

FINAL

Stroke and transient ischaemic attack in over 16s: diagnosis and initial management

[E] Evidence review for maintenance of homeostasis

NICE Guideline NG128

Intervention evidence review

May 2019

FINAL

*This evidence review was developed by
the National Guideline Centre*

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1 Restoration or maintenance of homeostasis

1.1 Review question: What is the safety and efficacy of measures to lower blood pressure versus standard treatment in people with acute intracerebral haemorrhage?

1.2 Introduction

Elevated blood pressure is common after acute stroke. Patients may have pre-existing hypertension or blood pressure changes may occur as a result of disturbed cardiovascular autonomic regulation. Evidence has consistently shown that there is no benefit of lowering blood pressure acutely in ischaemic stroke however there is still clinical uncertainty regarding the safety and efficacy of lowering blood pressure in acute intracerebral haemorrhage. Uncontrolled hypertension in acute intracerebral haemorrhage may result in haemorrhagic expansion and a worse neurological outcome, however there is clinical concern that aggressive blood pressure lowering may reduce blood flow to the brain and other vital organs resulting in adverse outcomes such as cerebral and cord ischaemia, acute kidney injury, and myocardial infarction.

People with intracerebral haemorrhage have a mortality of around 40% with 60-70% of those who survive having moderate or severe disability⁵⁴ and there are currently no treatment options beyond supportive management. If lowering blood pressure is safe and effective this may provide the opportunity improve the outcome in this type of stroke. As a number of clinical trials addressing the safety and efficacy of blood pressure lowering in acute intracerebral haemorrhage have been completed since the original guideline was published in 2008 it was important to review the current evidence regarding this clinical question.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 16 with acute intracerebral haemorrhage and high blood pressure at the time of assessment
Interventions	Intensive blood pressure reduction within 48 hours <ul style="list-style-type: none">• Calcium antagonists (e.g. intravenous isradipine, oral nimodipine, oral and intravenous nimodipine, urapidil, flunarizine, nifedipine and oral PY108-608)• Intravenous or transdermal glyceryl trinitrate (GTN)• Angiotensin II antagonist (e.g. cilixtil)• Beta-blockers (e.g. atenolol, propranolol and labetalol)
Comparisons	Standard care or no treatment/placebo
Outcomes	<u>Critical</u> Mortality at 24 hours/90 days Modified Rankin scale (mRS) score at 90 days and 1 year

	Important Symptomatic cerebral ischemia at 24 hours Haemorrhage expansion at 24 hours Neurological deterioration at 24 hours Adverse events (renal failure, spinal cord infarction, myocardial infarction) at 90 days Quality of life (both health- and social-related quality) at 90 days Percentage achieving blood pressure target
Study design	Randomised controlled trials Systematic reviews and meta-analyses of the above

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.¹⁸ Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy upto March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

1.5 Clinical evidence

1.5.1 Included studies

Seven studies were included in the review^{1, 3, 15, 32, 33, 41, 63} and evidence from these studies is summarised in the clinical evidence summary below (Table 2). The studies all compare intensive blood pressure therapy with standard blood pressure therapy; although some of the blood pressure lowering protocols had different targets. One study³³ was a subgroup analysis of those with intracerebral haemorrhage within a randomised trial.¹¹ Stroke type (ischaemic or haemorrhagic) was a pre-specified subgroup that was used as a stratification variable before initial randomisation; therefore, randomisation was not lost and the subgroup data were eligible for inclusion.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

See the excluded studies list in appendix H.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
<p>ATACH-2 2016, Qureshi et al⁴¹</p> <p>China, Germany, Japan, South Korea, Taiwan, USA</p>	<p>Intensive blood pressure therapy using intravenous nicardipine to target blood pressure vs standard blood pressure therapy using intravenous nicardipine</p> <p>Therapy started within 4.5 hours of presentation and continued for 24 hours Target to be achieved within 2 hours of randomisation</p>	<p>Acute intracerebral haemorrhage and systolic blood pressure ≥ 170 mmHg to ≤ 200 mmHg within 4.5 hours</p> <p>n=1000</p>	<p>90 day: Mortality mRS score EQ-5D utility index score EQ-5D visual analogue scale Renal failure</p> <p>24 hour: Haematoma expansion ($\geq 33\%$ at baseline) Neurological deterioration (Glasgow coma scale [GCS] decrease ≤ 2 from baseline or NIHSS increase ≥ 4)</p>	<p>Intensive systolic blood pressure target: 110 to 139 mmHg Target achieved: 87.8%</p> <p>Comparison systolic blood pressure target: 140 to 179 mmHg Target achieved: 99.2%</p> <p>Mean (SD) minimum systolic blood pressure during the first 2 hours was 128.9 (16) mmHg in the intensive treatment group and 141.1 (14.8) mmHg in the standard treatment group</p>
<p>ENOS-ICH 2016, Krishnan et al³³</p> <p>Australia, Canada, China, Denmark, Egypt, Georgia, Greece, Hong Kong, India, Ireland, Italy, Malaysia, New Zealand, Norway, Philippines, Poland, Romania, Singapore,</p>	<p>Transdermal glyceryl trinitrate (5 mg per day) vs no glyceryl trinitrate continued for 7 days</p>	<p>Acute intracerebral haemorrhage and systolic blood pressure ≥ 140 mm Hg within 48 hours of presentation</p> <p>n=629</p>	<p>90 day: Mortality mRS score Recurrent stroke Myocardial infarction</p>	<p>Pre-specified subgroup analysis of ENOS 2015¹¹, in which randomisation was stratified by stroke type</p> <p>Following first dose of transdermal glyceryl trinitrate vs no treatment, blood pressure fell by 7.5/4.2 mmHg</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Spain, Sri Lanka, Sweden, Turkey, United Kingdom				
ICH ADAPT 2013, Butcher et al ¹⁵ Canada	Intensive blood pressure therapy vs standard blood pressure therapy Details of specific antihypertensives used was not reported Target to be achieved within 1 hour of randomisation and continued for 24 hours	Acute intracerebral haemorrhage and systolic blood pressure >150 mmHg within <24 hours after symptom onset n=75	90 day: Mortality mRS score	Intensive systolic blood pressure target: <150 mmHg Target achieved: 79% Comparison systolic blood pressure target: <180 mmHg Target achieved: 100% Systolic blood pressure during at 1 hour was 150 mmHg in the intensive treatment group and 164 mmHg in the standard treatment group (estimated from graph)
INTERACT 2008, Anderson et al ³ Australia, China, South Korea	Intensive blood pressure therapy continued for 7 days vs standard blood pressure therapy continued for 7 days The majority of participants in both groups received the following antihypertensives: calcium channel blocker, ACE inhibitor, frusemide, urapidil	Acute intracerebral haemorrhage and systolic blood pressure of 150 to 220 mmHg within 6 hours of presentation n=404	90 day: Mortality mRS score EQ-5D utility index score Recurrent stroke Renal failure 24 hour: Haematoma expansion (≥33% at baseline)	Intensive systolic blood pressure target of <140 mmHg within 1 hour of randomisation Target achieved within 1 hour post randomisation: 42% Target achieved within 6 hour post randomisation: 66% Comparison systolic blood pressure target of <180 mmHg At 1 hour the mean systolic blood pressure in the intensive group was 153 mmHg and 167 mmHg in the standard group (difference 14 mmHg, 95%CI 9 to 18 mmHg)
INTERACT2 2013, Anderson et al ¹	Intensive blood pressure therapy vs standard blood pressure therapy	Acute intracerebral haemorrhage and systolic blood pressure	90 day: Mortality	Intensive systolic blood pressure target of <140 mmHg within 1 hour of randomisation Target achieved: 33.4% within 1 st hour

Study	Intervention and comparison	Population	Outcomes	Comments
Argentina, Australia, Austria, Belgian, Brazil, China, China Shanghai, China Hong, Chile, Finland, France, Germany, India, Italy, The Netherlands, Norway, Pakistan, Portugal, Spain, Switzerland, UK, US	continued for 7 days The majority of participants in both groups received the following: alpha-adrenergic antagonist, such as urapidil, calcium-channel blocker, such as nicardipine or nimodipine, combined alpha- and beta-blocker, such as labetalol, nitroglycerin	of 150 to 220 mmHg within 6 hours of presentation n=2839	mRS score Recurrent stroke 24 hour: Substantial haematoma expansion Neurological deterioration (GCS decrease ≤ 2 from baseline or NIHSS increase ≥ 4)	Comparison systolic blood pressure target of <180 mmHg At 1 hour the mean systolic blood pressure in the intensive group was 150 mmHg and 164 mmHg in the standard group (difference 14 mmHg, 95%CI 9 to 18 mmHg)
Koch 2008 ³² USA	Intensive blood pressure therapy vs standard blood pressure therapy continued for 48 hours The majority of participants in both groups received intravenous nicardipine	Acute intracerebral haemorrhage and mean arterial pressure ≥ 110 mmHg randomised within 8 hours of symptom onset n=42	90 day: Mortality mRS score Renal failure 24 hour: Haematoma expansion ($\geq 30\%$ at baseline)	Intensive mean arterial pressure target of <110 mmHg Target achieved after 3 hours of treatment: 67% Comparison mean arterial pressure target of 110-130 mmHg Target achieved after 3 hours of treatment: 90% Between 0 to 3 hours, mean (SD) arterial pressure in the intensive group was 113.8 (30) mmHg and 124.1 (12.8) in the standard group
PATICH 2017, Zheng et al ⁶³ China	Intensive blood pressure therapy vs standard blood pressure therapy continued for 7 days	Acute intracerebral haemorrhage undergoing surgical hematoma evacuation within 1 hour of	90 day: Mortality Renal failure EQ-5D utility index score	Intensive systolic blood pressure at the end of the first hour after randomization was between 140 and 160 mm Hg, at time of surgery was between 120 and 140 mm Hg, after the operation, the antihypertensive

Study	Intervention and comparison	Population	Outcomes	Comments
	Details of specific antihypertensives used was not reported	randomisation and systolic blood pressure of 150 to 220 mmHg n=201		<p>treatment began when the SBP became elevated to >140 mm Hg, the target postoperative SBP was between 120 and 140 mm Hg</p> <p>Comparison systolic blood pressure target of between 140 and 180 mm Hg</p> <p>Intraoperative systolic blood pressure was maintained at between 90 and 140 mm Hg by anaesthesiologists for both groups</p> <p>Target blood pressure achieved 1 hour after surgery, intensive group 97%, standard group 94%</p> <p>Systolic blood pressure before surgery began, mean (SD) mmHg: Intensive group 134 (15) Standard group 155 (13)</p> <p>Systolic blood pressure during surgery, mean (SD) mmHg: Intensive group 113 (16) Standard group 119 (20)</p> <p>Systolic blood pressure during first 24 hours, mean (SD) mmHg: Intensive group 132 (14) Standard group 148 (12)</p>

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Intensive blood pressure versus standard treatment

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard therapy	Risk difference with Intensive (95% CI)
Mortality at 90 days	5119 (7 studies)	⊕⊕⊕⊕ HIGH	RR 0.99 (0.85 to 1.15)	120 per 1000	1 fewer per 1000 (from 18 fewer to 18 more)
mRS: 0 to 2 at 90 days	3832 (3 studies)	⊕⊕⊕⊖ MODERATE ^a due to risk of bias	RR 1.06 (0.99 to 1.13)	440 per 1000	26 more per 1000 (from 4 fewer to 57 more)
mRS ordinal shift OR at 90 days (odds of greater disability in intervention group)	3832 (3 studies)	⊕⊕⊕⊖ MODERATE ^a due to risk of bias	0.93 (0.84 to 1.02)	-	-
Recurrent stroke at 90 days	3862 (3 studies)	⊕⊕⊖⊖ LOW ^b due to imprecision	RR 1.07 (0.59 to 1.94)	10 per 1000	1 more per 1000 (from 4 fewer to 9 more)
Haematoma expansion at 24 hours	2429 (4 studies)	⊕⊕⊕⊖ MODERATE ^c due to imprecision	RR 0.86 (0.74 to 1.00)	244 per 1000	34 fewer per 1000 (from 63 fewer to 0 more)
Neurological deterioration at 24 hours	3764 (2 studies)	⊕⊖⊖⊖ VERY LOW ^{c,d} due to inconsistency, imprecision	RR 1.10 (0.78 to 1.55)	116 per 1000	12 more per 1000 (from 26 fewer to 64 more)
Renal failure at 90 days	1647 (4 studies)	⊕⊕⊕⊖ MODERATE ^c due to imprecision	RR 2.07 (1.08 to 3.99)	14 per 1000	15 more per 1000 (from 1 more to 42 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard therapy	Risk difference with Intensive (95% CI)
Myocardial infarction at 90 days	629 (1 study)	⊕⊕⊖⊖ LOW ^c due to imprecision	RR 0.51 (0.05 to 5.65)	6 per 1000	3 fewer per 1000 (from 6 fewer to 28 more)
EQ-5D utility index at 90 days Scale 0-1 (high is good outcome)	3030 (2 studies)	⊕⊕⊕⊖ MODERATE ^e due to inconsistency	-	The mean EQ-5D utility index at 90 days in the control groups was 0.55	The mean EQ-5D utility index at 90 days in the intervention groups was 0.02 higher (0.05 lower to 0.09 higher)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b One out of three studies adjusted for confounders
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
d Heterogeneity I²=63% not explained by subgroup analysis because only 2 studies were included in the analysis
e Heterogeneity I²=74% not explained by subgroup analysis because only 2 studies were included in the analysis

See appendix F for full GRADE tables.

Table 4: Data not suitable for meta-analysis

Study	Outcome	Intensive therapy	n	Standard therapy	n	Risk of bias
ATACH-2 2016 ⁴¹	EQ-5D utility index score, median (range) at 90 days	0.7 (-0.1 to 1.0)	481	0.7 (0.1 to 1.0)	480	Low
	EQ-5D visual analogue scale, median (range) at 90 days	62.5 (0 to 100)	481	70 (0 to 100)	480	Low
INTERACT 2008 ³	EQ-5D utility index score, median (range) at 90 days	0.78 (0.59 to 1.00)	201	0.75 (0.53 to 1.00)	203	Low
ICH ADAPT 2013 ¹⁵	mRS score, median (range) at 90 days	2.5 (1 to 5.75)	37	4 (2 to 5)	36	Low
INTERACT 2008 ³	mRS score, median (IQR) at 90 days	2 (1 to 4)	1394	2 (1 to 4)	1421	Low

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were included.

1.6.2 Excluded studies

Two economic studies relating to this review question were identified but were excluded as they were not applicable.^{39, 52, 58} These are listed in appendix H, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

1.6.3 Unit costs

UK costs of drugs to lower blood pressure are presented in Table 5 and Table 6.

Table 5: UK costs of drugs to lower blood pressure

Drug	Assumed daily dose [BNF] ^(a)	Cost per unit (£)	Cost per week (£) ^(b)	Source
Calcium channel blockers				
Isradipine (intravenous)	Not found	-	-	-
Nimodipine 30mg tablets (oral)	60mg every 4 hours [60mg every 4 hours to be started within 4 days of aneurysmal SAH]	£0.40	£33.60	British national Formulary
Nimodipine 200µg/ml 50ml vials (intravenous)	2mg/hour for 5 days [Treatment of ischaemic neurological defects following aneurysmal SAH, body weight ≥70kg: Initially up to 1 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour]	£13.60	£326.40 ^(c)	British national Formulary
Urapidil	Not found	-	-	NHS Drug Tariff
Flunarizine	Not found	-	-	-
Nicardipine hydrochloride 20mg / 30mg capsules (oral)	3x 20mg daily for 3 days, then 3 x 30mg daily [Mild to moderate hypertension: Initially 20mg 3 times a day then increased to 30mg 3 times a day, dose increased after at least 3 days; usual dose 60-120 mg]	£0.11 / £0.12	£2.46	NHS Drug Tariff
Nicardipine hydrochloride 10mg/10ml solution for injection ampoules	15mg/hour for 12 hours then 2mg/hour [Life threatening hypertension by IV: initially 3-5mg/ hour for 15 minutes, increased in steps of 0.5-1mg every 15 minutes, adjusted according to	£10.00	£252 ^(d)	British national Formulary

Drug	Assumed daily dose [BNF] ^(a)	Cost per unit (£)	Cost per week (£) ^(b)	Source
	response. Maximum rate 15mg/hour, reduce dose gradually when target blood pressure achieved; maintenance 2-4mg/hour]			
Darodipine (PY108-608)	Not found	-	-	-
Angiotensin II Antagonists				
Candesartan cilexetil 8mg tablets	8mg once daily [Hypertension: 8mg once daily increased if necessary up to 32mg once daily, doses to be increased at intervals of 4 weeks; usual dose 8mg once daily]	£0.03	£0.21	NHS Drug Tariff
Beta-blockers				
Atenolol 50mg tablets	[Hypertension: 25-50mg daily]	£0.01	£0.08	British national Formulary
Atenolol 5mg/10ml solution for injection / 50mg tablets/ 100mg tablets	2 x 5mg/10ml solution for injection, one 50mg tablet after 15 minutes and one 50mg tablet after 12 hours. One 50mg tablet after 12 hours. One 100mg tablet after 12 hours then 100mg daily. [For within 12 hours of MI: 5–10 mg, to be given at a rate of 1 mg/minute, followed by (by mouth) 50 mg after 15 minutes, then (by mouth) 50 mg after 12 hours then (by mouth) 100 mg after 12 hours, then (by mouth) 100 mg once daily]	£3.45 / £0.01 / £0.02	£7.01	British national Formulary/ NHS Drug Tariff
Propranolol 80mg tablets	80mg twice daily [For hypertension: Initially 80 mg twice daily, dose should be increased at weekly intervals as required; maintenance 160–320 mg daily]	£0.02	£0.30	NHS Drug Tariff
Labetalol 100mg/20ml solution for injection ampoules	50mg per hour [For hypertension following MI: 15mg/hour, then increased to up to 120 mg/hour, dose to be increased gradually]	£10.44	£250.66 ^(d)	British national Formulary
Labetalol 100mg tablets	100mg twice daily [Hypertension: By mouth for hypertension Initially 100 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily]	£0.09	£1.31	British national Formulary
Other				
Intravenous	200µg/minute [Control of	£12.98	£149.53 ^(d)	British

Drug	Assumed daily dose [BNF] ^(a)	Cost per unit (£)	Cost per week (£) ^(b)	Source
glyceryl trinitrate 50mg per 10ml solution for infusion vials	hypertension and myocardial ischaemia during and after cardiac surgery 10–200 micrograms/minute (max. per dose 400 micrograms/minute)]			national Formulary
Transdermal glyceryl trinitrate 5mg per 24 hour patch	1 x 5mg Nitro-Dur® patch daily	£0.38	£2.65	British national Formulary

(a) Dosages for adults

(b) Depending on number of units taken

(c) Cost of 5 day course

(d) Cost of 2 day course

Table 6: UK costs of blood pressure lowering with labetalol

Drug	Assumed daily dose ^(a)	Cost per unit (£)	Cost per 2-day course	Number needed to treat (mRS 0-2)	Total cost
Labetalol 100mg/20ml solution for injection ampoules	50mg per hour [For hypertension following MI: 15mg/hour, then increased to up to 120 mg/hour, dose to be increased gradually]	£10.44 ^(a)	£250.66	39	£9,776

(a) Source: British National Formulary

(b) Number needed to treat (mRS 0-2) = 1 / absolute risk difference = 1/0.026 = 39 (rounded up to nearest whole number); absolute risk difference from Table 3

The clinical review found that 39 people with haemorrhagic stroke would need to be treated to yield one additional person with an mRS 0-2. At a total cost of £250.66 per person, the cost of treating 39 people with haemorrhagic stroke is £9,776 (Table 6). According to published literature, the cost saving between mRS 0-2 and mRS 3-5 is £7,813 within three months of stroke onset and £10,182 over the first year after stroke²³. Over a lifetime time horizon, further cost savings are therefore likely to be accrued. The committee therefore considered that the cost of treating 39 people with intravenous labetalol (£9,776) were likely to be recuperated over a year and would be cost saving over a lifetime time horizon. Nursing costs are not included in this calculation and it may be that additional nursing time is required for monitoring, however this is difficult to quantify as people will already be being managed in a high dependency area of an emergency department or hyperacute stroke unit and the additional time required is unclear.

1.7 Resource costs

The recommendation made by the committee based on this review (see section **Error! Reference source not found.**) that rapid blood pressure lowering should be offered in people with acute intracerebral haemorrhage and systolic blood pressure between 150 and 220 mmHg and presenting within 6 hours of symptom onset is not expected to have a substantial impact on resources to the NHS in England. The committee also made a recommendation based on this review (see section **Error! Reference source not found.**) that controlled blood pressure lowering should be ‘considered’ for people with acute intracerebral haemorrhage who present beyond 6 hours of symptom onset or have a systolic

blood pressure greater than 220 mmHg. Unlike for stronger recommendations stating that interventions should be adopted, it is not possible to make a judgement about the potential resource impact to the NHS of recommendations regarding interventions that could be used, as uptake is too difficult to predict. There was also uncertainty about current practice in this population. However, the committee noted that where this recommendation is implemented there would be additional costs relating to drug treatment to lower systolic blood pressure and there is potential for downstream cost savings if health outcomes are improved.

1.8 Evidence statements

1.8.1 Clinical evidence statements

- Seven trials in 5119 people were included investigating intensive blood pressure lowering within 48 hours of symptom onset in acute intracerebral haemorrhage versus standard blood pressure lowering. No clinical difference at 90 days was reported for mortality (7 trials, 5119 people, High quality), recurrent stroke (3 trials, 3832 people, Low quality), myocardial infarction (1 trial, 629 people, Low quality) and quality of life (EQ-5D utility index) (2 trials, 3030 people, Moderate quality). No clinical difference at 24 hours was reported for neurological deterioration (2 trials, 3764 people, Very Low quality) and haematoma expansion (4 trials, 2228 people, Moderate quality).
- Three trials in 3832 people examining functional outcome showed a clinical meaningful benefit of intensive blood pressure lowering versus standard blood pressure lowering as measured by mRS 0 to 2 at 90 days (Moderate quality). This was supported by the ordinal shift analysis of the mRS at 90 days from the same studies (Moderate quality).
- Four trials in 1647 people examining renal failure at 90 days showed clinical harm for intensive blood pressure lowering versus standard blood pressure lowering (Moderate quality).

1.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The critical outcomes identified for this review were the mRS at 90 days and 1 year, and mortality at 24 hours and 90 days. The committee considered both outcomes to be vital in decision making. Important outcomes included symptomatic cerebral ischaemia, haemorrhagic expansion, neurological deterioration, renal failure, spinal cord infarction, myocardial infarction, and quality of life.

No evidence was available for the adverse event outcomes of symptomatic cerebral ischaemia and spinal cord infarction.

1.9.1.2 The quality of the evidence

Seven studies were included in the review. Two large trials provided the majority of the body of evidence. The trials were all prospective randomized open blinded end-point (PROBE) trials. This meant that patient and care givers were not blinded to the intervention, but the outcome assessors were. Subjective outcomes (mRS and quality of life) were therefore downgraded for risk of bias. Outcomes such as renal failure and myocardial infarction had very few events resulting in estimates of effect with wide confidence intervals and therefore they were downgraded for imprecision.

Evidence ranged from very low to high quality, with the majority of the evidence rated as moderate quality. The good quality evidence from a large number of participants found that intensive or rapid systolic blood pressure lowering is likely to be safe therefore a strong recommendation was made.

1.9.1.3 Benefits and harms

The committee noted that for the recommended strategy there was no evidence of blood pressure lowering causing harm in people after intracerebral haemorrhage with high blood pressure, with no signal of increased neurological deterioration due to reduced blood flow to the brain. Rapid blood pressure lowering did not adversely affect renal function in the majority of trials. The exception was in a trial that used a more aggressive blood pressure reduction protocol, with a target for systolic blood pressure of 110-139 mmHg and treatment started within 4.5 hours of onset, where there was evidence of increased renal failure with 19 more cases per 1000 compared to the control rate of 14 per 1000. The committee agreed that rapid lowering of systolic blood pressure is safe when using less aggressive protocols, and so have included detail on the blood pressure target and time window in the recommendation. While there was no clear difference in the pooled common odds ratio from the mRS ordinal shift analysis, the committee considered the absolute benefit demonstrated for the dichotomous outcome of mRS 0 to 2 to be sufficiently clinically meaningful to recommend systolic blood pressure lowering. These outcomes were supported by the evidence for quality of life at 90 days from the INTERACT2 trial (but not in the pooled data for this outcome) and haematoma growth at 24 hours, which also favoured rapid treatment with no indication of harm.

In accordance with evidence from the trials where rapid systolic blood pressure lowering was found to be safe it was recommended that treatment should start within 6 hours and continue for 7 days, and that the target should be 130-140 mmHg within 1 hour. Regarding the target range, this was consistent with what was achieved in the INTERACT-2 trial and also avoids the potentially harmful aggressive reduction to a lower target, as in ATACH-2, that could be associated with renal failure. Also, lowering the systolic blood pressure below 130 mmHg

was noted to risk of excessive reduction, requiring intervention to raise the blood pressure back to a safe level in these patients and so should be avoided.

It was noted that this should be a strong recommendation because:

- There is good evidence that intensive or rapid systolic blood pressure lowering is safe and has some signal for effectiveness, which could have been underestimated by including ATACH2 in the meta-analysis, which has a more aggressive regimen in the control arm that is similar to the intervention arm of the other main trial, INTERACT-2
- The mortality rate from intracerebral haemorrhage without intervention is reported to be around 40% at 1 month⁵⁴ so any intervention to reduce this is important
- Up to 60% of those who survive currently have moderate or severe disability⁵⁴
- It will likely standardise care in this condition where much inconsistency is known to exist.

Additionally, based on the exclusion criteria for the INTERACT-2 trial, those with an underlying structural cause (for example tumour, arteriovenous malformation or aneurysm), a GCS of below 6, a massive haematoma with a poor expected prognosis or who are going to have early neurosurgery to evacuate the haematoma are not included in the recommendation as there is no evidence of benefit or absence of harm in these people because they were not included in the trial. Also, it will often not be appropriate to undertake an active management approach in these people because they are likely to be entering a palliative care pathway.

While there was limited evidence for people presenting after 6 hours (only one small study recruiting within 8 hours of presentation), the committee agreed that rapid systolic blood pressure lowering could be recommended for people presenting after 6 hours. No evidence of harm was found in the earlier presenting group, and there is no reason to believe that this would be different in the later group. Therefore, the consensus of the group was that the evidence could be extrapolated to people presenting beyond 6 hours.

Similarly, although the majority of the evidence was from trials that did not include people with a systolic blood pressure over 220 mmHg the committee agreed that current practice is to implement systolic blood pressure reduction as part of initiating secondary prevention as soon as possible. The committee also believed that this should not pose any greater harm than rapid systolic blood pressure reduction in those with a systolic blood pressure below 220 mmHg. The committee noted that the 'consider' recommendation would allow clinical discretion in these groups for instances where rapid lowering may not be appropriate, for example if the initial systolic blood pressure was more than 230 mmHg.

Overall, it was agreed that although there was little or no evidence for those presenting beyond 6 hours and those with a systolic blood pressure over 220 mmHg, it is logical to extrapolate from the available data to these groups and that guidance on how to manage these patients is required.

The committee noted that very aggressive systolic blood pressure lowering should be avoided in all groups because of the risk for renal impairment.

1.9.2 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of measures to manipulate systolic blood pressure versus treatment as usual in people with acute intracerebral haemorrhage. The committee expressed that there is variation between centres and consultants in current practice of systolic blood pressure lowering. Intravenous labetalol is commonly used as the first-line treatment for systolic blood pressure lowering in the UK. In the absence of relevant economic evaluations, the committee considered the unit costs of systolic blood pressure lowering agents. Labetalol 100mg/20ml solution for injection

ampoules currently have a unit cost of £10.44. For a two-day course of 50 mg/hour intravenous labetalol, the current total cost per person is £250.66.

Upon considering the cost of treatment with intravenous labetalol, the committee considered that the clinical evidence indicated that treatment of approximately 39 people within 6 hours of acute intracerebral haemorrhage would yield an additional person with an mRS score of 0-2 at 90 days. At a total cost of £250.66 per person, the total cost of treating 39 people with haemorrhagic stroke is £9,776. The committee noted that nursing costs are not included in this calculation and it may be that additional nursing time is required for monitoring, however this is difficult to quantify as people will already be being managed in a high dependency area of an emergency department or hyperacute stroke unit and the additional time required is unclear. In addition, the clinical evidence associated with rapid blood pressure lowering, found an absence of harm and a higher quality of life at 90 days in the intervention group than in the control. The committee noted, however, that very aggressive systolic blood pressure lowering (e.g. from a high baseline to a low target, as in ATACH2) could have deleterious effects on renal function and consequently impact long term costs and quality of life.

The cost of treating 39 people with haemorrhagic stroke was interpreted in light of the costs, obtained from the literature, of being in mRS 0-2 compared with mRS 3-5. A cost utility analysis from the UK NHS perspective obtained annual costs (adjusted to 2013/2014 UK pounds) of being in the independent and dependent health states from a second study. This study applied UK NHS reference costs to the resource use from a UK, single centre randomised controlled trial to calculate the costs of stroke. It did not differentiate between haemorrhagic and ischaemic strokes and excluded very mild and very severe strokes, as defined by the Barthel Index. The study assumed that mild and moderate strokes correspond to independent stroke survivors and severe stroke described the cost of dependent stroke survivors. These studies indicate that estimated cost savings of £7,813 within three months of stroke onset and £10,182 over the first year after stroke could be made by shifting one person from mRS 3-5 to mRS 0-2. Over a lifetime time horizon, further cost savings are therefore likely to be accrued. The committee therefore considered that the cost of treating 39 people with intravenous labetalol (£9,776) was likely to be recuperated over a year and would be cost saving over a lifetime time horizon.

The committee also noted that for the population of people with acute intracerebral haemorrhage, the distribution of mRS scores in those surviving is likely to be skewed towards higher scores, as up to 60% of survivors have moderate to severe disability. The cost differences between those with mRS scores of 5 and mRS scores 0-2 are likely to be higher than those mentioned above. In addition, the committee acknowledged the heterogeneity in the trials. The committee thought that by delivering the intervention in line with the trial with more favourable results (INTERACT 2), the treatment effect might be improved and the number needed to treat reduced, producing larger cost savings. On this basis, the committee agreed that rapid systolic blood pressure reduction could be offered to this population. While there is variation in current practice, this protocol is already being widely implemented in most trusts so the committee does not expect a very large impact on practice or a substantial resource impact to the NHS in England.

No clinical or economic evidence was identified for those presenting at 6-24 hours of symptom onset nor with systolic blood pressure exceeding 220 mmHg. The committee however agreed that rapid systolic blood pressure lowering should also be considered in this population, because haematoma expansion – the therapeutic target for rapid blood pressure reduction – can still occur up to 24 hours after symptom onset.

The committee noted that the unit costs of oral systolic blood pressure lowering agents are currently significantly lower than those of intravenous systolic blood pressure lowering agents. The committee stressed that after an intravenous course with an approximate duration of up to two days, people with haemorrhagic stroke should be maintained on oral

systolic blood pressure drugs when possible. Oral systolic blood pressure medicines should be introduced as soon as possible to prevent rebound of systolic blood pressure when the intravenous course is discontinued and maintain smooth blood pressure control beyond the hyperacute phase.

In conclusion, no relevant economic evaluations were identified which addressed the cost effectiveness of measures to manipulate systolic blood pressure versus treatment as usual in people with haemorrhagic stroke. The committee's discussion was informed by evidence that a greater proportion of people have mRS 0-2 at 90 days following rapid systolic blood pressure reduction than with usual care, with concomitant cost savings exceeding the costs of the intervention. The committee was confident in recommending that rapid systolic blood pressure lowering is offered to people presenting within 6 hours of symptom onset for acute intracerebral haemorrhage as it is likely to be cost saving, and confer health benefits to people with haemorrhagic stroke. They also agreed that it was reasonable to extrapolate this evidence to those presenting after 6 hours or with a systolic blood pressure exceeding 220 mmHg and that rapid blood pressure lowering should be considered in these groups.

1.9.3 Other factors the committee took into account

A recommendation to lower systolic blood pressure could encourage greater overall monitoring and drive up overall care quality. The committee were aware of emerging evidence that more intensive monitoring, which would be associated with blood pressure control, encourages a more intensive multimodal approach to patients with intracerebral haemorrhage and leads to overall improved outcomes in this patient cohort.

The committee also noted the distinction between acute treatment, which is designed to reduce effects of the index event by reducing systolic blood pressure, and secondary prevention. It was agreed that it is unclear at what point management changes from acute treatment to secondary prevention, but that one indicator may be when treatment is changed from IV to oral route of administration. However, this evidence review is primarily concerned with treatment within the first 48 hours.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: Maintenance or restoration of homeostasis

Field	Content
Review question	What is the safety and efficacy of measures to lower blood pressure versus standard treatment in people with acute intracerebral haemorrhage?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To identify if there is a benefit to lowering blood pressure in intracranial haemorrhage
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with acute intracerebral haemorrhage and high blood pressure at the time of assessment
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Intensive blood pressure reduction (for example to a target of <140 mmHg systolic) within 48 hours with: <ul style="list-style-type: none"> • Calcium antagonists (e.g. intravenous isradipine, oral nimodipine, oral and intravenous nimodipine, urapidil, flunarizine, nifedipine and oral PY108-608) • Intravenous or transdermal glyceryl trinitrate (GTN) • Angiotensin II antagonist (e.g. cilextil) • Beta-blockers (e.g. atenolol, propranolol and labetalol) All drug classes to be pooled for analysis
Eligibility criteria – comparator(s) / control or reference (gold) standard	Standard care (for example standard blood pressure lowering to a target of 140-180 mmHg systolic) Placebo or no treatment
Outcomes and prioritisation	<u>Critical</u> Mortality at 24 hours and 90 days mRS score at 90 days and 1 year <u>Important</u> Symptomatic cerebral ischemia at 24 hours Haemorrhage expansion at 24 hours Neurological deterioration at 24 hours Adverse events (renal failure, cord infarction, myocardial infarction) at 90 days Quality of life (both health- and social-related quality) at 90 days Percentage achieving blood pressure target
Eligibility criteria – study design	Randomised controlled trials Systematic reviews and meta-analyses of the above
Other inclusion exclusion criteria	Inclusion Settings: Emergency department, critical care, hyper acute stroke unit
Proposed sensitivity / subgroup analysis,	<u>Subgroups to investigate if heterogeneity is present</u> Lobar vs deep (haematoma location) Time to treatment (within 6 hours vs >6 hours of stroke onset)

or meta-regression	Age <80/>80 years Volume of haemorrhage (< 15, 15 – 30, >30 ml ³) NIHSS <15/ >15
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	<ul style="list-style-type: none"> • EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	<p>Databases: Medline, Embase, Cochrane Library, Language: Restrict to English only Date restriction: 2007</p> <p>Key papers</p> <ol style="list-style-type: none"> 1. Potter J, Mistri A, Brodie F et al. (2009) Controlling hypertension and hypotension immediately post stroke (CHHIPS)--a randomised controlled trial. <i>Health Technology Assessment (Winchester, England)</i> 13:iii-ixi. 2. Wilson EC, Ford GA, Robinson T et al. (2010) Controlling hypertension immediately post stroke: a cost utility analysis of a pilot randomised controlled trial. <i>Cost Effectiveness & Resource Allocation</i> 8:3. 3. Geeganage C and Bath PM. (2008) Interventions for deliberately altering blood pressure in acute stroke. [Review] [92 refs][Update of Cochrane Database Syst Rev. 2001;(3):CD000039; PMID: 11686949]. <i>Cochrane Database of Systematic Reviews</i> CD000039. 4. Geeganage C and Bath PM. (2010) Vasoactive drugs for acute stroke. [Review] [183 refs][Update of Cochrane Database Syst Rev. 2000;(4):CD002839; PMID: 11034772]. <i>Cochrane Database of Systematic Reviews</i> CD002839. 5. Anderson CS, Huang Y, Wang JG et al. (2008) Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. <i>Lancet Neurology</i> 7:391-399. 6. Anderson CS, Huang Y, Arima H et al. (2010) Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). <i>Stroke</i> 41:307-312. 7. Koch S, Romano JG, Forteza AM et al. (2008) Rapid blood pressure reduction in acute intracerebral hemorrhage: feasibility and safety. <i>Neurocritical Care</i> 8:316-321. 8. Jusufovic M, Sandset EC, Bath PM et al. (2014) Blood pressure-lowering treatment with candesartan in patients with acute hemorrhagic stroke. <i>Stroke</i> 45:3440-3442.
Identify if an update	<p>Yes</p> <p>Question in CG68: What is the safety and efficacy of measures to manipulate blood pressure versus treatment as usual in patients with acute stroke?</p> <p>Recommendations from CG68</p> <p>1.5.3.1 Anti-hypertensive treatment in people with acute stroke is recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues:</p>

	<ul style="list-style-type: none"> • hypertensive encephalopathy • hypertensive nephropathy • hypertensive cardiac failure/myocardial infarction • aortic dissection • pre-eclampsia/eclampsia • intracerebral haemorrhage with systolic blood pressure over 200 mmHg. <p>1.5.3.2 Blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for thrombolysis.</p>
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ [Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.]
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where

	appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).³⁷</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.

- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017
<https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869>

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 22 June 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 6 of 12 CENTRAL to 2018 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp "Intracranial Embolism and Thrombosis"/
10.	exp Carotid Artery Thrombosis/
11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or

	emboli* or occlus* or hypoxi*).ti,ab.
12.	exp Brain Ischemia/
13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
14.	Ischemic Attack, Transient/
15.	(isch?emi* adj2 attack*).ti,ab.
16.	TIA*.ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
39.	37 not 38
40.	exp hypotension/
41.	Hypotension.ti,ab.
42.	((low* or depress* or decreas* or reduc* or drop* or diminish* or control* or regulat* or down) adj3 (blood pressure* or BP)).ti,ab.
43.	or/40-42
44.	39 and 43
45.	randomized controlled trial.pt.
46.	controlled clinical trial.pt.
47.	randomi#ed.ab.
48.	placebo.ab.
49.	randomly.ab.
50.	clinical trials as topic.sh.
51.	trial.ti.
52.	or/45-51

53.	Meta-Analysis/
54.	Meta-Analysis as Topic/
55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/53-62
64.	44 and (52 or 63)

Embase (Ovid) search terms

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*brain embolism/
10.	*Carotid Artery Thrombosis/
11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
12.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
14.	*Transient ischemic attack/
15.	(isch?emi* adj2 attack*).ti,ab.
16.	TIA*.ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.

23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	*hypotension/
39.	Hypotension.ti,ab.
40.	((low* or depress* or decreas* or reduc* or drop* or diminish* or control* or regulat* or down) adj3 (blood pressure* or BP)).ti,ab.
41.	or/38-40
42.	37 and 41
43.	random*.ti,ab.
44.	factorial*.ti,ab.
45.	(crossover* or cross over*).ti,ab.
46.	((doubl* or singl*) adj blind*).ti,ab.
47.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
48.	crossover procedure/
49.	single blind procedure/
50.	randomized controlled trial/
51.	double blind procedure/
52.	or/43-51
53.	systematic review/
54.	Meta-Analysis/
55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/53-62
64.	42 and (52 or 63)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Stroke] explode all trees
#2.	(stroke or strokes):ti,ab
#3.	((cerebro* or cerebral*) near/2 (accident* or apoplexy)):ti,ab
#4.	(CVA or poststroke or poststrokes):ti,ab
#5.	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#6.	(brain near/2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)):ti,ab
#7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) near/3 (hemorrhag* or haemorrhag* or bleed*)):ti,ab
#8.	MeSH descriptor: [Brain Infarction] explode all trees
#9.	MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#10.	MeSH descriptor: [Carotid Artery Thrombosis] explode all trees
#11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) near/3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab
#12.	MeSH descriptor: [Brain Ischemia] explode all trees
#13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#14.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#15.	(isch?emi* near/2 attack*):ti,ab
#16.	TIA*:ti,ab
#17.	(or #1-#16)
#18.	MeSH descriptor: [Hypotension] explode all trees
#19.	Hypotension:ti,ab
#20.	((low* or depress* or decreas* or reduc* or drop* or diminish* or control* or regulat* or down) near/3 (blood pressure* or BP)):ti,ab
#21.	(or #18-#20)
#22.	#17 and #21

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the stroke population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies

Database	Dates searched	Search filter used
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 – March 2015	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/

31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/
40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/
46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

Embase (Ovid) search terms

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/

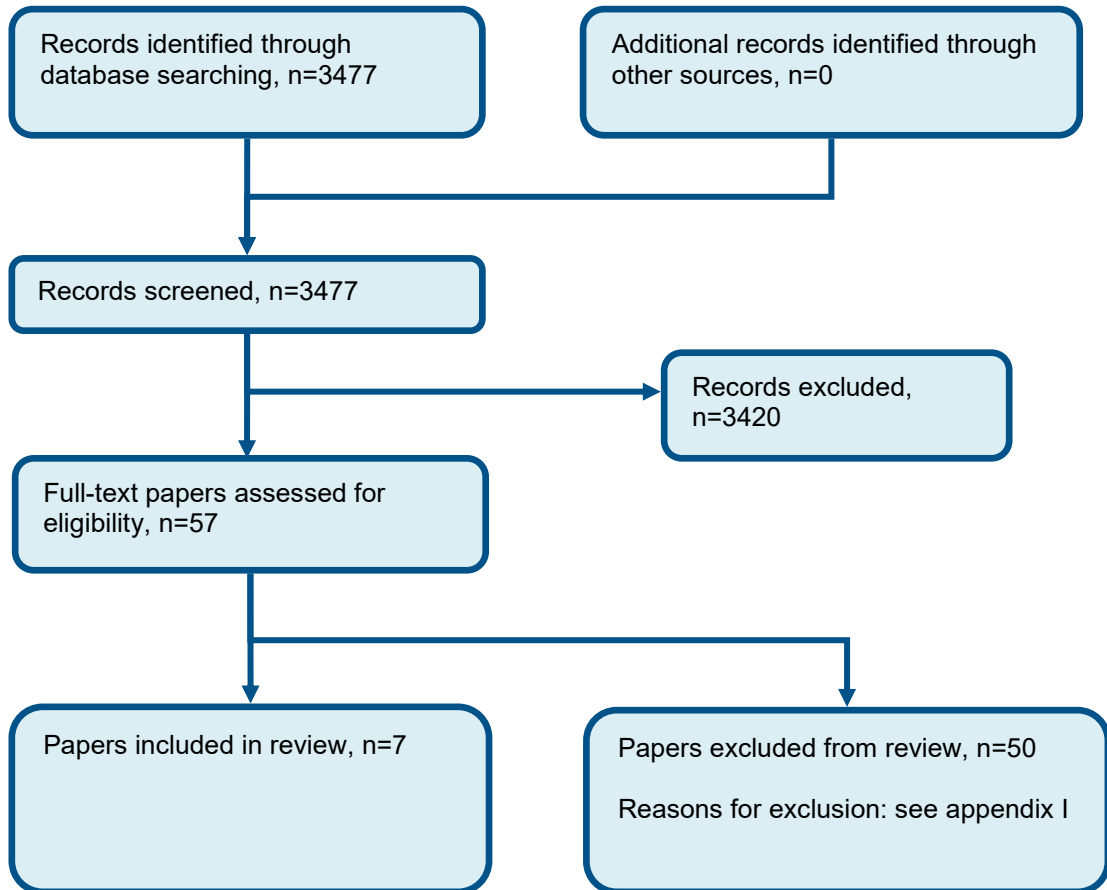
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(finance* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy))
#4.	((CVA or poststroke or poststrokes))
#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*))
#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of maintenance or restoration of homeostasis



Appendix D: Clinical evidence tables

Study	ATACH-2 trial: Qureshi 2016 ⁴¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1000)
Countries and setting	Conducted in Multiple countries; Setting: ED, secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Intervention 24 hours, follow-up at 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Spontaneous intracerebral hemorrhage who had a systolic blood pressure of 150 to 220 mm Hg within 6 hours after symptom onset. At least one reading of systolic blood pressure of 180 mm Hg or more between symptom onset and the initiation of intravenous antihypertensive treatment
Exclusion criteria	Ischaemic stroke
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Other: Mean 61.9 years. Gender (M:F): 38.0%/62%. Ethnicity: 56.2% Asian

Further population details	1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable
Indirectness of population	No indirectness
Interventions	(n=500) Intervention 1: Intensive therapy. Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg. Duration 24 hours. Concurrent medication/care: Standard therapy. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours (n=500) Intervention 2: Conservative therapy. Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg. Duration 24 hour. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours
Funding	Academic or government funding (National Institute of Neurological Disorders and Stroke, Intramural Research Fund for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center. National Institute of Neurological Disorders and Stroke and by a grant (H23-4-3, to Dr. Toyoda) from the Intramural Research Fund for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE THERAPY versus CONSERVATIVE THERAPY</p> <p>Protocol outcome 1: Mortality at 90 days - Actual outcome: Mortality at 90 days; Group 1: 33/481, Group 2: 34/480 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19; Group 2 Number missing: 20</p> <p>Protocol outcome 2: EQ-5D utility index score at 90 days - Actual outcome: EQ-5D utility index score at 90 days: Group 1: median (IQR): 0.7 (-0.1 to 1.0): group 2: median (IQR): 0.7 (0 to 1.0).</p>	

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19; Group 2 Number missing: 20

Protocol outcome 3: EQ-5D visual analogue scale at 90 days

- Actual outcome: EQ-5D visual analogue scale at 90 days; ; Group 1: median (IQR): 62.5 (0 to 100); group 2: median (IQR): 70 (0 to 100).

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19; Group 2 Number missing: 20

Protocol outcome 4: Neurological decline at 24 hours

- Actual outcome: Neurological decline at 90 days; Group 1: 55/500, Group 2: 40/500

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Haematoma growth at 24 hours

- Actual outcome: Haematoma growth at 90 days; Group 1: 85/450, Group 2: 104/426

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19, Reason: No CT; Group 2 Number missing: 20, Reason: No CT

Protocol outcomes not reported by the study

Mortality at 24 hours; mRS score at 90 days; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; mRS score at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS score 0-3 vs 4-6 at 90 days; Renal failure at 90 days; Myocardial infarction at 90 days; Neurological decline at 90 days; Barthel index at 90 days; mRS score at 1 year; EQ-5D at 90 days

Study	ENOS-ICH trial: Krishnan 2016 ³³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=629)
Countries and setting	Conducted in Multiple countries; Setting: ED, Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days, 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT / MRI
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Systolic blood pressure between 150 and 220 mm Hg, no definite indication for or contraindication to blood-pressure-lowering treatment that could be commenced within 6 hours after the onset of spontaneous intracranial hemorrhage
Exclusion criteria	Structural cerebral cause for the intracerebral hemorrhage, deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale in which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Mean (SD): 67.0 (12.4(. Gender (M:F): 66% male. Ethnicity: Not stated
Further population details	1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable
Indirectness of population	No indirectness

Interventions	<p>(n=310) Intervention 1: Intensive therapy - Intravenous or transdermal glyceryl trinitrate (GTN). 5 mg/day. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not stated / Unclear</p> <p>(n=319) Intervention 2: Standard care. No GTN. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours):</p>
Funding	Other (Bupa UK Foundation and Medical Research Council (G0501797). Agency for Science, Technology and Research (Singapore), Hypertension Trust (United Kingdom), Queen Elizabeth II Health Sciences Centre Research Fund (Canada), and Reichstadt family (United Kingdom))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS OR TRANSDERMAL GLYCERYL TRINITRATE (GTN) versus STANDARD CARE

Protocol outcome 1: Mortality at 90 days

- Actual outcome: Mortality at 90 days; Group 1: 42/310, Group 2: 47/319

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: mRS score at 90 days

- Actual outcome: mRS score at 90 days; ; Adjusted common OR: 1.04 (0.78 to 1.38), p=0.81;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Myocardial infarction at 90 days

- Actual outcome: Myocardial infarction at 90 days; Group 1: 1/310, Group 2: 2/319

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1). Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ;

<p>Group 2 Number missing:</p> <p>Protocol outcome 4: Barthel index at 90 days - Actual outcome: mRS score at 90 days; Group 1: mean 62.3 (SD 38.1); n=310, Group 2: mean 61.4 (SD 39.7); n=319 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 4: Recurrent stroke at 90 days - Actual outcome: Recurrent stroke at 90 days; Group 1: 7/304, Group 2: 7/318 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ; Group 2 Number missing:</p>	
<p>Protocol outcomes not reported by the study</p>	<p>Mortality at 24 hours; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; EQ-5D utility index score at 90 days; EQ-5D visual analogue scale at 90 days; mRS score at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS score 0-3 vs 4-6 at 90 days; Renal failure at 90 days; Neurological decline at 24 hours; Neurological decline at 90 days; Haematoma growth at 24 hours; mRS score at 1 year; EQ-5D at 90 days</p>

Study	ICH-ADAPT trial: Butcher 2013 ⁴⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in Canada; Setting: ED, Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours, follow-up 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 years of age, with spontaneous cerebral haemorrhage diagnosed on noncontrast computed tomography (CT) <24 hours after onset. SBP was ≥150 mm Hg (≥2 readings ≥5 minutes apart)
Exclusion criteria	evidence of secondary cerebral haemorrhage (vascular malformation), planned surgical resection, or contraindications to CT perfusion (CTP; eg, contrast allergy or renal impairment)
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Mean (SD): Intensive 70.7 (12.5), conservative therapy 68.7 (11.1). Gender (M:F): Intensive 67% male, conservative therapy 78%. Ethnicity: Not reported
Further population details	1. Age <80 vs ≥/80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable
Indirectness of population	No indirectness

Interventions	<p>(n=39) Intervention 1: Intensive therapy. Intensive therapy. Duration 24 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable</p> <p>(n=36) Intervention 2: Conservative therapy. Conservative care. Duration 24 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable</p>
Funding	Academic or government funding (Alberta Innovates Health Solutions, Heart and Stroke Foundation of Canada)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE THERAPY versus CONSERVATIVE THERAPY</p> <p>Protocol outcome 1: Mortality at 90 days - Actual outcome: Mortality at 90 days; Group 1: 7/37, Group 2: 4/39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Very serious indirectness, Comments: Mortality at 30 days not 90 days; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated</p> <p>Protocol outcome 2: mRS score at 90 days - Actual outcome: mRS score at 90 days; 0 to 6 Top=High is poor outcome; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated</p> <p>Protocol outcome 3: Neurological decline at 24 hours - Actual outcome: Neurological decline at 2 hours; Group 1: 3/37, Group 2: 2/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Decline at 2 hours not 24 hours; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated</p>	

<p>Protocol outcome 4: Haematoma growth at 24 hours - Actual outcome: Haematoma growth at 2 hours; Group 1: 9/37, Group 2: 4/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Growth at 2 hours not 24 hours; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated</p>	
<p>Protocol outcomes not reported by the study</p>	<p>Mortality at 24 hours; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; EQ-5D utility index score at 90 days; EQ-5D visual analogue scale at 90 days; mRS score at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS score 0-3 vs 4-6 at 90 days; Renal failure at 90 days; Myocardial infarction at 90 days; Neurological decline at 90 days; Barthel index at 90 days; mRS score at 1 year; EQ-5D at 90 days</p>

Study	INTERACT-2 trial: Anderson 2013 ¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2839)
Countries and setting	Conducted in Multiple countries; Setting: ED, Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Intervention 7 days, follow-up 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Intracerebral haemorrhage within previous 6 hours, structural cerebral cause for the intracerebral hemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale in which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), if they had a massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned, age ≥ 18 years, at least 2 systolic BP measurements of ≥ 150 and ≤ 220 mmHg, recorded 2 or more minutes apart. Patients with initial systolic BP levels outside of this range (<150 or >220 mmHg) may be randomised should the BP levels fulfill entry criteria on re- checking up to 6 hours after the onset of ICH., patients with an initial systolic BP >220 at least 2 systolic BP measurements of ≥ 150 and ≤ 220 mmHg, recorded 2 or more minutes apart. Patients with initial systolic BP levels outside of this range (<150 or >220 mmHg) may be randomised should the BP levels fulfill entry criteria on re- checking up to 6 hours after the onset of ICH. Patients with an initial systolic BP >220 at least 2 systolic BP measurements of ≥ 150 and ≤ 220 mmHg, recorded 2 or more minutes apart. Patients with initial systolic BP levels outside of this range (<150 or >220 mmHg) may be randomised should the BP levels fulfill entry criteria on re- checking up to 6 hours after the onset if intracerebral haemorrhage
Exclusion criteria	Structural cerebral cause for the structural cerebral cause for the intracerebral hemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale) in which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), if they had a massive hematoma with a poor prognosis, or if early surgery

	to evacuate the hematoma was planned if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale in which scores range from 3 to 15, with lower scores indicating reduced levels of consciousness), if they had a massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Mean (SD): Intensive therapy 63.0 (13.1), conservative therapy 64.1 (12.6) years. Gender (M:F): Intensive therapy 898/501, conservative therapy 882/548. Ethnicity: Not reported
Further population details	1. Age <80 vs >=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not stated / Unclear 4. Volume of haemorrhage: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=1399) Intervention 1: Intensive therapy. Intensive therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours (n=1430) Intervention 2: Conservative therapy. Conservative therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours
Funding	Academic or government funding (National Health and Medical Research Council of Australia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE THERAPY versus CONSERVATIVE THERAPY

Protocol outcome 1: Mortality at 90 days

- Actual outcome: Mortality at 90 days; Group 1: 166/1394, Group 2: 170/1421

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4% conservative 72.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 2: Recurrent and /or extended stroke at 90 days

- Actual outcome: Recurrent stroke at 90 days; Group 1: 12/1399, Group 2: 12/1430

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 72.5%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: EQ-5D at 90 days

- Actual outcome: EQ-5D at 90 days; Group 1: mean 0.6 (SD 0.39); n=1394, Group 2: mean 0.55 (SD 0.4); n=1421

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 72.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 4: mRS score 0-2 vs 3-6 at 90 days

- Actual outcome: mRS score 0-2 vs 3-6 at 90 days; Group 1: 663/1382, Group 2: 627/1412; ordinal analysis: pooled OR: 0.87 (0.77 to 1.00)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 5: mRS score 0-3 vs 4-6 at 90 days

- Actual outcome: mRS score 0-3 vs 4-6 at 90 days; Group 1: 883/1382, Group 2: 861/1412

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 6: Neurological decline at 24 hours

- Actual outcome: Neurological decline at 90 days; Group 1: 198/1369, Group 2: 211/1395

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low,

Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 7: Haematoma growth at 24 hours

<p>- Actual outcome: Haematoma growth at 90 days; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated</p>	
<p>Protocol outcomes not reported by the study</p>	<p>Mortality at 24 hours; mRS score at 90 days; Recurrent and /or extended stroke at 24 hours; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; EQ-5D visual analogue scale at 90 days; mRS score at 90 days; Renal failure at 90 days; Myocardial infarction at 90 days; Neurological decline at 90 days; Barthel index at 90 days; mRS score at 1 year; EQ-5D utility index score at 90 days</p>

Study	INTERACT trial: Anderson 2008 ³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=404)
Countries and setting	Conducted in Multiple countries; Setting: ED, Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days intervention, 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were at least 18 years of age, had spontaneous ICH confirmed by CT and elevated systolic blood pressure (≥ 2 measurements of 150–220 mm Hg, recorded ≥ 2 min apart), and were able to commence the randomly assigned treatment within 6 hours of ICH onset
Exclusion criteria	Clear indication for intensive lowering of blood pressure (eg, systolic blood pressure > 220 mm Hg or hypertensive encephalopathy); a clear contraindication to intensive lowering of blood pressure, clear evidence that the ICH was secondary to a structural cerebral abnormality, or the use of a thrombolytic agent, an ischaemic stroke within 30 days, a score of 3–5 on the Glasgow coma scale (GCS) indicating deep coma, significant prestroke disability or medical illness; or early planned decompressive neurosurgical intervention
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Mean (SD): Intervention 62 (13), control 63 (12) years. Gender (M:F): Intensive 63% male, conservative 62% male. Ethnicity: Not reported

Further population details	1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable
Indirectness of population	No indirectness
Interventions	(n=201) Intervention 1: Conservative therapy. Conservative therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable (n=203) Intervention 2: Intensive therapy. Intensive therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours
Funding	Academic or government funding (National Health and Medical Research Council of Australia)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE THERAPY versus CONSERVATIVE THERAPY</p> <p>Protocol outcome 1: Recurrent and /or extended stroke at 90 days - Actual outcome: Recurrent stroke at 90 days; Group 1: 2/203, Group 2: 3/201 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up</p> <p>Protocol outcome 2: mRS score at 90 days - Actual outcome: mRS score at 90 days; 0 to 6 Top=High is poor outcome; median (IQR) Group 1: 2 (1-4); group 2: 2 (1-4) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up</p>	

Protocol outcome 2: EQ-5D at 90 days

- Actual outcome: EQ-5D at 90 days; OR; Median (range) intensive: 0.75 (0.52 to 1.00), conservative: 0.78 (0.59 to 1.00);

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 3: Mortality at 90 days

- Actual outcome: Mortality at 90 days; Group 1: 21/202, Group 2: 25/200

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 4: Renal failure at 90 days

- Actual outcome: Renal failure at 90 days; Group 1: 4/203, Group 2: 2/201

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 5: Neurological decline at 24 hours

- Actual outcome: Neurological decline at 72 hours; Group 1: 31/203, Group 2: 30/201

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: Serious indirectness, Comments: 72 hours not 24 hours; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 6: Haematoma growth at 24 hours

- Actual outcome: Haematoma growth at 24 hours; Group 1: 26/174, Group 2: 40/172

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 27, Reason: Loss to follow-up; Group 2 Number missing: 29, Reason: Loss to follow-up

Protocol outcomes not reported by the study	Mortality at 24 hours; Mortality at 90 days; mRS score at 90 days; Recurrent and /or extended stroke at 24 hours; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; EQ-5D visual analogue scale at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS score 0-3 vs 4-6 at 90 days; Myocardial infarction at 90 days; Neurological decline at 90 days; Barthel index at 90 days; mRS score at 1 year; EQ-5D utility index score at 90 days

Study	Koch 2008 ³²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in USA; Setting: ED, Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 48 hours, 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Radiologically confirmed acute spontaneous intracerebral haemorrhage within 8 hours of symptom onset, age ≥18 years
Exclusion criteria	History of head trauma, coma, coagulopathy, MAP <100 mmHg, arteriovenous malformations, trauma aneurysms or other secondary causes, surgical haematoma evacuation, inability to give consent
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Mean (SD): intensive 60 (11), conservative 62 (13). Gender (M:F): Intensive 43% male, conservative 67%. Ethnicity: African descent 57%, Hispanic 41%
Further population details	1. Age <80 vs ≥/80 years: Not stated / Unclear 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not stated / Unclear 4. Volume of haemorrhage: Not stated / Unclear
Indirectness of population	No indirectness

Interventions	<p>(n=21) Intervention 1: Intensive therapy. Intensive therapy. Duration 48 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): >6 hours (Within 8 hours).</p> <p>(n=21) Intervention 2: Conservative therapy. Conservative therapy. Duration 48 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): >6 hours (Within 8 hours).</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE THERAPY versus CONSERVATIVE THERAPY</p> <p>Protocol outcome 1: Mortality at 90 days - Actual outcome: Mortality at 90 days; Group 1: 3/21, Group 2: 3/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: mRS score at 90 days - Actual outcome: mRS score at 90 days; Group 1: 10/21, Group 2: 8/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Renal failure at 90 days - Actual outcome: Renal failure at 90 days; Group 1: 1/21, Group 2: 1/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 4: Neurological decline at 90 days - Actual outcome: Neurological decline at 48 hours; Group 1: 2/21, Group 2: 1/21 Risk of bias: All domain - High. Selection - High. Blinding - Low. Incomplete outcome data - Low. Outcome reporting - Low. Measurement - Low. Crossover - Low:</p>	

<p>Indirectness of outcome: Serious indirectness, Comments: Decline at 48 hours not 24 hours; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 5: Haematoma growth at 24 hours - Actual outcome: Haematoma growth at 24 hours; Group 1: 6/21, Group 2: 6/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0</p>	
<p>Protocol outcomes not reported by the study</p>	<p>Mortality at 24 hours; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; EQ-5D utility index score at 90 days; EQ-5D visual analogue scale at 90 days; mRS score at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS score 0-3 vs 4-6 at 90 days; Myocardial infarction at 90 days; Neurological decline at 24 hours; Barthel index at 90 days; mRS score at 1 year; EQ-5D at 90 days</p>

Study	PATICH trial: Zheng 2017 ⁶³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=201)
Countries and setting	Conducted in China; Setting: ED, Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 days + 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT / MRI
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged ≥18 years, had computed tomography- or magnetic resonance imaging–confirmed sICH with elevated systolic BP between 150 and 220 mm Hg (at least 2 measurements) and were able to receive surgery within 24 hours after ictus
Exclusion criteria	Definite indication or contraindications to antihypertensives, secondary intracerebral hemorrhage, a Glasgow Coma Scale score between 3 and 5, a definite contraindication to operation, advanced dementia or disability before ICH onset, or comorbidities that would interfere with the outcome assessment and follow-up.
Recruitment/selection of patients	ED
Age, gender and ethnicity	Age - Mean (SD): Intensive 54 (14), conservative 55 (12). Gender (M:F): Male sex intensive 75%, conservative 69%. Ethnicity: Chinese
Further population details	1. Age <80 vs ≥/80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not stated / Unclear 4. Volume of haemorrhage: Not stated / Unclear

Indirectness of population	No indirectness
Interventions	<p>(n=101) Intervention 1: Intensive therapy. Intensive therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours</p> <p>(n=101) Intervention 2: Conservative therapy. Conservative care. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable</p>
Funding	Academic or government funding (The National Key Technology R&D Program for the 12th Five-year Plan of P.R. China)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE THERAPY versus CONSERVATIVE THERAPY</p> <p>Protocol outcome 1: Mortality at 90 days - Actual outcome: Mortality at 90 days; Group 1: 13/96, Group 2: 18/99 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD), intensive 181 (16), conservative 183 (19), diastolic blood pressure mmHg, mean (SD) intensive 103 (12), conservative 104 (13), Prior hypertension intensive 51% conservative 59%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 2, Reason: Not stated</p> <p>Protocol outcome 2: EQ-5D utility index score at 90 days - Actual outcome: EQ-5D utility score at 90 days; Group 1: mean 0.54 (SD 0.23); n=96, Group 2: mean 0.56 (SD 0.23); n=99 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD), intensive 181 (16), conservative 183 (19), diastolic blood pressure mmHg, mean (SD) intensive 103 (12), conservative 104 (13), Prior hypertension intensive 51% conservative 59%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 2, Reason: Not stated</p>	
Protocol outcomes not reported by the study	Mortality at 24 hours; mRS score at 90 days; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours: EQ-5D visual analogue scale at 90 days: mRS score at 90 days: mRS score 0-2 vs 3-6 at 90 days: mRS

score 0-3 vs 4-6 at 90 days; Renal failure at 90 days; Myocardial infarction at 90 days; Neurological decline at 24 hours; Neurological decline at 90 days; Barthel index at 90 days; mRS score at 1 year; EQ-5D at 90 days

Appendix E: Forest plots

E.1 Intensive versus standard blood pressure lowering in people with acute intracerebral haemorrhage and high blood pressure

Figure 2: Mortality at 90 days

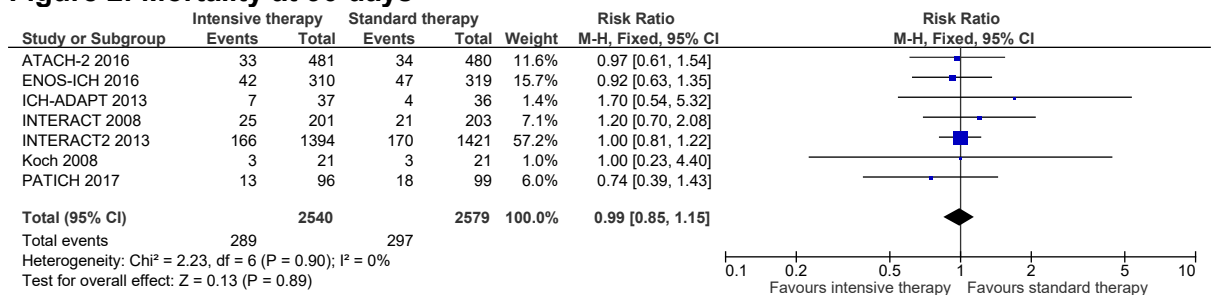


Figure 3: mRS score (0 to 2) at 90 days

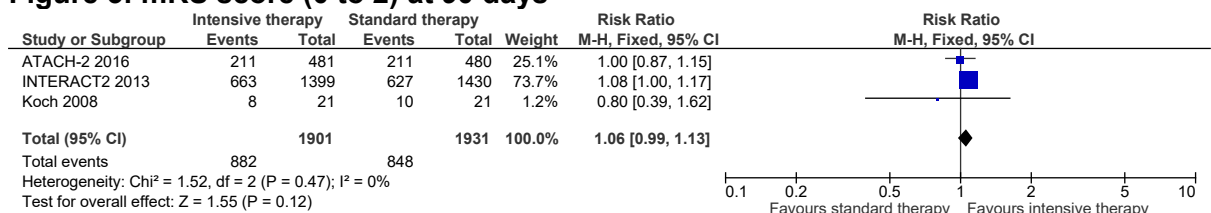


Figure 4: mRS ordinal shift at 90 days – odds ratio for greater disability

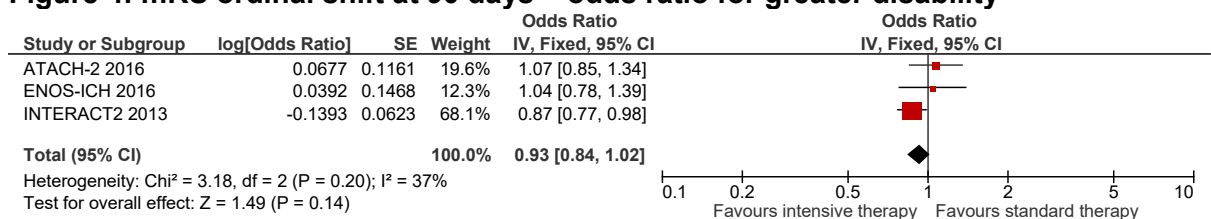


Figure 5: Recurrent stroke at 90 days

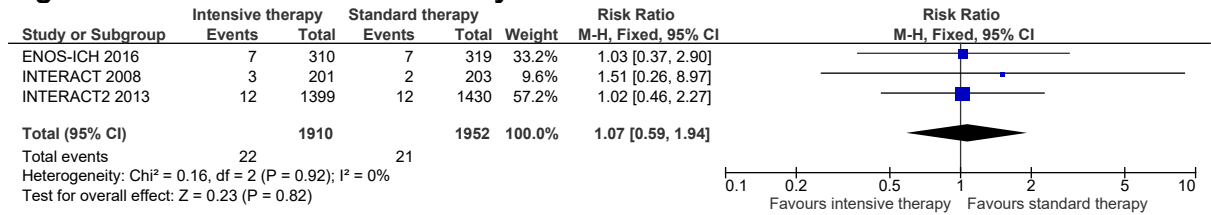


Figure 6: Haematoma growth at 24 hours

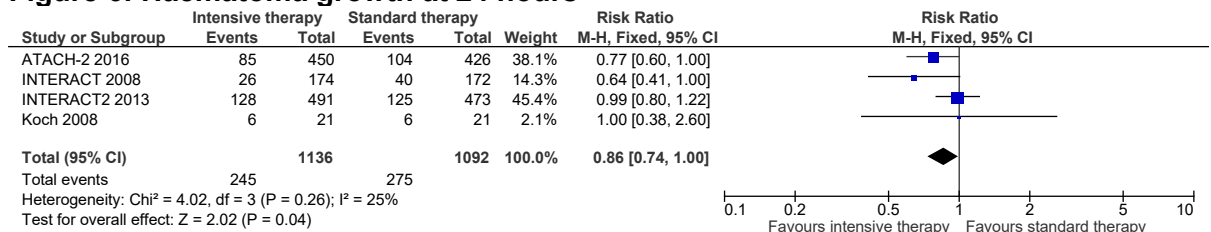


Figure 7: Neurological deterioration at 24 hours

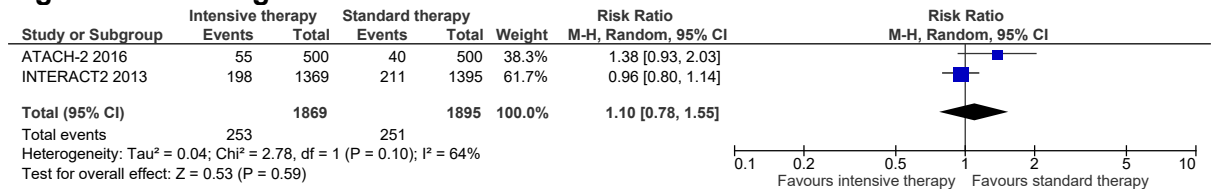


Figure 8: Renal failure at 90 days

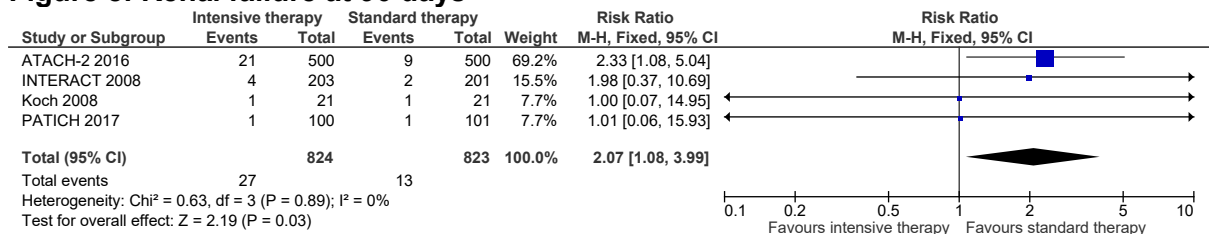


Figure 9: Myocardial infarction at 90 days

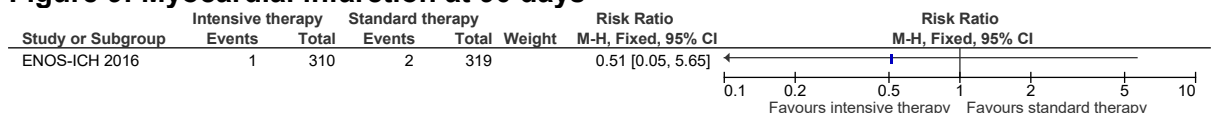


Figure 10: EQ-5D utility score at 90 days

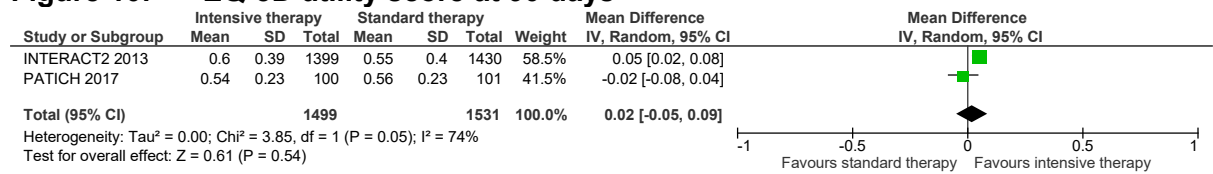
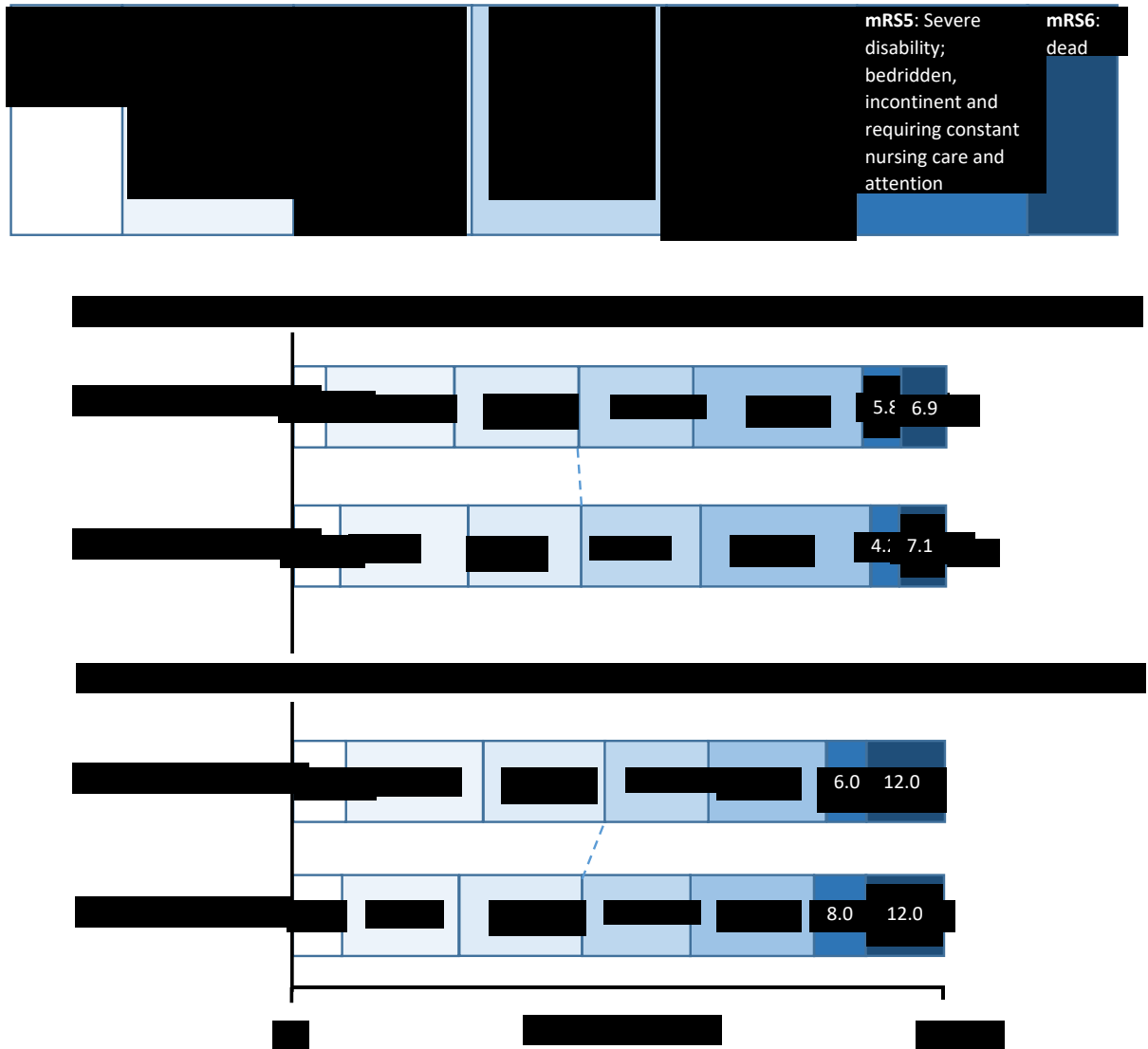


Figure 11: mRS ordinal shift at 90 days



Appendix F: GRADE tables

Table 11: Clinical evidence profile: Intensive blood pressure lowering versus standard treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive	Standard therapy	Relative (95% CI)	Absolute		
Mortality at 90 days												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	289/2540 (11.4%)	12%	RR 0.99 (0.85 to 1.15)	1 fewer per 1000 (from 18 fewer to 18 more)	⊕⊕⊕⊕ HIGH	CRITICAL
mRS: 0 to 2 at 90 days												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	882/1901 (46.4%)	44%	RR 1.06 (0.99 to 1.13)	26 more per 1000 (from 4 fewer to 57 more)	⊕⊕⊕○ MODERATE	CRITICAL
mRS ordinal shift OR at 90 days												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	0.93 (0.84 to 1.02)	-	⊕⊕⊕○ MODERATE	CRITICAL
Recurrent stroke at 90 days												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	22/1910 (1.2%)	1%	RR 1.07 (0.59 to 1.91)	1 more per 1000 (from 4 fewer to 9 more)	⊕⊕○○ LOW	IMPORTANT

									1.94)	more)		
Haematoma expansion at 24 hours												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	245/1136 (21.6%)	24.4%	RR 0.86 (0.74 to 1.00)	34 fewer per 1000 (from 63 fewer to 0 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Neurological deterioration at 24 hours												
2	randomised trials	no serious risk of bias	serious ³	no serious indirectness	very serious ²	none	253/1869 (13.5%)	11.6%	RR 1.1 (0.78 to 1.55)	12 more per 1000 (from 26 fewer to 64 more)	⊕○○○ VERY LOW	IMPORTANT
Renal failure at 90 days												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	27/824 (3.3%)	1.4%	RR 2.07 (1.08 to 3.99)	15 more per 1000 (from 1 more to 42 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Myocardial infarction at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	1/310 (0.32%)	0.6%	RR 0.51 (0.05 to 5.65)	3 fewer per 1000 (from 6 fewer to 28 more)	⊕⊕○○ LOW	IMPORTANT
EQ-5D utility index at 90 days (Better indicated by higher values)												
2	randomised trials	no serious risk of bias	serious ⁴	no serious indirectness	no serious imprecision	none	1499	1531	-	MD 0.02 higher (0.05 lower to 0.09 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

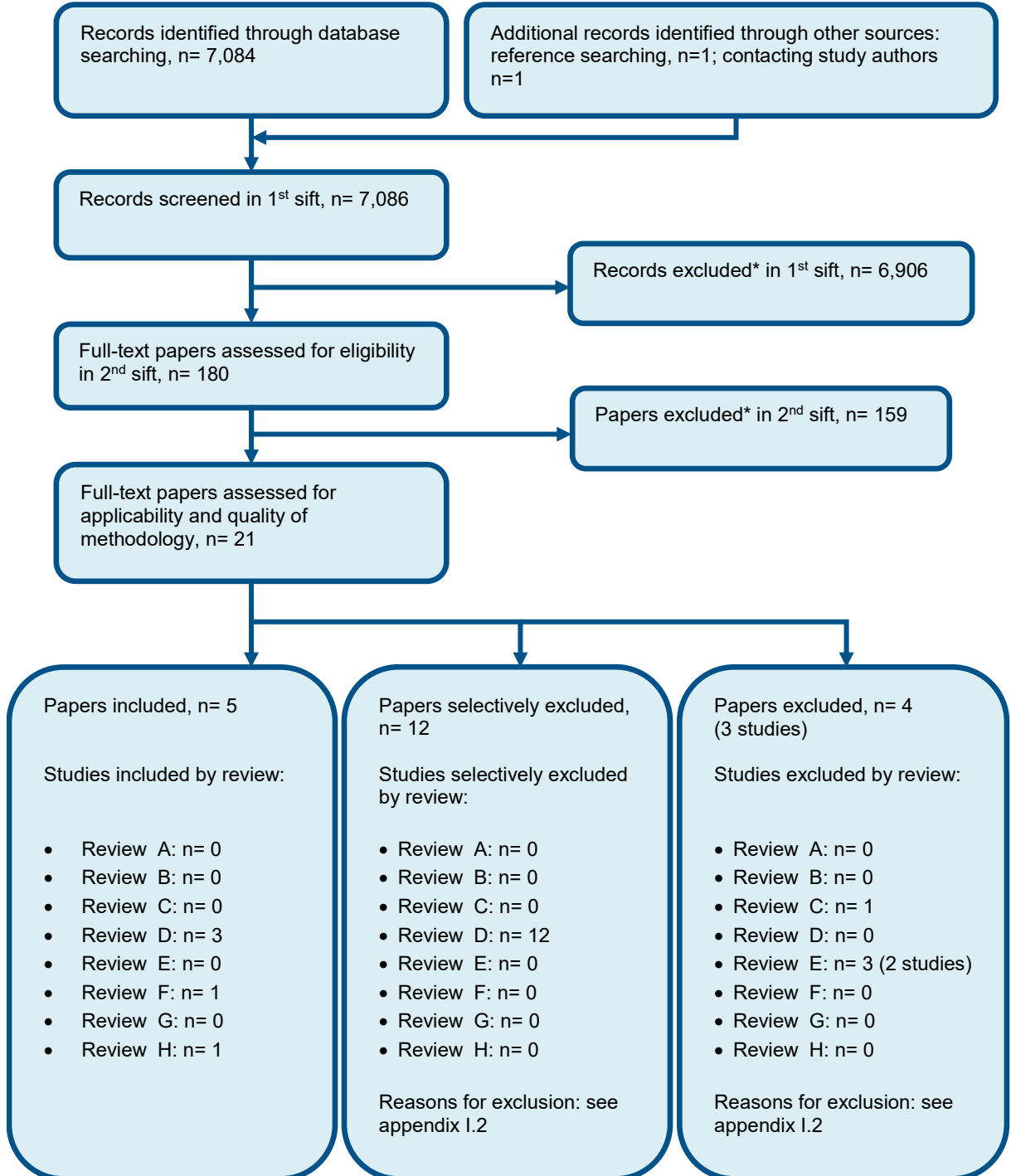
² Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

³ Heterogeneity I²=63% not explained by subgroup analysis because only 2 studies included in the analysis

⁴ Heterogeneity I²=74% not explained by subgroup analysis because only 2 studies included in the analysis

Appendix G: Health economic evidence selection

Figure 12: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Anderson 2010 ²	Outcomes not relevant
Antihypertensive treatment of acute cerebral hemorrhage investigators 2010 ⁴	Incorrect study design, observational
Appleton 2017 ⁵	Incorrect study type, protocol
Arima 2012 ⁷	No outcomes of interest
Arima 2015 ⁶	No outcomes of interest
Bath 2001 ¹⁰	Mixed ischaemic and intracerebral haemorrhage stroke population
Bath 2014 ⁸	Mixed ischaemic and intracerebral haemorrhage stroke population
Bath 2015 ¹¹	Mixed ischaemic and intracerebral haemorrhage stroke population
Bath 2017 ⁹	SR on mixed ischaemic and intracerebral haemorrhage stroke population
Biffi 2015 ¹²	Incorrect study type, observational
Boulouis 2017 ¹³	Systematic review: quality assessment is inadequate
Butcher 2013 ¹⁴	Not RCT, conference abstract
Carandini 2018 ¹⁶	Systematic review: quality assessment is inadequate
Chen 2014 ¹⁷	No outcomes of interest
Delcourt 2012 ¹⁹	No outcomes of interest
Delcourt 2012 ²⁰	Foreign language, French
Delcourt 2017 ²¹	Pooled analysis of 2 RCTs already included in this review.
Dirks 2015 ²²	Not review population
Geeganage 2010 ²⁴	SR on mixed ischaemic and intracerebral haemorrhage stroke population
Haley 1994 ²⁵	Not review population
Hankey 2011 ²⁶	Mixed ischaemic and intracerebral haemorrhage stroke population
Hornslie 2013 ²⁸	Mixed ischaemic and intracerebral haemorrhage stroke population
Hornslie 2014 ²⁷	Mixed ischaemic and intracerebral haemorrhage stroke population
Hornslie 2015 ³⁰	Mixed ischaemic and intracerebral haemorrhage stroke population
Hornslie 2015 ²⁹	Mixed ischaemic and intracerebral stroke population
Jusufovic 2014 ³¹	No outcomes of interest
Lattanzi 2017 ³⁴	Systematic review: quality assessment is inadequate
Manning 2014 ³⁵	Wrong study type, post hoc analysis
Morotti 2017 ³⁶	No outcomes of interest
Pan 2015 ³⁸	Systematic review: quality assessment is inadequate
Potter 2009 ³⁹	Mixed ischaemic and intracerebral haemorrhage stroke population
Potter 2009 ⁴⁰	Mixed ischaemic and intracerebral haemorrhage stroke population
Radholm 2015 ⁴²	Post-hoc analysis
Rashid 2003 ⁴³	Mixed ischaemic and intracerebral haemorrhage stroke population
Robinson 2010 ⁴⁴	Mixed ischaemic and intracerebral haemorrhage stroke population

Study	Exclusion reason
Sandset 2011 ⁴⁵	Mixed ischaemic and intracerebral haemorrhage stroke population
Sandset 2012 ⁴⁶	Mixed ischaemic and intracerebral haemorrhage stroke population
Sato 2014 ⁴⁷	No outcomes of interest
Schrader 2003 ⁴⁸	Not review population
Shi 2017 ⁴⁹	SR did not identify one study
Song 2016 ⁵⁰	Post-hoc analysis
Starke 2016 ⁵¹	Not RCT, narrative review
Tsivgoulis 2014 ⁵³	Systematic review: quality assessment is inadequate
Wang 2014 ⁵⁵	Mixed ischaemic and intracerebral haemorrhage stroke population
Willmot 2004 ⁵⁷	SR on mixed ischaemic and intracerebral haemorrhage stroke population
Willmot 2006 ⁵⁶	Mixed ischaemic and intracerebral haemorrhage stroke population
Woodhouse 2017 ⁵⁹	Mixed ischaemic and intracerebral haemorrhage stroke population
Xu 2011 ⁶⁰	Not English language, Chinese
Ye 2017 ⁶¹	Not RCT, study protocol
Zhang 2017 ⁶²	Not review population

H.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2002 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 13: Studies excluded from the health economic review

Reference	Reason for exclusion
Tavakoli 2009 ⁵²	This study was assessed as not applicable as the intervention was not delivered within 48 hours of stroke onset.
Potter 2009, Wilson 2010 ^{39, 58}	This study was assessed as not applicable as the population was mixed ischaemic stroke and haemorrhagic stroke. The intervention was also not delivered in the hyper-acute phase post-stroke.