-/+** Low/acceptable quality. Post hoc analysis with subgroup analysis not pre-specified a priori for ATACH-2 trial. Small number of patients analysed therefore effects may be underestimated. Patients analysed may not be representative of population relevant (ie indirectness). Note SBP > 220 mmHg may be observed in patients with severe neurological injury (ie lobar haemorrhages with raised ICP).
145	A. I. Qureshi et al. (2020). Systolic Blood Pressure Reduction and Acute Kidney Injury in Intracerebral Hemorrhage. *Stroke,* : 3030-3038	Post hoc analysis of ATACH 2 study evaluating proportion of patients with Acute Kidney Injury (AKI), Renal adverse effects and their association with death and dependency. 1000 ICH evaluated in ICH with two treatment arms:	Intensive BP vs Standard goal target < 4.5 hours and maintained at 24 hours.	AKI: stage 1-3 {>1.5, 2 and 3 fold from baseline creatinine). Measured at 24,48 and 72 hours.	14.9% AKI 6.5% Renal adverse events. Higher creatinine> 100mmol/l associated with AKI and renal adverse events.	**+** Post hoc analysis of a RCT with sub group analyses. Not generalisable due to selection of patients

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		> 180 mmHg {intensive goal 100-139 mmHg vs standard goal 140-179 mmHg) randomised <4.5 hours.		Renal events (measured but no documented how grouped) up to 7 days or hospital discharge. Death and dependency at 90 days.	Intensive BP reduction associated with Renal adverse events but not AKI. Use of IV nicardipine was associated with AKI and Renal adverse events. AKI associated with death and dependency (significant) but no Renal adverse events at 90 days.	randomised in the trial and does not specifically answer the question that has been asked.
145	A. I. Qureshi et al. (2020). Systolic Blood Pressure Reduction and Acute Kidney Injury in Intracerebral Hemorrhage. *Stroke,* : 3030-3038	Setting: Multicentre in secondary care. Design: One parallel group RCT, but analysed as an observational study. Subjects: 1,000 adults with intracerebral haemorrhage and systolic BP ≥180 mm Hg.	Intervention: Intensive BP reduction with intravenous nicardipine (goal 110–139 mm Hg) within 4.5h of symptom onset. Comparator: standard BP reduction with intravenous nicardipine (goal 140–179 mm Hg) within 4.5h of symptom onset.	Acute kidney injury and renal adverse events at 3 days.	AKI and renal AEs were observed in 149 patients (14.9%) and 65 patients (6.5%) among 1000 patients, respectively. Higher baseline serum creatinine (≥110 µmol/L) was associated with AKI (OR 2.4 [95% CI, 1.2–4.5]) and renal AEs (OR 3.1 [95% CI, 1.2–8.1]). Higher area under the curve for intravenous nicardipine dose was associated with AKI. There was a higher risk of death (RR 2.6 [95% CI, 1.6–4.2]) and death or disability (relative risk 1.5 [95% CI, 1.3–1.8]) at 90 days in patients with AKI but not in those with renal AEs.	**++** Selection, assessment, confounding and statistical analysis all addressed appropriately. Valid association.
146	A. I. Qureshi et al. (2016). Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *New*	110 acute hospitals in US, China, Germany, Japan, Taiwan, South Korea RCT, open label N=1000 (500 each group) 56.2% participants Asian/	Intensive BP target (110-139) vs standard (140-179) within 2 hr IV Nicardipine administered within	mRS 4-6 (disability or death) at 3 months. EQ-5D, physical/neurological examination, expansion	38.7% (intensive group) vs 37.7% in standard group had death or disability (mRS>=4) at 3 months (RR 1.04 (0.85-1.27). Treatment related SAE within 72 hours of randomisation	**++** Large trial, baseline characteristics balanced. Trial was open label.

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	England Journal of Medicine, 375:11 1033-1043		4.5 hours of symptoms onset.	CT haematoma, safety outcomes, NIHSS, GCS.	1.6% vs 1.2%. renal adverse events at 7 days higher in intensive (9.0%) vs standard (4.0%) P=0.002)	Trial halted before planned 1280 recruited
146	A. I. Qureshi et al. (2016). Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *New England Journal of Medicine,* 375:11 1033-1043	Randomised, multi-centre, 2 group, open label trial. Subjects recruited within 4.5 hours of symptom onset. BP was at least 180 mm Hg or higher, GCS was 5 or more, ICH volume was < 60 cc. 110 centres in 6 countries 56.2% Asian. 8532 patients screened, 1000 recruited, mean age 61.9 years, females 38.0%, mean baseline BP 200.6/27.0 mm Hg. Median NIHSS 11, large majority of ICH in thalamus and basal ganglia.	To reduce and maintain minimum hourly SBP in the range of 140-179 mm Hg versus 110-139 mm Hg during the 24 hours post randomisation with aim to reach target BP within 2 hours of randomisation. IV nicardipine 5-15 mg/hour was 1st line agent 2nd line agent IV labetolol or if not available IV diltiazem or urapidil.	Primary outcome – death or disability (mRS 4-6) at 90 days. Secondary outcomes-EQ-5D utility index, haematoma expansion > 33% at 24 hours. Safety outcomes – Neurologic deterioration, SAEs within 72 hours and death at 90 days.	Enrolment was stopped because of futility at a pre-specified interim analysis. Death or disability occurred in 38.7% in the intensive group vs 37.7% in standard-treatment group, RR 1.04, 0.85-1.27. No significant difference across pre-specified subgroups. Haematoma expansion, neurological deterioration within 24 hours, treatment-related SAE or hypotension within 72 hours were not significantly different. SAE within 90 days were higher in the intensive treatment group (25.6% vs 20.0% aRR 1.30, 1.0-1.69, p=0.05). The rate of renal adverse events was higher in the intensive treatment group (9.0% vs 4.0%, p=0.002)	**+** Subjects and investigators not blinded to treatment assignment. Pre-randomisation BP lowering treatment was allowed to ensure timely compliance with existing guidelines and may have obscured a treatment effect. Lower mortality in this trial (37.7%) than expected on the basis of previous literature (60%). High percentage of patients with favourable baseline characteristics might make it difficult to detect an intensive treatment effect. The early BP lowering effect in ATACH2 standard treatment arm was similar to the effect seen for the intensive therapy arm of INTERACT2 trial.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
147	E. C. Sandset et al. (2021). European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *European Stroke Journal,* 6:2 XLVIII-LXXXIX	Setting: European Stroke Organisation guidelines on blood pressure management in acute ICH Design: Developed using ESO SOP and GRADE methodology. Includes one relevant PICO question: Does intensive BP lowering with and vasodepressor drug compared to control improve outcome? Systematic review performed for this PICO and extracted papers reviewed by 3-4 group members. Meta-analysis undertaken where appropriate.	Intensive BP lowering with a vasopressor drug.	Mortality at 3-6 months, mRS 0-2 3-6 months after onset), haematoma expansion, acute renal injury.	No effect on mortality: OR 1.01(0.86 to 1.18), no heterogeneity by time to treatment (< 6 h, 6-24, 24-72). No effect on good functional outcome: OR 1.05 (0.91 to 1.20) or by subgroups with relation to time to treatment (groups as above). No overall effect on haematoma expansion: OR 0.84 (0.62 to 1.13), but significant if time to treatment is < 6 h: OR 0.81 (0.67 to 0.99) No overall effect on acute renal injury: OR 0.87 (0.28 to 2.74)	**++** Well conducted systematic reviews and meta-analyses. On basis of findings, recommend lowering to below 140 (keeping above 110 mmHg) to reduce haematoma expansion. Consensus statement to treat as early as possible and ideally within 2 h and to avoid decrease in SBP of > 90 mmHg.
147	E. C. Sandset et al. (2021). European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *European Stroke Journal,* 6:2 XLVIII-LXXXIX	PICO: Does intensive blood pressure lowering with vasodepressor drugs improve outcome after ICH. Analysis of RCT with random effects meta-analysis carried out with GRADE recommendations formulated. Analysis of 12 RCT with varied numbers (range 18 to 1394) with different target ranges in BP and varied randomisation timings < 6 hr, < 24 hours and < 72 hours. Different agents also used.	Intensive BP lowering. Summarised two largest trials. INTERACT 2 < 140 mmHg within 1 hour < 6 hours of onset versus standard (<180 mmHg) with a variety of agents (urapadil-50% cases). ATACH-2 Intensive BP lowering (IV nicardipine). Targets 110-140 mmHg< 4.5 hours.	Mortality 90 days. Functional Outcome 90 days. Haematoma expansion. Acute Kidney Injury.	For mortality (12 RCT) no significant difference with intensive BP lowering and no difference in time to treatment. For functional outcome (10 RCT) no significant difference in outcome and in treatment time. Haematoma expansion (RCT). Blood pressure lowering < 6 hours reduced haematoma expansion significantly. Note: INTERACT 2 (no effect on primary outcome but secondary outcome in ordinal scale of MRS was significant	**++** Studies deemed as moderate quality by group members of committee. However results are not generalisable due to patient selection (small deep ICH with small haematoma volumes and intervention deployed beyond first few hours). Excludes large haematomas and those requiring surgery. Studies selected by 2 reviewers. Comprehensive search include pre-hospital cases.

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			Other included ENOS (GTN), RIGHT 2 (pre-hospital study n= 73).		with haematoma expansion reduction. ATACH-2 no difference in primary outcome of death and disability), but noted when BP lowering < 2 hours this resulted in improved functional outcome and haematoma expansion (significant but post hoc analysis). 4 RCT reported no association between intensive BP lowering and AKI however observational data suggesting AKI was associated with SBP baseline changes > 90 mmHg.	Relevant characteristics described with meta-analysis carried out for each outcome domain. However, consensus statement made based on post hoc analysis of ATACH-2 {initiate BP lowering < 2 hours).
148	E. C. Sandset et al. (2019). Associations between change in blood pressure and functional outcome, early events and death: Results from the Efficacy of Nitric Oxide in Stroke trial. *Journal of Hypertension,* 37:10 2104-2109	Setting: Multicentre in secondary care. Design: One parallel group RCT, but analysed as an observational study. Subjects: 3,851 adults (594 with ICH) within 48h of intracerebral haemorrhage or ischaemic stroke and systolic BP 140-220 mm Hg.	Intervention: GTN. Comparator: No GTN. Exposure: The greatest change in systolic BP from baseline to day 1 categorized as: more than 15% decrease, 15–5% decrease, 5% decrease to 5% increase (no change - reference) and more than 5% increase.	Functional outcome (modified Rankin scale) score at 90 days.	Amongst patients with ICH, there was no statistically significant difference in the association between the extent of decreases in SBP relative to patients with no change in BP and shifts in the modified Rankin scale or death at 90d, and recurrent stroke/neurological deterioration by 7d (Table 5).	++ Good internal validity.
148	E. C. Sandset et al. (2019). Associations between change in blood pressure and functional outcome, early events and	International multi-centre, randomised, placebo controlled, patient masked, outcome assessor-masked, parallel group design.	Patients had SBP 140-200 mm Hg, treated within 48 hours of stroke onset.	A pre-specified analysis in the main trial suggested a benefit of GTN with reduced odds of poor outcome in patients	Among 594 ICH cases, no association between change in BP at 24 hours and recurrent stroke/neurological deterioration at day 7 or mRS at day 90.	++ Pre-specified secondary analysis of sub-group of ICH cases within larger trial

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	death: Results from the Efficacy of Nitric Oxide in Stroke trial. *Journal of Hypertension,* 37:10 2104-2109	Trial ran 2001-2013, 79% enrolled in 2008 or later. 173 sites in 23 countries over 5 continents. Both ischemic (n=3342) and haemorrhagic strokes (n=629) included. Mean NIHSS equivalent 11.2 (5.7) Mean age 70 years, 75% had pre-morbid mRS 0, median time to treatment 26 hours. UK 64%, Europe 16%, Asia 14%. Mean baseline BP 167/90	Randomly assigned to 7 days of transdermal GTN or no GTN for 7 days. In a factorial design, the subset of patients already on BP meds were randomly assigned to continue usual BP meds or stop same for 7 days.	treated within 6 hours of stroke onset. This secondary analysis looked at change in SBP within 1 day of randomisation and early events at 7 days and death and functional outcome at 90 days. BP change within 24 hours was classified as > 15% decrease, 5-15% decrease, -5 to + 5% increase and > 5% increase.	Trend to higher mortality at day 90 with either > 15% decrease and > 5% increase (n.s. p=0.08)	including both ICH (15.8%) and ischemic strokes (84.2%).
149	K. Toyoda et al. (2019). Clinical Outcomes Depending on Acute Blood Pressure After Cerebral Hemorrhage. *Annals of Neurology,* 85:1 105-113	Secondary analysis of ATACH-II RCT assessing average hourly minimum systolic BP and effects on clinical and radiological outcomes. N=1000.	This was a pooled analysis using whole trial data.	mRS 4-6 90 days Haematoma expansion. Cardiorenal events.	Lowering and maintaining SBP 120-130mmHg during first 24hours was associated with less death and disability, less haematoma expansion but more cardiorenal events.	**+** Acceptable quality. Secondary analysis of ATACH-II. No use of randomisation, therefore observational findings.
149	K. Toyoda et al. (2019). Clinical Outcomes Depending on Acute Blood Pressure After Cerebral Hemorrhage. *Annals of Neurology,* 85:1 105-113	Setting: Multicentre in secondary care. Design: One parallel group RCT, but analysed as an observational study. Subjects: 995 adults with intracerebral haemorrhage and systolic BP ≥180 mm Hg.	Intervention: Intensive BP reduction with intravenous nicardipine (goal 110–139 mm Hg) within 4.5h of symptom onset. Comparator: standard BP reduction with intravenous nicardipine (goal 140–179 mm Hg) within	90-day modified Rankin Scale (mRS) 4 to 6; haematoma expansion, defined as an increase ≥6 ml from baseline to 24-hour computed tomography; and cardiorenal adverse events within 7 days.	Achieved average systolic BP in the 2-24h after randomisation 140-150mmHg vs. 120-130mmHg was associated with higher odds of mRS 4-6 (OR 1.62, 95%CI 1.02-2.58) and haematoma growth (OR 1.80, 95%CI 1.05-3.09), but a lower risk of cardiorenal events (OR 0.43, 95%CI 0.19-0.88).	**+** Good internal validity, but not blinded.

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			4.5h of symptom onset.			
150	K. Toyoda et al. (2021). Intensive blood pressure lowering with nicardipine and outcomes after intracerebral hemorrhage: An individual participant data systematic review. *International Journal of Stroke,* :	IPD meta-analysis of trials/prospective studies assessing the effect of BP lowering of nicardipine in acute ICH.	Nicardipine intravenous. No comparator.	mRS day 90 Haematoma expansion	Mean hourly SBP during initial 24hours associated with death or disability and haematoma expansion.	**+** Acceptable quality. IPD meta-analysis of nicardipine effects on BP. No use of randomisation to BP lowering vs standard.
150	K. Toyoda et al. (2021). Intensive blood pressure lowering with nicardipine and outcomes after intracerebral hemorrhage: An individual participant data systematic review. *International Journal of Stroke,* :	Individual patient data systematic review for intensive BP lowering with IV Nicardipine on outcomes after ICH. Involving 3 studies (1256 patients). ATACH-1, ATCH-2, SAMURAI-ICH.	Intravenous Nicardipine delivered within 12 hours whereby SBP was analysed hourly during 24 hours. Multiple BP targets within three studies.	Hourly SBP (1-24 hours). Primary Outcome (mRS, death and disability). Secondary Outcome (Haematoma expansion). Serious adverse events.	1256 patients, 61% Asians. Increase in SBP (every 10mmHg) resulted in increased odds in death and dependency (OR: 1.2 95% 1 – 1.26). Evident in Asians. Effects observed within 24 hours. Lowering SBP < 140 mmHg < 4 hours less lower odds of death and dependency. Late time to reach SBP < 140 mmHg also lead to significant odds to death and disability. Increase in SBP increased odds to haematoma expansion. Serious Adverse events to Nicardipine (10%).	**+** Low to Acceptable. 2 observational studies included as well as one large RCT (1000). Predominately Asian population. Not all ICH patients (non severe). IV nicardipine not commonly used in the UK (indirectness). IPD included ATACH-2 which was not primarily set up to answer specific question posed.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
						1 study excluded but were not informed what this study was?
151	X. Wang et al. (2016). Degree and Timing of Intensive Blood Pressure Lowering on Hematoma Growth in Intracerebral Hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2 Results. *Stroke,* 47:6 1651-1653	Setting: Patients participating in the INTERACT-2 trial, an RCT at 144 sites in 21 countries. 69% of the patients were recruited in China. Design: Post-hoc secondary analysis of INTERACT-2 to examine associations between categories of SBP reduction and 24 haematoma growth Subjects: 2839 patients in INTERACT2, key inclusions being < 6 h since onset, SBP 150-220. 964 (40%) had a 24 h CT and were included in this analysis.	The INTERACT2 intervention was to lower SBP to 130-140 within 1 h of starting treatment, but the present analysis is observational and not by treatment group.	The primary outcome is haematoma growth as absolute difference in mL from baseline to 24 h.	A greater degree of SBP reduction was associated with less hematoma growth: ΔSBP1–24 h at <10-, 10- to 20-, and ≥20-mm Hg reduction was associated with hematoma growth (mL) of 13.3 (9.0–17.5), 5.0 (1.6–8.4), and 3.0 (0.5–5.4), respectively (P trend<0.001). In 491 patients randomised to intensive treatment, the least hematoma growth (mL) was in those achieving target SBP early (≤1 hour; 2.6; 95% confidence interval, 0.1–5.2) compared with later periods 1 to 6 hour (4.7; 95% confidence interval, 1.8–7.5) and >6 hours (5.4; 95% confidence interval, 2.4–8.3; P trend=0.029). Hematoma growth was 5.2 (95% confidence interval, 2.7–1.8), 3.1 (0.3–6.0), and 0.4 (–1.1 to 5.1), respectively, according to 0 to 2, 3 to 4, and 5 to 8 times to target SBP (Ptrend=0.018).	**+** This is an exploratory, post-hoc secondary analysis of a high-quality RCT. It is an observational analysis, testing for associations between achieved blood pressure and haematoma expansion.
151	X. Wang et al. (2016). Degree and Timing of Intensive Blood Pressure Lowering on Hematoma Growth in Intracerebral	Secondary analysis of INTERACT-2 with CT data available at 24hours. N=964	Intensive vs standard BP lowering.	Haematoma growth at 24hours.	Intensive BP lowering with greater systolic BP reduction was associated with less haematoma growth at 24hours.	**+** Acceptable quality. Selection biased, post-hoc, not-prespecified, hypothesis-

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2 Results. *Stroke,* 47:6 1651-1653					generating RCT secondary analysis, which did not look at the effects of randomization on outcomes.
152	X. Wang et al. (2021). Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Journal of neurology, neurosurgery, and psychiatry,* :	Individual patient data meta-analysis and systematic review encompassing several trials with pre-specified criteria for eligibility. Trials included RCT assessing effects of different BP lowering strategies within 7 days of ICH (active agent/intensive titrated lowering to BP targets versus guideline/placebo targets). 16 studies included (6221 patients). Outcomes include primary outcome: ordinal distribution of mRS (90 days). Secondary outcomes: mRS 3-6. Radiological outcomes: > 6mls and > 33% haematoma growth at 24 hours. Safety outcomes: symptomatic hypotension and early neurological deterioration. Assess whether early lowering BP is modified by a number of factors (patient characteristics, timing of intervention and type of agents). Tests for heterogeneity (statistical) also measured to evaluate effects of blood pressure lowering using chi square and I square modelling.	Active BP lowering agents versus placebo or intensive BP lowering versus guideline BP lowering agents. Agents frequently analysed: Renin angiotensin blockers Alpha blockers Beta blockers Calcium channel blockers.	Outcomes include Primary outcome: ordinal distribution of mRS (90 days). Secondary outcomes: mRS 3-6. Radiological outcomes: > 6mls and > 33% haematoma growth at 24 hours. Safety outcomes: symptomatic hypotension and early neurological deterioration	Patient characteristics well matched between Active/Intervention and Placebo/Guideline groups Median NIHSS 11 Mean SBP [177.3mmHg) Mean DBP [100mm/Hg) Onset to randomisation (3.8 hours) Haematoma Volume [10.7 mls) BP difference between both groups: 1. 7.5 mmHg within 1 hr 2. 12.1 mmHg 1-24 hours 3. 7.3 mmHg 2-7 days No effect of active/intensive BP reduction on functional outcome, death or death and dependency Effects of active/intensive BP lowering were consistent across a number of patient groups however tests for heterogeneity evident for	**++** Large IPD meta-analysis > 6000 with comprehensive inclusion of relevant high quality RCT. Powered to detect heterogeneity Note > 2500 patients evaluating haematoma volumes. Reviewed independently by two authors. Cochrane collaboration included for comprehensive eligibility.

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					intensive BP lowering for functional outcome (non sig increase) as well as alpha and beta blockers being associated with non significant increase in functional outcome. No SAE. Mean difference in haematoma growth 1.1 mls at 24 hours. Odds were higher for reduction in haematoma growth in the active/intensive arm with no heterogeneity noted (5 trials). Effects particularly pronounced between 2-4 hours of onset. Only 326 patients had incomplete data (small number).	
152	X. Wang et al. (2021). Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Journal of neurology, neurosurgery, and psychiatry,* :	Prespecified systematic review of the Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE databases from inception to 23 June 2020 to identify randomised controlled trials that compared active BP-lowering agents versus placebo or intensive versus guideline BP-lowering targets for adults <7 days after ICH onset.	Active BP-lowering agents versus placebo or intensive versus guideline BP-lowering.	Function (distribution of scores on the modified Rankin scale) 90 days after randomisation. Radiological outcomes were absolute (>6 mL) and proportional (>33%) haematoma growth at 24 hours.	!6 trials shared patient-level data from 6221 (54.1%) patients (mean age 64.2 [SD 12.9], 2266 [36.4%] females) with a median time from symptom onset to randomisation of 3.8 hours (IQR 2.6–5.3). Active/intensive BP-lowering interventions had no effect on the primary outcome compared with placebo/guideline treatment (adjusted OR for unfavourable shift in modified Rankin scale	**++** Meta-analysis of RCTs.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					scores: 0.97, 95% CI 0.88 to 1.06; p=0.50), but there was significant heterogeneity by strategy (pinteraction=0.031) and agent (pinteraction <0.0001). Active/intensive BP-lowering interventions clearly reduced absolute(>6 ml, adjusted OR 0.75, 95%CI 0.60 to 0.92; p=0.0077) and relative (≥33%, adjusted OR 0.82, 95%CI 0.68 to 0.99; p=0.034) haematoma growth.	
153	A. D. Warren et al. (2020). Ultra-Early Blood Pressure Reduction Attenuates Hematoma Growth and Improves Outcome in Intracerebral Hemorrhage. *Annals of Neurology,* 88:2 388-395	Setting: Patients participating in the ATACH-2 trial, an RCT at 110 sites in the United States, Japan, China, Taiwan, South Korea, and Germany. In the main trial, A total of 38.0% of the patients were women, and 56.2% of the patients were Asian. Design: Post-hoc secondary analysis of ATACH-2 RCT splitting population in to time to treatment < 2h or > 2 h. Subjects: 1000 subjects from ATACH-2, 87 excluded for missing data. Key ATACH-2 inclusions: GCS>/= 5, ICH vol < 60 ml.	Reduce and maintain SBP to target of 140-179 in standard treatment group vs 110-139 in the intensive treatment group using IV nicardipine started < 4.5 h after symptom onset.	For published secondary analysis – the primary outcome is haematoma growth (>33% between baseline and follow up CT). Secondary outcomes were delayed IVH, mRS at 3 months.	354 (38.7%) participants had nicardipine in < 2 h from onset. Intensive treatment in this subgroup was associated with an adjusted lower frequency of ICH expansion (OR 0.56, 95%CI: 0.34-0.92,p=0.02), higher rate of mRS 0-2 (OR 2.17, 95%CI 1.28-3.68, p=0.004), mRS 0-3 (OR 1.68, 95%CI 1.01-2.83, p=0.048) as well as by ordinal shift (p=0.04).	**+** This is an exploratory, post-hoc secondary analysis of a high-quality RCT. As it is post-hoc and secondary it requires confirmation in a further RCT recruiting patients who can be treated within 2 h of symptom onset.
153	A. D. Warren et al. (2020). Ultra-Early Blood Pressure Reduction Attenuates Hematoma Growth and Improves Outcome in	Post-hoc exploratory analysis of ATACH-2 trial which took place in 110 acute hospitals in US, China, Germany, Japan, Taiwan, South Korea.	Intensive BP target (110-139) vs standard target (140-179) within 2 hour of commencing IV Nicardipine	ICH expansion, haematoma growth, mRS at 90 days.	In patients treated <=2 hours, the attained BP was 120.5 (13.9) in intensive group and 140.6 (16.7) in standard group (P<0.001) Intensive BP group had a reduced frequency of ICH expansion (p=0.02)	**+** Subgroup analysis, exploratory. Requires validation in prospective trials

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Intracerebral Hemorrhage. *Annals of Neurology,* 88:2 388-395	RCT, open label, n=1000 (n=913 with complete imaging and follow-up data) This paper explored just participants (N=354) who received treatment with IV nicardipine within 2 hours of symptom onset.	Treated within 2 hours of symptoms n=354 (n=192 intensive BP reduction, n=162 standard BP reduction). Treated > 2 hours after symptoms onset n=559 (n=274 intensive BP reduction, n=285 standard BP reduction).		decreased risk of haematoma growth (OR 0.56, 0.34-0.92, P=0.02), increased rate of functional independence (OR 2.17, 1.28-3.68, P=0.004), and good outcome at 90 days (OR 1.68, 1.01-2.83, P=0.048) with favourable shift in mRS (P=0.04). In patients treated with nicardipine >2 hours after symptoms, no significant differences in mRS in intensive versus standard BP target groups.	Some missing data on time to nicardipine treatment, mRS scores and other variables Baseline clinical characteristics evenly matched in participants recruited within 2 hours of onset who had BP treated intensively vs standard
154	L. J. Woodhouse et al. (2019). Prehospital Transdermal Glyceryl Trinitrate for Ultra-Acute Intracerebral Hemorrhage: Data From the RIGHT-2 Trial. *Stroke,* 50:11 3064-3071	Setting: Multicentre in ambulances. Design: One parallel group RCT, pre-specified sub-group analysis. Subjects: 145 adults within 4h of intracerebral haemorrhage onset and systolic BP ≥120mmHg.	Intervention: GTN 5mg once daily for 4d. Comparator: Sham dressing once daily for 4d.	Functional outcome (modified Rankin scale) score at 90 days.	mRS at 90 days was nonsignificantly higher in the GTN group: adjusted common odds ratio for poor outcome, 1.87 (95% CI, 0.98–3.57). A prespecified global analysis of 5 clinical outcomes (dependency, disability, cognition, quality of life, and mood) was worse with GTN; Mann-Whitney difference, 0.18 (95% CI, 0.01–0.35; Wei-Lachin test). GTN was associated with larger hematoma and growth, and more mass effect and midline shift on neuroimaging, and altered use of hospital resources. Death in hospital but not at day 90 was increased with GTN. There were no significant between	**++** Good internal validity. Paramedics were unmasked to treatment, whereas participants were masked. Sham-controlled treatment allocation.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					group differences in serious adverse events	
154	L. J. Woodhouse et al. (2019). Prehospital Transdermal Glyceryl Trinitrate for Ultra-Acute Intracerebral Hemorrhage: Data From the RIGHT-2 Trial. *Stroke,* 50:11 3064-3071	Pre-specified Subgroup analysis from RIGHT-2 Trial. Participants within 4 hours of stroke symptoms were randomised by paramedics and treated in ambulances. Subgroup with ICH n=145.	Intervention: GTN 5mg patches started in ambulance and given for <=3 days in hospital n=74 Control: No GTN n=71	mRS at 90 days secondary outcomes: global analysis of 5 clinical outcomes (dependency, disability, cognition, quality of life, mood).	Onset to radnomisation median 74 mins (IQR 45-110 mins) mRS non significantly higher in GTN group (adj OR 1.87, 0.98-3.57) i.e. technically neutral result 5-outcome global analysis worse with GTN (0.18 (0.01-0.35) Participants recruited within 1 hour of symptoms onset fared worse with GTN (forest plots favour sham). No differences in SAE.	**+** Outcomes blinded but researchers not blind to treatment allocation High levels of adherence, low attrition. Baseline characteristics well balanced GTN vs sham. For the purposes of this question (ICH patients), numbers randomised were small TIGHT-2 had limited exclusion criteria therefore representative of population with ICH.
155	X. Wang et al. (2022). J-shape relation of blood pressure reduction and outcome in acute intracerebral hemorrhage: A pooled analysis of INTERACT2 and ATACH-II individual participant data. *Int J Stroke,* : 1.7474930211e+16	Pooled analysis of INTERACT2 and ATACH-II, n=3796. Specifically investigated the relationship between the magnitude of BP reduction and outcome.	As per trials, but this study is no longer truly randomised and can only test associations.	Modified Rankin scale (mRS) scores at 90 days.	Among 3796 patients (mean age 63.1 (SD = 13.0) years; female 37.4%), with a mean magnitude (< 1 h) of SBP reduction of 28.5 (22.8) mmHg, those with larger magnitude were more often non-Asian and female, had higher baseline SBP, received multiple blood pressure (BP) lowering agents, and achieved lower SBP levels in 1–24 h. Compared to those patients with no SBP reduction within 1 h (reference), the adjusted odds of unfavorable functional outcome, according to a shift in mRS scores, were lower for	**+** Non-randomised.

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					SBP reductions up to 60 mmHg with an inflection point between 32 and 46 mmHg, but significantly higher for SBP reductions > 70 mmHg. Similar J-shape associations were evident across various time epochs across 24 h and consistent according to baseline hematoma volume and SBP and history of hypertension.	
155	X. Wang et al. (2022). J-shape relation of blood pressure reduction and outcome in acute intracerebral hemorrhage: A pooled analysis of INTERACT2 and ATACH-II individual participant data. *Int J Stroke,* : 1.7474930211e+16	Pooled analysis of individual participant data from INTERACT2 and ATACH2. N=3796 (mean age 63.1, 37.4% female).	Analysis: Magnitude of early (<1hr) BP reduction in relation to outcome Reference group were those with no SBP reduction.	mRS at 90 days and safety outcomes (deterioration in NIHSS, GCS, SAE at 90 days) As well as SBP reduction within 1hr, graphs were presented with best fit curves for outcomes versus 2) SBP reduction within 30 min and 30-60 min, 1-6 hr and 6-24 hr 3) "achieved BP (mean and SD (variability) in SBP across 5 timepoints 1-24 hr.	Mean /SD magnitude BP reduction <1hr = 28.5 (22.8) Odds of unfavourable outcome in relation to magnitude of SBP reduction was J-shaped Data suggests that there might be an "optimal" magnitude of SBP reduction (between 32 and 46 mmHg) within first hour of treatment. If SBP reduction was less than 32 or more than 46 (and particularly if more than 72 mmHg), the odds of unfavourable outcome were greater than for the reference group (no SBP reduction).	**+** Analysis not prespecified. Authors retrospectively used cubic splines on the data to fit best possible U or J shaped curves to the data. Potential for incomplete adjustment for prognostic variables. Baseline characteristics differed amongst subgroups according to SBP reduction ((<20, 20-40, 40-60, >60mmHg).
156	T. J. Moullaali et al. (2022). Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of	Setting: All international studies meeting inclusion criteria were included, no language restrictions. Design: Systematic review and meta-analysis of RCTs that assessed the effects of different	RCTs that assessed the effects of different BP lowering strategies during the first 7 days of stroke.	Primary outcome was ordinal distribution of the mRS at the end of trial follow up. Secondary outcomes were mRS 3-6, mRS 4-6 & death. Haeamatoma growth as >	Active/intensive BP-lowering interventions had no effect on the primary outcome compared with placebo/guideline treatment (adjusted OR for unfavourable shift in modified Rankin scale	**++** Well conducted SR & MA. Wide array of interventions combined in the analysis with significant heterogeneity by fixed active agent vs. titrated

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	individual patient data. *Journal of Neurology, Neurosurgery & Psychiatry,* 93:1 6	BP lowering strategies during the first 7 days of stroke. Subjects: 7094 studies identified, 50 trials involving 11,494 patients were eligible and 16 (32.0%) shared patient-level data from 6221 (54.1%) patients (mean age 64.2 [SD 12.9], 2266 [36.4%] females) with a median time from symptom onset to randomisation of 3.8 hours (IQR 2.6–5.3).		6 mL or > 33%. Safety outcomes were early neurological deterioration, symptomatic hypotension, any other SAE.	scores: 0.97, 95% CI 0.88 to 1.06; p=0.50). Significant heterogeneity by strategy (pinteraction=0.031) and agent (pinteraction <0.0001). Active/intensive BP-lowering interventions clearly reduced absolute (>6 ml, adjusted OR 0.75, 95%CI 0.60 to 0.92; p=0.0077) and relative (≥33%, adjusted OR 0.82, 95%CI 0.68 to 0.99; p=0.034) haematoma growth.	to intensive target and by most frequently used agent (renin angiotensin system blocker worse than others).
156	T. J. Moullaali et al. (2022). Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Journal of Neurology, Neurosurgery & Psychiatry,* 93:1 6	SR and MA using IPD by Blood Pressure in Acute Stroke (BASC) Investigators. Acute ICH within 7 days. 50 eligible studies IPD obtained from 16 studies, n=6221 of 11494 (32.0%), > 18 years, 56.2 % recruited in Asia, 27.2% in Europe/Australia and 16.6% in the Americas. Mean age 64.2, females 36.4% median NIHSS 11 Median baseline BP 177/100 mm Hg. Median onset to randomisation 3.8 hours (range 2.6-5.3) Median hematoma volume 10.7cc (IQR 5.2-20.7 cc).	Comparison of active BP lowering agents versus placebo or intensive vs guideline BP lowering targets for adults < 7 days since ICH onset.	Primary outcome – ordinal distribution of mRS at 90 days Secondary outcomes – Death or dependency mRS 3-6). Death or severe dependency mRS 4-6. All cause death. Radiological outcomes Absolute and proportional haematoma expansion at 24 hours.	No effect of active/intensive BP management on distribution of mRS scores OR 0.97 (0.88-1.06). No effect of treatment allocation on death (OR 1.01, 0.85-1.20. p=0.91). BP reduction was greater in the intensive group at 1 hour (-7.5/-3.8), 1-24 hours (-12.1/-5.3) and 2-7 days (-7.3/-3.9). No heterogeneity of primary outcome findings seen in pre-specified subgroups by age, sex, baseline NIHSS, baseline hematoma volume, timing of intervention or hospital vs pre-hospital. Suggestion of improved primary outcome with	**++** IPD analyses suggest heterogeneity of intensive treatment effects worthy of further study. No safety concerns raised.

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					titration to intensive target over fixed active agent. RAAS blockers were associated with significantly increased odds of unfavourable shift in mRS (OR 1.57, 1.00-2.45). In contrast, calcium channel blockers (OR 0.94, 0.77-1.15) and alpha- and beta-blockers (0.90, 0.80-1.02) may be associated with lower likelihood of unfavourable shift in mRS. No significant difference any SAE, severe hypotension, cardiac SAE or renal SAE. Haematoma growth at 24 hours was significantly less with intensive BP lowering Mean 3.2 vs 4.3 cc (difference 1.10 ml, -2.22 to 0.01 ml, p=0.05). Absolute (> 6ml) haematoma growth at 24 hours was less in intensive group aOR 0.75, 0.60-0.92, p=0.0077 as was relative haematoma growth (≥ 33% increase) aOR 0.82, 0.68-0.99, p=0.034). No heterogeneity seen across pre-specified sub-groups.	

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
157	T. J. Moullaali et al. (2019). Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol,* 18:9 857-864	Post hoc, pre-planned analysis of pooled individual patient data from INTERACT-2 and ATACH-2. Both trials multicentre, international, recruited from acute hospitals Age 19-99, spontaneous ICH and BP 150-220 (INTERACT2) or >=180 (ATACH2) who were not for immediate neurosurgery	Analysis of 3 pre-specified summary measures of systolic BP control: 1. Difference between sys BP at randomisation and lowest attained within 1 hour 2. Mean achieved sys BP at 5 time points (1-24 h) 3. Variability in sys BP between 1h and 24 h	mRS at 90 days Secondary outcomes: haematoma volume, expansion, NIHSS, safety outcomes	There were linear associations between reducing achieved/sustained sys BP over 24 h and favourable outcomes. Every 10mm Hg reduction in sys BP was associated with a 10% increase in odds of better functional recovery (potentially down to BP of 120-130 although numbers achieving such low BP were small)	**+** Post hoc pooled analysis, unable to account for some potential confounders, multiple testing might have produced some chance associations.
157	T. J. Moullaali et al. (2019). Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol,* 18:9 857-864	Preplanned pooled analysis of individual participant data from INTERACT2 and ATACH-II.	As per individual trials, but this analysis is no longer truly randomised.	Functional status, as defined by the distribution of scores on the modified Rankin Scale at 90 days post-randomisation.	The mean magnitude of early systolic blood pressure reduction was 29 mm Hg (SD 22), and subsequent mean systolic blood pressure achieved was 147 mm Hg (15) and variability in systolic blood pressure was 14 mm Hg (8). Achieved systolic blood pressure was continuously associated with functional status (improvement per 10 mm Hg increase adjusted odds ratio [OR] 0·90 [95% CI 0·87–0·94], p<0·0001). Symptomatic hypotension occurred in 28 (1%) patients, renal serious adverse events occurred in 26 (1%) patients, and cardiac serious adverse events occurred in 99 (3%) patients.	**+** Non-randomised.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
158	P. M. Bath et al. (2019). Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *The Lancet,* 393:10175 1009-1020	Setting: Multicentre in ambulances. Design: One parallel group RCT. Subjects: 1,149 adults within 4h of stroke onset, face-arm-speech-time score of 2 or 3, and systolic BP ≥120mmHg. 597 (52%) patients had ischaemic stroke, 145 (13%) had intracerebral haemorrhage, 109 (9%) had transient ischaemic attack, and 297 (26%) had a non-stroke mimic at the final diagnosis of the index event.	Intervention: GTN 5mg once daily for 4d. Comparator: Sham dressing once daily for 4d.	Functional outcome (modified Rankin scale) score at 90 days.	There was no evidence of a difference in mRS between the groups in participants with a final diagnosis of stroke or transient ischaemic stroke (cohort 1): 3 (IQR 2–5; n=420) in the GTN group versus 3 (2–5; n=408) in the sham group, adjusted common odds ratio for poor outcome 1·25 (95% CI 0·97–1·60; p=0·083). There was no difference in mRS between all patients (cohort 2: 3 [2–5]; n=544, in the GTN group vs 3 [2–5]; n=558, in the sham group; 1·04 [0·84–1·29]; p=0·69).	**++** Good internal validity. Paramedics were unmasked to treatment, whereas participants were masked. Sham-controlled treatment allocation.
158	P. M. Bath et al. (2019). Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *The Lancet,* 393:10175 1009-1020	Setting: UK, multicentre RCT involving 184 ambulance stations and 54 hospitals. Design: Randomised controlled trial of GTN patch in prehospital suspected stroke patients Subjects: 1149 suspected stroke patients in the UK prehospital setting	Participants were randomly assigned (1:1) to receive transdermal GTN (5 mg once daily for 4 days; the GTN group) or a similar sham dressing (the sham group) in UK-based ambulances by paramedics, with treatment continued in hospital.	Primary outcome was mRS at 90 days. Secondary outcomes were Barthel Index at day 90, telephone mini-mental state examination, TICS-M, EQ-5D-3L, EQ-VAS, Zung depression score.	Of the 1149 participants, 145 (13%) had ICH. Overall, there was no improvement of functional outcome in all patients with presumed stroke. There was no significant heterogeneity by diagnosis (p=0.43). Haematoma diameter larger on diagnostic, post-treatment CT (2 cm[2-3], vs. 2[1-3]). No baseline CT.	**++** Well conducted RCT but for relevance to question, small number of ICHs and not powered to definitively test the study question in this subgroup.