National Institute for Health and Care Excellence

Final

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

[E] Evidence review for intensive interventions to lower blood pressure in people with acute intracerebral haemorrhage

NICE guideline NG128

Evidence reviews underpinning recommendations 1.5.4 to 1.5.8 and research recommendations in the NICE guideline

April 2022

Final

These evidence reviews were developed by Guideline Development Team

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1.1 Review question

What is the safety and efficacy of intensive interventions to lower blood pressure versus less intensive interventions in people with acute intracerebral haemorrhage?

1.1.1 Introduction

People with acute intracerebral haemorrhage have a mortality of around 40% with 60-70% of those who survive having moderate or severe disability. Currently, the 2019 NICE guideline on Stroke and transient ischaemic attack in over 16s recommends intensive blood pressure reduction protocol with a systolic blood pressure target of 130 to 140 mmHg for people with acute intracerebral haemorrhage that present within 6 hours of symptom onset and have a systolic blood pressure between 150 and 220 mmHg.

However, new evidence from a pooled analysis of individual patient-level data from INTERACT2 and ATACH-2 showed that these thresholds may be harmful, and that a very large reduction (>60 mmHg) in blood pressure within the first hour may be harmful. This new evidence was reviewed by NICE'S surveillance team which prompted a partial update of the guideline. This review aims to determine the clinical and cost effectiveness of intensive interventions to lower blood pressure versus less intensive interventions in people with acute intracerebral haemorrhage.

1.1.2 Summary of the protocol

PICO Table	
Population	People aged over 16 with acute intracerebral haemorrhage and high systolic blood pressure between 150 and 220 mmHg and over 220 mmHg at the time of assessment Exclusion: Children under the age of 16
Intervention	Intensive blood pressure reduction within 24 hours of admission: o Calcium channel blocker o Intravenous or transdermal glyceryl trinitrate (GTN) o Angiotensin II antagonist o Beta-blockers All drug classes to be pooled (IV and oral if the data allows) for analysis
Comparator	Less intensive blood pressure lowering treatment o Calcium channel blocker o Intravenous or transdermal glyceryl trinitrate (GTN) o Angiotensin II antagonist o Beta-blockers

PICO Table	
	All drug classes (IV and oral to be subgrouped if the data allows) to be pooled for analysis
Primary Outcomes	• Mortality at 24 hours and 90 days • Functional status as measures by the modified Rankin Scale mRS score at 90 days and 1 year
Secondary outcomes	• Symptomatic cerebral ischemia at 24 hours • Haemorrhage expansion at 24 hours • Neurological deterioration at 24 hours • Adverse events (renal failure, cord infarction, symptomatic hypotension, myocardial infarction) up to 90 days • Quality of life (both health- and social-related quality) up to 90 days • Quality of life up to 6 months/ 12 months • Mortality up to 30 days • Percentage achieving blood pressure target

1.1.3 Methods and process

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A total of 2,743 RCTs and systematic reviews were identified in the search. After removing duplicate references, 2,743 RCTs and systematic reviews were screened at title and abstract stage.

Following title and abstract screening, 44 studies were included for full text screening. These studies were reviewed against the inclusion criteria as described in the review protocol (Appendix A). 11 studies were included

The studies included examined the following interventions:

Intensive blood pressure reduction therapy versus Standard (Guideline) blood reduction therapy (10 RCTs), the following studies were analysed to compare the efficacy and safety of intensive blood pressure reduction therapies compared to less intensive blood pressure reduction therapies.

An analysis of individual patient data (IPD) from the two largest trials of early intensive SBP lowering in ICH to determine associations of systolic blood pressure (SBP) parameters with outcomes. The parameters: Mean achieved (mmHg, Magnitude of reduction (mmHg) and

Variability (mmHg) (1) were analysed to determine the association of various blood pressure target ranges to outcomes.

1.1.4.2 Excluded studies

33 studies were excluded. See appendix J for the list of excluded studies with reasons for their exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Reference	Study type	Population	Intervention	Comparator	Outcomes
Anderson, 2013	RCT	People who had a systolic blood pressure between 150- and 220-mmHg and who did not have a definite indication for/or contraindication to blood-pressure–lowering treatment that could be commenced within 6 hours after the onset of spontaneous intracranial haemorrhage. The diagnosis of intracranial haemorrhage was confirmed by means of computed tomography (CT) or magnetic resonance imaging (MRI) Patients were excluded if there was a structural cerebral cause for the intracerebral haemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale [GCS], if they had a massive hematoma with a poor prognosis, or if early	Intensive Treatment (N = 1399) In participants who were assigned to receive intensive treatment to lower their blood pressure (intensive-treatment group), intravenous treatment and therapy with oral agents were initiated according to prespecified treatment protocols that were based on the local availability of agents. The blood pressure was a systolic blood-pressure level of less than 140 mmHg within 1 hour after randomization and	Standard Treatment (N =1430) In participants who were assigned to receive guideline-recommended treatment (standard-treatment group),A blood-pressure–lowering treatment was administered if their systolic blood pressure was higher than 180 mmHg; no lower level was stipulated.	Mortality at 90 days EQ-5D utility index score at 90 days Neurological decline at 24 hours Recurrent stroke at 90 days Modified Rankin Scale at 90 days Haematoma growth at 90 days. All odds ratios are unadjusted.

Reference	Study type	Population	Intervention	Comparator	Outcomes
		surgery to evacuate the hematoma was planned.	this was maintained level for 7 days		
Anderson, 2008	RCT	People 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 h of ICH symptom onset in a suitably monitored environment People were excluded for the following reasons:: a clear indication for intensive lowering of blood pressure (e.g., systolic blood pressure >220 mm Hg or hypertensive encephalopathy); a clear contraindication to intensive lowering of blood pressure (e.g., severe cerebral artery stenosis or renal failure); clear evidence that the ICH was secondary to a structural cerebral abnormality (e.g., arteriovenous malformation,	Intensive Treatment Group (N = 203) The intensive group, were treated to achieve a systolic blood pressure of 140 mm Hg within 1 h of randomisation and to maintain this target blood pressure for the next 7 days or until discharge from hospital if this occurred earlier	Standard Treatment Group (N = 201) Treatment was to achieve a target systolic blood pressure of 180 mmHg.	Mortality at 90 days EQ-5D utility index score at 90 days Neurological decline at 24 hours Haematoma growth at 24 hours Recurrent stroke at 90 days Modified Rankin Scale at 90 days Renal failure at 90 days Model was unadjusted, all odds ratios are unadjusted.

Reference	Study type	Population	Intervention	Comparator	Outcomes
		intracranial aneurysm, or tumour) 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;17 significant pre-stroke disability or medical illness; or early planned decompressive neurosurgical intervention.			
Butcher, 2013	RCT	Eligible patients were ≥18 years of age, with spontaneous ICH diagnosed on non-contrast computed tomography (CT) & 24 hours after onset. SBP was ≥150 mmHg (≥2 readings ≥5 minutes apart). The following patient groups were excluded: Patients with evidence of secondary ICH (e.g., vascular malformation), planned surgical resection Contraindications to CT perfusion e.g., contrast allergy or renal impairment)	Intensive treatment (N = 39) Patients with spontaneous ICH <24 hours after onset and systolic BP > 150 mmHg were randomly assigned to an intravenous antihypertensive treatment protocol targeting a systolic BP of <150 mmHg	Standard Treatment (N = 36) Patients with spontaneous ICH <24 hours after onset and systolic BP > 150 mmHg were randomly assigned to an intravenous antihypertensive treatment protocol targeting a systolic BP of<180 mmHg	Mortality at 90 days Modified Rankin Scale at 90 days Haematoma growth at 2 hours* Neurological decline at 2 hours* 30-day mortality All odds/risk ratios are unadjusted.

Reference	Study type	Population	Intervention	Comparator	Outcomes
Koch, 2008	RCT	People 18 years of age or older with radiologically confirmed acute spontaneous supratentorial ICH within 8 hours of symptom onset The following criteria excluded patients from study participation: People with history of head trauma, coma with signs of herniation, coagulopathy defined as platelet count <50,000 mm^3 or INR C 1.8, MAP & lt; 110 mmHg at presentation, ICH secondary to arteriovenous malformations, trauma, aneurysms or other secondary causes, surgical hematoma evacuation, or inability to give informed consent.	Intensive Treatment Group (N = 21) For the Intensive arm, an aggressive BP lowering target of less than 110 mmHg) median atrial pressure (MAP) within 8 hours of symptom onset.	Standard Treatment Group (N = 21) A standard BP treatment group with a target MAP of 110–130 mmHg according to American Heart Association (AHA) guidelines for the management of ICH	Mortality at 90 days Haematoma growth at 24 hours Modified Rankin Scale at 90 days Renal failure at 90 days Neurological decline at 48 hours Model was unadjusted.
Krishnan, 2016	RCT	People who had a systolic blood pressure between 150 and 220 mmHg and who did not have a definite indication for or contraindication to blood-pressure–lowering treatment that could be commenced	Intensive Treatment Group: Transdermal GTN (N = 310) Patients were treated with transdermal GTN (5 mg daily) for	Standard Treatment Group: No Transdermal GTN (N = 319) no GTN, given for 1 week, in patients with acute stroke (randomization	Mortality at 90 days Recurrent stroke at 90 days Modified Rankin Scale at 90 days Myocardial infarction at 90 days

Reference	Study type	Population	Intervention	Comparator	Outcomes
		within 6 hours after the onset of spontaneous intracranial haemorrhage; the diagnosis of intracranial haemorrhage was confirmed by means of computed tomography (CT) or magnetic resonance imaging (MRI) were included in this study. Patients were excluded if there was a structural cerebral cause for the intracerebral haemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale [GCS], if they had a massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned.	1 week, in patients with acute stroke (randomization within 48 hours of ictus) and high systolic BP (140–220 mmHg).	within 48 hours of ictus) and high systolic BP (140–220 mmHg).	Barthel index at 90 days Model was adjusted for age, sex, severity (Scandinavian Stroke Scale), and time from stroke onset to imaging
Toyoda, 2019	RCT	Patients 18 years of age or older with a Glasgow Coma Scale (GCS) score of 5 or more (on a scale from 3 to 15, with lower scores indicating a worse condition) at the time of arrival in the emergency department and with a measurement of the	Intensive Treatment (N=498) Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg initiated within 4.5 hours after symptom	Standard Treatment (N=497*)* Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg within 24 hours Concurrent medication/care: Standard therapy. Before	Mortality at 90 days Modified Rankin Scale at 90 days Haematoma growth at 90 days. Cardiorenal Adverse Event at 90 days

Reference	Study type	Population	Intervention	Comparator	Outcomes
		intraparenchymal hematoma of less than 60cm3 on initial computed tomographic (CT) scan were eligible for inclusion in the trial if antihypertensive treatment could be initiated within 4.5 hours after symptom onset. Exclusion criteria People with Ischaemic stroke and patients were not eligible if their systolic blood pressure was lowered to less than 140 mm Hg before randomisation during concurrent treatment	onset and continued for 24 hours. Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,	randomization, intravenous antihypertensive medication, including nicardipine was administered to lower the systolic blood pressure to less than 180 mmHg,	Adjusted for sex, Asian race, age (quartile), onset-to-randomization time (quartile), baseline National Institutes of Health Stroke Scale (quartile), baseline hematoma volume (quartile), and lobar hematoma
Moullaali, 2019	RCT	Patients aged 19–99 years with spontaneous(non-traumatic) intracerebral haemorrhage and elevated systolic blood pressure (defined as 150–220 mmHg in INTERACT2 and ≥180 mm Hg in ATACH-II), without a clear indication or contraindication to treatment. Patients without any systolic blood pressure data poor prognosis cases of	INTERACT2 (N = 2829) Lowering mean SBP to a target of <140 mmHg within 1 h of randomization. Treated with any IV or oral agents available to the treating physician. Mean SBP maintained at target level from 1 h to 7	INTERACT2 Control group: Lowering and maintaining mean SBP according to standard guidelines (<180 mmHg), at the discretion of the responsible physician. IV treatment was stopped if SBP dropped below 130 mmHg at any time point ATACH-II Control group:	Modified Rankin Scale at 90 days Renal serious adverse events at 90 days Cardiac serious adverse events at 90 days Adverse symptomatic hypotension at 90 days

Reference	Study type	Population	Intervention	Comparator	Outcomes
		intracerebral haemorrhage were excluded, including people with cerebral oedema, raised intracranial pressure, or requiring decompressive surgery.	days. IV treatment was stopped if SBP dropped below 130 mmHg at any time points. ATACH-II (N = 1000) Intervention group: Lowering minimum SBP to a target of 110–139 mmHg within 2 h of randomization. Treat with IV nicardipine only but allow IV rescue medications. Minimum hourly SBP maintained at target level from 2 to 24 h Control group: Lowering minimum SBP to 140–179 mmHg within 2 h of randomization Treat with IV nicardipine only but allow IV rescue meds. Minimum hourly SBP maintained at the target level for 2 to 24 h	Lowering minimum SBP to 140–179 mmHg within 2 h of randomization Treat with IV nicardipine only but allow IV rescue meds. Minimum hourly SBP maintained at the target level for 2 to 24 h	Odds ratio per 10 mm Hg increase in SBP summary measure, adjusted for age (<65 years vs ≥65 years), Asian versus non-Asian ethnicity, time from onset of intracerebral haemorrhage to randomisation (<4 h vs ≥4 h), and degree of neurological impairment (National Institutes of Health Stroke Scale [NIHSS] score <10 vs ≥10), medical history of diabetes, hypertension, cardiac disease, intracerebral haemorrhage volume (<15 mL vs ≥15 mL), and presence of intraventricular haemorrhage at baseline.

Reference	Study type	Population	Intervention	Comparator	Outcomes
Qureshi, 2016	RCT	Patients 18 years of age or older with a Glasgow Coma Scale (GCS) score of 5 or more (on a scale from 3 to 15, with lower scores indicating a worse condition) at the time of arrival in the emergency department and with a measurement of the intraparenchymal hematoma of less than 60cm3 on initial computed tomographic (CT) scan were eligible for inclusion in the trial if antihypertensive treatment could be initiated within 4.5 hours after symptom onset People with Ischaemic stroke and patients were not eligible if their systolic blood pressure was lowered to less than 140 mm Hg before randomisation during concurrent treatment	Intensive treatment (N = 500) Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg initiated within 4.5 hours after symptom onset and continued for 24 hours. Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,	Standard-treatment (N = 500) Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg within 24 hours	Mortality at 90 days EQ-5D utility index score at 90 days Neurological decline at 24 hours Haematoma growth at 24 hours EQ-5D visual analogue scale at 90 days The analysis was adjusted for age, baseline Glasgow Coma Scale (GCS) score, and the presence or absence of intraventricular haemorrhage at baseline.

Reference	Study type	Population	Intervention	Comparator	Outcomes
Qureshi, 2020 (a)	RCT	Patients aged ≥18 years with a GCS score of 5 or more and with a measurement of the intraparenchymal hematoma of <60 mL on initial computed tomographic (CT) scan were eligible for inclusion. Patients with moderate to severe grade ICH were identified based on previously published criteria, baseline GCS score <13 or NIHSS score ≥10; baseline intraparenchymal haemorrhage volume ≥30 mL; or presence of IVH. Patients with intraventricular haemorrhage (IVH) associated with intraparenchymal haemorrhage and blood completely filling one lateral ventricle or more than half of both ventricles on initial CT scan were excluded	Mild Grade ICH Patients Patients who did not meet any of the moderate to severe grade criteria were classified as mild grade. Among subjects with mild grade ICH. 164 were assigned to intensive treatment Moderate to Severe Grade ICH Patients Among subjects with moderate to severe grade ICH 336 were assigned to intensive SBP reduction	Mild Grade ICH Patients who did not meet any of the moderate to severe grade criteria were classified as mild grade. Among subjects with mild grade ICH. 154 were assigned to standard treatment. Moderate to Severe Grade ICH Patients Among subjects with moderate to severe grade ICH 346 were assigned to standard SBP reduction.	EQ-5D utility index score at 90 days EQ-5D visual analogue scale at 90 days Modified Rankin Scale at 90 days
Qureshi, 2020 (b)	RCT	Patients with intracerebral haemorrhage and initial systolic blood pressure of 180 mm Hg or more, randomized	Intensive SBP reduction (N = 110)	Standard SBP reduction (N = 118)	Neurological decline at 24 hours Haematoma growth at 24 hours

Reference	Study type	Population	Intervention	Comparator	Outcomes
		within 4.5 hours after symptom onset, were included	for the intensive arm the SBP goal, was 110-139 mm Hg) in patients with intracerebral haemorrhage and an initial systolic blood pressure of 220 mmHg or more	For the patients in st standard goal, 140-179 mmHg) systolic blood pressure reduction in patients with intracerebral haemorrhage and an initial systolic blood pressure of 220 mmHg or more	Modified Rankin Scale at 90 days Renal failure at 90 days Any serious adverse event at 90 days The model is adjusted for age, baseline National Institutes of Health Stroke Scale score, and initial hematoma volume
Zheng, 2017	RCT	Conducted in China; Eligible patients were aged ≥ 18 years, had computed tomography- or magnetic resonance imaging–confirmed sICH with elevated systolic BP (SBP) between 150 and 220 mmHg (at least 2 measurements) and were able to receive surgery within 24 hours after ictus. Patients were excluded for having a definite indication or contraindications to antihypertensive, second intracerebral haemorrhage, a Glasgow Coma Scale score	In the intensive group, (N-100) The target SBP at the end of the first hour after randomization was between 140 and 160 mmHg. At the time of surgery the SBP target was between 120 and 140 mmHg using intravenous drugs. . After the operation,	In the conservative group (N-101) The target perioperative SBP was between 140 and 180 mmHg	Mortality at 90 days EQ-5D utility index score at 90 days Modified Rankin Scale at 90 days 30-day mortality The model is adjusted for age, baseline National Institutes of Health Stroke Scale score, and initial hematoma volume

Reference	Study type	Population	Intervention	Comparator	Outcomes
		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	antihypertensive treatment was started when the SBP elevated to >140 mmHg. The target postoperative SBP was between 120 and 140 mmHg. The target SBP was maintained for 7 days after randomization or until hospital discharge within 7 days. The oral antihypertensive drugs were administered as soon as possible		

See appendix D for full evidence tables

1.1.6 Summary of the effectiveness evidence

For the interpretation of effect, MIDs were used to interpret evidence as follows, a) No meaningful difference: 95% CI completely between MIDs and crossing line of no effect; Could not differentiate: 95% CI is crossing line of no effect and also crossing one or two of the MID thresholds; Favours: standard /intensive therapies statistically significant, Reference. Significant associations explored using SBP parameters compared with a clinically relevant reference range.

Intensive blood pressure reduction therapy vs. Standard blood pressure reduction therapy

Primary outcomes

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Mortality at 90 days - RR less than 1 favours Intensive blood pressure reduction therapy					
7	RCT	5099	RR: 0.99 [0.85, 1.16]	High	Could not differentiate between standard and intensive therapies
Modified Rankin Scale at 90 days (a score of 0 to 2) RR greater than 1 favour Intensive blood pressure reduction therapy					
3	RCT	3832	RR: 1.06 [0.99, 1.13]	Moderate	Could not differentiate between standard and intensive therapies
Modified Rankin Scale at 90 days (a score of 4 to 6) RR less than 1 favours Intensive blood pressure reduction therapy					
3	RCT	3832	0R: 0.93 [0.84, 1.02]	Low	Could not differentiate between standard and intensive therapies

Secondary Outcomes

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Symptomatic cerebral ischemia at 24 hours RR less than 1 favours Intensive blood pressure reduction therapy					
1	RCT	201	RR: 1.30 [0.68, 2.47]	Low	Could not differentiate between standard and intensive therapies
Haemorrhage expansion at 24 hours RR less than 1 favours Intensive blood pressure reduction therapy					
6	RCT	3417	RR: 0.82 [0.73, 0.93]	Moderate	**Favours Intensive blood pressure reduction therapy**
Neurological deterioration at 24 hours RR less than 1 favours Intensive blood pressure reduction therapy					
5	RCT	5065	RR: 1.11 [0.96, 1.28]	Low	Could not differentiate between standard and intensive therapies
Recurrent Stroke at 90 days RR less than 1 favours Intensive blood pressure reduction therapy					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
3	RCT	3862	RR: 1.07 [0.59, 1.94]	Moderate	Could not differentiate between standard and intensive therapies
Adverse events (myocardial infarction) up to 90 days RR less than 1 favours Intensive blood pressure reduction therapy					
1	RCT	629	RR: 0.51 [0.05, 5.65]	Low	Could not differentiate between standard and intensive therapies
Adverse events (Renal failure) up to 90 days RR less than 1 favours intensive blood pressure reduction therapy					
4	RCT	1647	RR: 2.07 [1.08, 3.99]	Moderate	Favours standard blood pressure reduction therapy
Mortality up to 30 days RR less than 1 favours Intensive blood pressure reduction therapy					
2	RCT	268	RR: 0.91 [0.29, 2.90]	Very Low	Could not differentiate between standard and intensive therapies
The EQ-5D utility index score up to 90 days MD greater than 0 favours Intensive blood pressure reduction therapy					
2	RCT	3030	MD: 0.02 [-0.05, 0.09]	Low	Could not differentiate between standard and intensive therapies

Associations of categorised systolic blood pressure summary measures and with 90-day functional independence (scores 0-2 on the mRS)

SBP parameters and definitions:

- **Mean achieved (mmHg):** Mean of the mean a SBP measurements taken at each time point during 1–24 h (at 1, 6, 12, 18, and 24 hours [6 time points])
- **Magnitude of reduction (mmHg)** Difference between randomization SBP and the attained minimum mean a SBP within the first hour
- **Variability (mmHg)** Standard deviation and coefficient of variation of the mean observed mean a SBP measures during 1–24 h (6 time points)

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
2	RCT	(n=74)	OR: 1·00 (reference)	Moderate	Reference
120-130 mmHg					
2	RCT	(n=429)	OR: 0.94 [0.51, 1.73]	Very low	No significant association between SBP
130–140 mmHg					
2	RCT	(n=854)	OR: 1·00 (0.55, 1.82]	Very low	No significant association between SBP
140–150 mmHg					
2	RCT	(n=895)	OR: 0·79 [0.44, 1.42]	Very low	No significant association between SBP
150–160 mmHg					
2	RCT	(n=806)	OR:0.81 [0.45, 1.46]	Very low	No significant association between SBP
160–170 mmHg					
2	RCT	(n=474)	OR: 0.70 [0.38, 1.29]	Very low	No significant association between SBP
≥170 mmHg					
2	RCT	(n=284)	OR: 0.63 [0.33, 1.20]	Low	No significant association between SBP

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<5 mmHg					
2	RCT	(n=281)	OR: 1·00 (reference)	Moderate	Reference
5-10 mmHg					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2	RCT	(n=1005)	OR: 1.10 [0.79, 1.53]	Low	No significant association between SBP
10-15 mmHg					
2	RCT	(n=1103)	OR: 1.04 [0.76, 1.42]	Low	No significant association between SBP
15-20 mmHg					
2	RCT	(n=735)	OR: 1.00 [0.71, 1.41]	Very low	No significant association between SBP
≥20 mmHg					
2	RCT	(n=685)	OR: 0.93 [0.66, 1.31]	Very low	No significant association between SBP

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<20 mmHg					
2	RCT	(n=1354)	OR: 1·00 (reference)	Moderate	Reference
20-40 mmHg					
2	RCT	(n=1350)	OR: 1.36 [1.13, 1.64]	Low	SBP in this range associated with better outcome
40-60 mmHg					
2	RCT	(n=731)	OR: 1.35 [1.07, 1.70]	Low	SBP in this range associated with better outcome
≥60 mmHg					
2	RCT	(n=381)	OR: 0.79 [0.60, 1.04]	Low	No significant association between SBP

Associations of categorised systolic blood pressure summary measures and with 90-day good outcome (scores 0-3 on the mRS)

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
2	RCT	(n=74)	OR: 1·00 (reference)	Moderate	Reference
120-130 mmHg					
2	RCT	(n=429)	OR: 0.92 [0.47, 1.80]	Very Low	No significant association between SBP
130–140 mmHg					
2	RCT	(n=854)	OR: 0.89 [0.47, 1.69]	Very Low	No significant association between SBP
140–150 mmHg					
2	RCT	(n=895)	OR: 0.81 [0.42, 1.56]	Very Low	No significant association between SBP
150–160 mmHg					
2	RCT	(n=806)	OR: 0.75 [0.39, 1.44]	Very Low	No significant association between SBP
160–170 mmHg					
2	RCT	(n=474)	OR: 0.69 [0.35, 1.36]	Very Low	No significant association between SBP
≥170 mmHg					
2	RCT	(n=284)	OR: 0.56 [0.28, 1.12]	Low	No significant association between SBP

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<5 mmHg					
2	RCT	(n=281)	OR: 1·00 (reference)	Moderate	Reference
5-10 mmHg					
2	RCT	(n=1005)	OR: 1.18 [0.84, 1.66]	Low	No significant association between SBP
10-15 mmHg					
2	RCT	(n=1103)	OR: 1.16 [0.82, 1.64]	Low	No significant association between SBP
15-20 mmHg					
2	RCT	(n=735)	OR: 1.10 [0.78, 1.55]	Low	No significant association between SBP
≥20 mmHg					
2	RCT	(n=685)	OR: 0.81 [0.57, 1.15]	Low	No significant association between SBP

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<20 mmHg					
2	RCT	(n=1354)	OR: 1·00 (reference)	Moderate	Reference
20-40 mmHg					
2	RCT	(n=1350)	OR: 1.29 [1.06, 1.57]	Low	SBP in this range associated with better outcome
40-60 mmHg					
2	RCT	(n=731)	OR: 1.23 [0.97, 1.56]	Low	No significant association between SBP
≥60 mmHg					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2	RCT	(n=381)	OR: 0.63 [0.47, 0.84]	Low	SBP in this range associated with worse outcome

Associations of categorised systolic blood pressure summary measures and haematoma expansion >6mL at 24 hours

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
2	RCT	(n=45)	OR: 1·00 (reference)	Low	Reference
120-130 mmHg					
2	RCT	(n=295)	OR: 0.94 [0.36, 2.45]	Low	No significant association between SBP
130–140 mmHg					
2	RCT	(n=464)	OR: 0.93 [0.36, 2.40]	Low	No significant association between SBP
140–150 mmHg					
2	RCT	(n=436)	OR: 1.28 [0.50, 3.28]	Low	No significant association between SBP
150–160 mmHg					
2	RCT	(n=399)	OR: 1.63 [0.63, 4.22]	Low	No significant association between SBP
160–170 mmHg					
2	RCT	(n=213)	OR: 1.55 [0.58, 4.14]	Low	No significant association between SBP
≥170 mmHg					
2	RCT	(n=84)	OR: 1.90 [0.66, 5.47]	Low	No significant association between SBP

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<5 mmHg					
2	RCT	(n=109)	OR: 1·00 (reference)	Low	Reference
5-10 mmHg					
2	RCT	(n=547)	OR: 0.97 [0.53, 1.78]	Low	No significant association between SBP
10-15 mmHg					
2	RCT	(n=565)	OR: 1.12 [0.61, 2.06]	Low	No significant association between SBP
15-20 mmHg					
2	RCT	(n=383)	OR: 1.22 [0.65, 2.29]	Low	No significant association between SBP
≥20 mmHg					
2	RCT	(n=332)	OR: 1.21 [0.64, 2.29]	Low	No significant association between SBP

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<20 mmHg					
2	RCT	(n=646)	OR: 1·00 (reference)	Low	Reference
20-40 mmHg					
2	RCT	(n=637)	OR: 0.94 [0.69, 1.28]	Low	No significant association between SBP
40-60 mmHg					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2	RCT	(n=419)	OR: 0.78 [0.55, 1.11]	Low	No significant association between SBP
≥60 mmHg					
2	RCT	(n=234)	OR: 1.14 [0.75, 1.73]	Low	No significant association between SBP

Associations of categorised systolic blood pressure summary measures and neurological deterioration at 24 hours

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
2	RCT	(n=73)	OR: 1·00 (reference)	Moderate	Reference
120-130 mmHg					
2	RCT	(n=424)	OR 0.32 [0.15, 0.68]	Moderate	SBP in this range associated with better outcome
130–140 mmHg					
2	RCT	(n=845)	OR: 0.57 [0.29, 1.12]	Moderate	No significant association between SBP
140–150 mmHg					
2	RCT	(n=886)	OR: 0.58 [0.29, 1.16]	Moderate	No significant association between SBP
150–160 mmHg					
2	RCT	(n=797)	OR: 0.49 [0.24, 1.00]	Moderate	SBP in this range associated with better outcome
160–170 mmHg					
2	RCT	(n=466)	OR: 0.66 [0.33, 1.32]	Low	No significant association between SBP
≥170 mmHg					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
2	RCT	(n=261)	OR: 0.97 [0.46, 2.05]	Low	No significant association between SBP

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<5 mmHg					
2	RCT	(n=267)	OR: 1·00 (reference)	Low	Reference
5-10 mmHg					
2	RCT	(n=1000)	OR: 0.89 [0.55, 1.44]	Low	No significant association between SBP
10-15 mmHg					
2	RCT	(n=1097)	OR: 0.91 [0.57, 1.45]	Low	No significant association between SBP
15-20 mmHg					
2	RCT	(n=719)	OR: 1.09 [0.68, 1.75]	Low	No significant association between SBP
≥20 mmHg					
2	RCT	(n=668)	OR: 1.71 [1.07, 2.73]	Moderate	SBP in this range associated with worse outcome

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<20 mmHg					
2	RCT	(n=1322)	OR: 1·00 (reference)	Low	Reference

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
20-40 mmHg					
2	RCT	(n=1334)	OR: 0.81 [0.63, 1.04]	Moderate	No significant association between SBP
40-60 mmHg					
2	RCT	(n=721)	OR: 0.87 [0.64, 1.18]	Moderate	No significant association between SBP
≥60 mmHg					
2	RCT	(n=374)	OR: 1.13 [0.79, 1.62]	Moderate	No significant association between SBP

Associations of categorised systolic blood pressure summary measures and death at 90 days

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
2	RCT	(n=71)	OR: 1·00 (reference)	Low	Reference
120-130 mmHg					
2	RCT	(n=421)	OR 0.83 [0.31, 2.22]	Low	No significant association between SBP
130–140 mmHg					
2	RCT	(n=836)	OR: 0.86 [0.34, 2.18]	Low	No significant association between SBP
140–150 mmHg					
2	RCT	(n=877)	OR: 0.94 [0.37, 2.39]	Low	No significant association between SBP
150–160 mmHg					
2	RCT	(n=793)	OR: 0.81 [0.32, 2.05]	Low	No significant association between SBP

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
160–170 mmHg					
2	RCT	(n=463)	OR: 1.37 [0.53, 3.54]	Low	No significant association between SBP
≥170 mmHg					
2	RCT	(n=274)	OR: 2.41 [0.92, 6.31]	Low	No significant association between SBP

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<5 mmHg					
2	RCT	(n=275)	OR: 1·00 (reference)	Low	Reference
5-10 mmHg					
2	RCT	(n=983)	OR: 0.60 [0.36, 1.00]	Moderate	SBP in this range associated with better outcome
10-15 mmHg					
2	RCT	(n=1087)	OR: 0.55 [0.34, 0.89]	Moderate	SBP in this range associated with better outcome
15-20 mmHg					
2	RCT	(n=720)	OR: 0.87 [0.53, 1.43]	Low	No significant association between SBP
≥20 mmHg					
2	RCT	(n=671)	OR: 0.89 [0.54, 1.47]	Low	No significant association between SBP

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<20 mmHg					
2	RCT	(n=1329)	OR: 1·00 (reference)	Low	Reference
20-40 mmHg					
2	RCT	(n=1323)	OR: 0.78 [0.58, 1.05]	Moderate	No significant association between SBP
40-60 mmHg					
2	RCT	(n=711)	OR: 0.71 [0.49, 1.03]	Moderate	No significant association between SBP
≥60 mmHg					
2	RCT	(n=373)	OR: 1.14 [0.75, 1.73]	Moderate	No significant association between SBP

Associations of categorised systolic blood pressure summary measures and any serious adverse events at 90 days

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
2	RCT	(n=74)	OR: 1·00 (reference)	Low	Reference
120-130 mmHg					
2	RCT	(n=428)	OR 1.14 [0.56, 2.32]	Low	No significant association between SBP
130–140 mmHg					
2	RCT	(n=854)	OR: 1.06 [0.53, 2.12]	Low	No significant association between SBP
140–150 mmHg					
2	RCT	(n=895)	OR: 1.15 [0.58, 2.28]	Low	No significant association between SBP

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
150–160 mmHg					
2	RCT	(n=806)	OR: 1.04 [0.52, 2.08]	Low	No significant association between SBP
160–170 mmHg					
2	RCT	(n=474)	OR: 1.32 [0.65, 2.68]	Low	No significant association between SBP
≥170 mmHg					
2	RCT	(n=278)	OR: 2.16 [1.04, 4.49]	Moderate	SBP in this range associated with worse outcome

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<5 mmHg					
2	RCT	(n=281)	OR: 1·00 (reference)	Moderate	Reference
5-10 mmHg					
2	RCT	(n=1005)	OR 1.05 [0.72, 1.53]	Low	No significant association between SBP
10-15 mmHg					
2	RCT	(n=1103)	OR: 0.83 [0.57, 1.21]	Low	No significant association between SBP
15-20 mmHg					
2	RCT	(n=735)	OR: 1.19 [0.80, 1.77]	Moderate	No significant association between SBP
≥20 mmHg					
2	RCT	(n=685)	OR: 1.55 [1.05, 2.29]	Moderate	SBP in this range associated with worse outcome

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<20 mmHg					
2	RCT	(n=1351)	OR: 1·00 (reference)	Moderate	Reference
20-40 mmHg					
2	RCT	(n=1348)	OR: 1.01 [0.82, 1.24]	High	No significant association between SBP
40-60 mmHg					
2	RCT	(n=729)	OR: 0.91 [0.71, 1.17]	Moderate	No significant association between SBP
≥60 mmHg					
2	RCT	(n=381)	OR: 1.29 [0.95, 1.75]	Moderate	No significant association between SBP

Outcomes by Average Hourly Minimum Systolic Blood Pressure Intensive Blood pressure reduction VS Standard Blood pressure reduction

mRS 4 to 6 at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
Toyoda, 2019	RCT	199	OR 1.00 [0.62, 1.61]	Very Low	No significant association between SBP
120-130 mmHq					
Toyoda, 2019	RCT	301	OR 1 (reference)	Low	Reference

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
130-140 mmHg					
Toyoda, 2019	RCT	139	OR 1.41 [0.83, 2.40]	Low	No significant association between SBP
140-150 mmHg					
Toyoda, 2019	RCT	221	OR 1.62 [1.02, 2.57]	Low	SBP in this range associated with worse outcome
150 mmHg					
Toyoda, 2019	RCT	135	OR: 0.93 [0.55, 1.57]	Very Low	No significant association between SBP

Death at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
Toyoda, 2019	RCT	199	OR: 0.84 [0.35, 2.02]	Low	No significant association between SBP
120-130 mmHq					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Toyoda, 2019	RCT	301	OR: 1 (reference)	Low	Reference
130-140 mmHg					
Toyoda, 2019	RCT	139	OR: 1.27 [0.51, 3.16]	Low	No significant association between SBP
140-150 mmHg					
Toyoda, 2019	RCT	221	OR: 1.30 [0.53, 3.19]	Low	No significant association between SBP
150 mmHg					
Toyoda, 2019	RCT	135	OR: 1.19 [0.43, 3.29]	Low	No significant association between SBP

Hematoma expansion

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
Toyoda, 2019	RCT	199	OR: 1.35 [0.77, 2.37]	Low	No significant association between SBP
120-130 mmHq					
Toyoda, 2019	RCT	301	OR: 1 (reference)	Low	Reference
130-140 mmHg					
Toyoda, 2019	RCT	139	OR: 1.57 [0.86, 2.87]	Moderate	No significant association between SBP
140-150 mmHg					
Toyoda, 2019	RCT	221	OR: 1.80 [1.05, 3.09]	Moderate	SBP in this range associated with worse outcome
150 mmHg					
Toyoda, 2019	RCT	135	OR: 1.98 [1.12, 3.50]	Moderate	SBP in this range associated with worse outcome

Cardiorenal Adverse Events

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<120 mmHg					
Toyoda, 2019	RCT	199	OR: 0.86 [0.46, 1.61]	Low	No significant association between SBP
120-130 mmHq					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Toyoda, 2019	RCT	301	OR: 1 (reference)	Moderate	Reference
130-140 mmHg					
Toyoda, 2019	RCT	139	OR: 0.72 [0.35, 1.48]	Low	No significant association between SBP
140-150 mmHg					
Toyoda, 2019	RCT	221	OR: 0.43 [0.19, 0.97]	Moderate	SBP in this range associated with better outcome
150 mmHg					
Toyoda, 2019	RCT	135	OR: 0.44 [0.18, 1.08]	Moderate	No significant association between SBP

Outcomes by Absolute Reduction of Average Hourly Minimum Systolic Blood Pressure (SBP) From the Initial SBP

mRS 4 to 6 at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<40 mmHg					
Toyoda, 2019	RCT	164	OR 1 (reference)	Low	Reference
40-58 mmHg					
Toyoda, 2019	RCT	180	OR: 0.74 [0.43, 1.27]	Low	No significant association between SBP
58-76 mmHg					

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Toyoda, 2019	RCT	253	OR: 0.90 [0.55, 1.47]	Very Low	No significant association between SBP
76-94 mmHg					
Toyoda, 2019	RCT	200	OR: 0.87 [0.52, 1.46]	Very Low	No significant association between SBP
>96 mmHg					
Toyoda, 2019	RCT	161	OR: 0.79 [0.45, 1.39]	Very Low	No significant association between SBP

Mortality at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<40 mmHg					
Toyoda, 2019	RCT	164	OR: 1 (reference)	Low	Reference
40-58 mmHg					
Toyoda, 2019	RCT	180	OR: 1.13 [0.48, 2.66]	Low	No significant association between SBP
58-76 mmHg					
Toyoda, 2019	RCT	253	OR: 0.55 [0.23, 1.32]	Low	No significant association between SBP
76-94 mmHg					
Toyoda, 2019	RCT	200	OR: 0.49 [0.20, 1.20]	Moderate	No significant association between SBP
>96 mmHg					
Toyoda, 2019	RCT	161	OR: 0.25 [0.07, 0.89]	Moderate	SBP in this range associated with better outcome

Hematoma expansion at 24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<40 mmHg					
Toyoda, 2019	RCT	164	OR 1 (reference)	Low	Refence
40-58 mmHg					
Toyoda, 2019	RCT	180	OR0.90 [0.52, 1.56]	Low	No significant association between SBP
58-76 mmHg					
Toyoda, 2019	RCT	253	OR: 0.48 [0.28, 0.82]	Moderate	SBP in this range associated with better outcome
76-94 mmHg					
Toyoda, 2019	RCT	200	OR: 0.36 [0.19, 0.68]	High	SBP in this range associated with better outcome
>96 mmHg					
Toyoda, 2019	RCT	161	OR: 0.36 [0.19, 0.68]	High	SBP in this range associated with better outcome

Cardiorenal Adverse Events

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
<40 mmHg					
Toyoda, 2019	RCT	164	OR 1 (reference)	Low	Reference
40-58 mmHg					
Toyoda, 2019	RCT	180	OR: 0.95 [0.41, 2.20]	Low	No significant association between SBP
58-76 mmHg					
Toyoda, 2019	RCT	253	OR: 1.09 [0.52, 2.28]	Low	No significant association between SBP
76-94 mmHg					
Toyoda, 2019	RCT	200	OR: 1.22 [0.58, 2.57]	Low	No significant association between SBP
>96 mmHg					
Toyoda, 2019	RCT	161	OR: 2.11 [1.01, 4.41]	Moderate	SBP in this range associated with better outcome

Data not suitable for meta-analysis

No. of studies	Study design	Sample size	Intervention	Control	Quality
mRS score at 90 days - median (IQR)					
Anderson 2008	RCT	2815	2 (1-4)	2 (1-4)	Moderate
mRS score at 90 days - median (IQR)					
Butcher 2013	RCT	73	4 (2–5)	2.5 (1–5.75)	Moderate
mRS score at 90 days - median (IQR)					
Krishnan 2016	RCT		3 [2]	3 [2]	Moderate

No. of studies	Study design	Sample size	Intervention	Control	Quality
EQ-5D utility index score, median (range) at 90 days					
Anderson 2008	RCT	2815	2 (1-4)	2 (1-4)	Moderate
EQ-5D utility index score, median (IQR) at 90 days (-0.1 to 1.0)					
Qureshi,2016	RCT	961	0.7	0.7	Moderate
EQ-5D visual analogue scale at 90 days (0 to 100)					
Qureshi,2016	RCT	961	70	62.5	Moderate
EQ-visual analogue scale at 90 days (0 to 100)					
Krishnan 2016	RCT		55.1 (31.5)	54.6 (31.3)	Moderate
Mild ICH group					
EQ-5D utility index score, median (range) (with scores ranging from −0.109 [least favourable health state] to 1 [most favourable health state					
Qureshi 2020	RCT	318	0.8 (0.1–1)	0.8 (0.1–1)	Moderate
EQ-5D visual-analog scale score, median (range) (with scores ranging from 0 [least favourable health state] to 100 [most favourable health state					
Qureshi 2020	RCT	318	75 (10–100)	70 (8–100)	Moderate
(Moderate-to-severe ICH group)					
EQ-5D utility index score, median (range) (with scores ranging from −0.109 [least favourable health state] to 1 [most favourable health state					
Qureshi 2020	RCT	682	0.8 (0.1–1)	0.8 (0.1–1)	Moderate
EQ-5D visual-analog scale score, median (range) (with scores ranging from 0 [least favourable health state] to 100 [most favourable health state					
Qureshi 2020	RCT	682	75 (10–100)	70 (8–100)	Moderate

See appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

No relevant health economic studies were included.

1.1.7.2 Excluded studies

No economic studies relating to this review question were identified.

See the health economic study selection flow chart presented in Appendix G.

1.1.8 Unit costs

UK costs of drugs to lower blood pressure are presented in Table 1 to Table 5.

Table 1: UK costs of calcium channel blockers to lower blood pressure

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Cost per week (£)	Source
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 daily]	£0.11 / £0.12	£2.46	NHS Drug Tariff December 2021
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 response. Maximum rate 15mg/hour, reduce dose gradually when target blood pressure achieved; maintenance 2-4mg/hour]	£10.00	£252.00 (a)	British national formulary December 2021

(a) Cost of 2-day course, it should be noted this cost is likely to vary between patients depending on the exact dosage and treatment duration required to meet the target blood pressure threshold.

Table 2: UK costs of angiotensin II antagonists to lower blood pressure

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Cost per week (£)	Source
Candesartan cilexetil 8mg tablet	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]	£0.05	£0.34	NHS Drug Tariff December 2021

Table 3: UK costs of beta-blockers to lower blood pressure

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Cost per week (£)	Source
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]	£25.29	£606.96 (a)	NHS Drug Tariff December 2021
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]	£0.10	£1.35	NHS Drug Tariff December 2021

(a) Cost of 2-day course, it should be noted this cost is likely to vary between patients depending on the exact dosage and treatment duration required to meet the target blood pressure threshold.

Table 4: UK costs of glyceryl trinitrate to lower blood pressure

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Cost per week (£)	Source
Intravenous glyceryl trinitrate 50mg per 10ml solution for infusion vials	200micrograms/minute [Control of hypertension and myocardial ischaemia during and after cardiac surgery 10–200 micrograms/minute (max. per dose 400 micrograms/minute)]	£12.98	£149.53 (a)	British national Formulary December 2021
Transdermal glyceryl trinitrate 5mg per 24-hour patch	1 x 5mg patch daily	£0.46	£3.19	NHS Drug Tariff December 2021

(a) Cost of 2-day course, it should be noted this cost is likely to vary between patients depending on the exact dosage and treatment duration required to meet the target blood pressure threshold.

Table 5: UK costs of hydralazine hydrochloride to lower blood pressure

Resource	Assumed daily dose [BNF]	Cost per unit (£)	Cost per week (£)	Source
Hydralazine hydrochloride 20 mg powder for concentrate for solution for injection ampoules	Initially 200–300 micrograms/minute; usual maintenance 50–150 micrograms/minute. [hypertensive emergencies]	£14.83	(a)	British national Formulary December 2021
Hydralazine hydrochloride 25 mg	25mg twice daily [Moderate to severe hypertension initially 25 mg twice daily, increased if necessary up to 50 mg twice daily]	£0.07	£1.00	NHS Drug Tariff December 2021

(a) The cost per week is not included because this will vary on an individual basis depending on the duration and the dosage of treatment needed.

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1. The outcomes that matter most

The critical outcomes identified for this review were the modified Rankin Scale (mRS) at 90 days), serious adverse events (renal failure) at 90 days, and mortality at 90 days. The committee considered these three outcomes to be vital in decision making. Important outcomes also included symptomatic cerebral ischaemia, haemorrhagic expansion, neurological deterioration, and quality of life. No evidence was available for the outcomes of quality of life at 6 and 12-months that assesses cognitive function The committee agreed that this was another vital outcome in decision making if evidence was available.

The committee also considered the pooled individual participant data, that assessed the strength and direction of systolic blood pressure parameters and outcomes from ATACH-2 and INTERACT-2. The three parameters used to assess the association were: 1) the mean achieved systolic blood pressure, 2) the variability (standard deviation) of systolic blood pressure and 3) the magnitude of systolic blood pressure reduction after 1 hour of randomization. It reviewed all the evidence and agreed that the mean achieved and magnitude reduction within 1-hour of randomization of systolic blood pressure parameters will be critical in decision making.

The committee identified and prioritised a number of subgroups, including people who are frail, the time of treatment/presentation (within 6 hours/ >6 hours), the location of haematoma and the NIH Stroke Scale at baseline, however no evidence was found for these subgroups.

1.1.9.2 The quality of the evidence

Eleven studies were included in the review. The majority of the data were from two clinical trials. The studies were designed as prospective randomized open-label blinded endpoint (PROBE)-type trials, in which patients were randomly allocated to different regimens and both

the patients and doctors are aware of the regimen being administered. The evidence also included a pre-planned pooled individual participant data (IPD) analysis of the ATACH-2 and INTERACT-2 trials.

The committee also considered the pooled individual participant data that assessed the association of outcomes from the ATACH-2 and INTERACT-2 trials within three categories: 1) the mean achieved systolic blood pressure, 2) the variability (standard deviation) of systolic blood pressure and 3) the magnitude of systolic blood pressure reduction after 1 hour of randomization. The committee reviewed all the evidence and agreed that the achieved and magnitude reduction of SBP category were very important.

Evidence ranged from very low to high quality, with the majority of the evidence rated as moderate quality. Subjective outcomes such as the mRS Scale and the EQ-5D index (Quality of life index) were downgraded for risk of bias as the patients and trial personnel were not blinded to the intervention.

Research Recommendations

The committee discussed gaps in the data such as importance of QALY outcomes at 6 months and 12 months that assess cognitive function, cognitive ability, Quality of life and also the assessment of frailty to measure the health status of people who are frail. This can serve as a surrogate outcome and a proxy measure of vulnerability. Frailty consideration can be useful in predicting bits association with good and poor outcomes with intensive blood pressure reduction therapies. These gaps in the data have been developed into research recommendations by the committee. (Appendix K)

1.1.9.3 Benefits and harms

The committee discussed the benefits and harm reported in the primary studies, INTERACT-2 reported modest benefit and no safety concerns for intensive blood pressure lowering treatment in people after intracerebral haemorrhage with a high systolic blood pressure of 150-220 mmHg. The data highlighted no clinical difference for mortality and functional independence as measured using the mRS Scale at 90 days. Haematoma expansion at 24 hours and quality of life (EQ-5D utility index) favoured intensive blood pressure reduction treatment with no indication of harm. There were very few Myocardial infarction events reported resulting in estimates of effect with wide confidence intervals and they were downgraded for imprecision.

The committee reviewed the evidence on adverse renal failure at 90 days, ATACH-2 showed intensive blood pressure lowering adversely affected renal function, The committee noted there were differences in the treatment regimen of ATACH-2 and the other studies included in the review. The trial 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. The committee also considered that renal serious adverse events were infrequent, and without any appreciable trends for harm evident across a wide range of systolic blood pressure levels.

The committee agreed that there is sufficient evidence to show that intensive lowering of systolic blood pressure can be safe when using less aggressive protocols, and so have included a recommendation on the blood pressure target.

The committee noted that the evidence showed that higher variability in systolic blood pressure from 1 hour to 24 hours resulted in higher adverse outcomes and poorer 90-day mortality. The committee agreed there are beneficial effects of even and smooth control of systolic blood pressure. However, for the recommendation strategy, the committee decided not to include a recommendation on the variability of systolic blood pressure from 1 hour to 24 hours data for the following reasons: The RCT protocols included in this review allowed for a variation of agents to be used in different centres. and the available evidence is based on the use of

different classes in combination or as standalone antihypertension agents to achieve the target systolic blood pressure.

Therefore, it was agreed, the current evidence cannot provide insight as to which agents, if any, are better than others, or of the optimal time to achieve a target systolic blood pressure more smoothly to produce a favourable outcome after acute intracerebral haemorrhage. The committee were also uncertain over how best to routinely: identify, quantify, and manage a variability parameter in clinical practice.

An individual patient data meta-analysis appraising all the available data on the variability of blood pressure lowering by agent and time period from the onset of symptoms up to 24 hours is required to inform management. Therefore, including a variability of blood pressure range limitation was agreed to be too restrictive and, not practical. It agreed this should be dependent on local medication availability and clinician preference.

Lower levels of mean achieved systolic blood pressure from 1 hour to 24 hours were associated with reductions in haematoma expansion, early neurological deterioration, death, and serious adverse events (renal and cardiovascular). The committee agreed that there appears to be a pattern showing that lower categories of achieved mean systolic blood pressure were associated with better outcomes, down to 120–130 mmHg compared with a reference category of less than 120 mmHg systolic blood pressure.

For the parameter of magnitude of systolic blood pressure reduction after 1 hour of randomization compared with a reference category of less than 20 mmHg. It was clear that a moderate category reduction in systolic blood pressure of 20–40 mmHg and 40–60 mmHg within 1 hour were weakly associated with both a good outcome and functional independence on the mRS score (quality-of-life index). Whereas a large reduction of 60 mmHg or more within 1 hour of randomisation was significantly associated with lower odds of a good outcome on the mRS scale. In in accordance with these findings, the outcomes of serious adverse event (renal failure), early neurological deterioration and mortality at 90 days showed that a rapid and large reduction of systolic blood pressure that is greater than 60 mmHg within the first hour of the initiation of treatment might cause harm for people with acute intracerebral haemorrhage stroke.

The committee concluded that on balance, the available data supports a recommendation for rapidly lowering blood pressure in people with acute intracerebral haemorrhage. The committee concluded it is safe to aim to reach a systolic blood pressure target of 140mmHg or lower. Whilst ensuring the magnitude drop does not exceed 60mmHg within 1 hour of starting to treat.

In accordance with evidence from the trials the recommendation included that treatment should start within 6 hours and continue for 7 days. However, the committee decided to remove the time window to initiate treatment for the following reasons: The committee saw that only a minority (33.4%) of participants in the INTERACT2 trial achieved the target of 140mmHg within 1 hour. And more importantly so that the potential harm associated with a systolic blood pressure reduction greater than 60mmHg, within the first hour can be avoided.

It was also agreed the evidence to support the previous recommendation text stating “maintain this blood pressure for at least 7 days” is weak. The committee highlighted this will clearly have an impact on patient flow, bed management and resources in the NHS. Thus, this time frame was removed from both recommendation 1.5.4 and 1.5.5.

The 130 mmHg lower limits included as part of the previous recommendations 1.5.4 and 1.5.5 were removed. The committee was concerned that a narrow range would be too restrictive in clinical practice. They also considered the potential risk of systolic blood pressure dropping too low but noted this potential concern is addressed by the avoidance of a large reduction of 60 mmHg or more within 1 hour in recommendation 1.5.6. The committee agreed that while there

is some evidence of benefit supporting rapid blood lowering treatment, they had concerns around the increase in adverse renal events and the absence of evidence in clinically frail adults. Taking this into account the committee agreed that rapid blood pressure lowering treatment should be considered as an option for treatment except for the groups highlighted in recommendation 1.5.7.

The committee agreed that some guidance is needed on treating hypertension in people that present beyond 6 hours of symptom onset or have a systolic blood pressure greater than 220 mmHg They agreed and that it is appropriate to extrapolate from the available evidence to these groups. The committee decided that a consider recommendation is appropriate for the following reasons: caution should be taken in extrapolating these findings across the range of cases of intracerebral haemorrhage because these data were derived from clinical trial populations. There were concerns for patients presenting with a blood pressure of 220 mmHg or more should be treated based on clinicians' judgement as there is no conclusive evidence to support the safety and effectiveness of intensive blood pressure lowering in this group of patients. It was agreed that this would be conveyed by the addition of 'on a case-by-case' wording to the recommendation. It would also allow clinical discretion in these groups for instances where intensive blood pressure lowering may not be appropriate.

The committee emphasised that the target systolic blood pressure and the systolic blood pressure reduction caveat are very important and made a stand-alone recommendation highlighting this.

For recommendation 1.5.7 the committee discussed the exclusion criteria, and if there is a need to update the exclusion criteria for recommendation 1.5.4, 1.5.5. and 1.5.6. The committee were in agreement with the current wording, and there was no new evidence that that retains to the population covered by the recommendation.

The committee discussed while the population in this scope is 16 and over, the evidence reviewed only covered adults, aged 18 and over. It agreed it was appropriate to extrapolate current evidence to this younger age group. The committee also suggested that a paediatric specialist should be consulted in the treatment pathway of hypertension in young people (aged 16 and 17) that present with ICH who do not have any of the exclusions listed in recommendation 1.5.7.

1.1.9.4 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. Intravenous labetalol, intravenous glyceryl trinitrate (GTN), intravenous hydralazine and intravenous nicardipine were identified as the treatments mainly used for the first-line treatment for systolic blood pressure lowering in the UK. The committee expressed that whilst most centres in the UK use labetalol IV for the emergency treatment of blood pressure for haemorrhagic strokes there is some variation between centres for when labetalol is contraindicated. Some centres use GTN IV as the next option and the GTN patches may be used when transitioning patients from IV to oral medications when the blood pressure is within the target range. Whilst other centres use hydralazine IV as the second choice of treatment and nicardipine is only rarely used.

In the absence of relevant economic evaluations, the committee provided the unit costs of systolic blood pressure lowering agents. Labetalol 100mg/20ml solution for injection ampoules currently have a unit cost of £606.96 for a two-day course. GTN 50mg/10ml solution for infusion vials currently have a unit cost of £149.53 for a two-day course. Hydralazine hydrochloride 20mg powder for injection ampoules have a unit cost of £14.83, however the estimated dose per person is unable to be estimated due to the substantial variation between patients. Nicardipine 10mg/10ml solution of injection ampoules have an estimated unit cost of £252.00 for a two-day course. The committee discussed that intravenous administration was the

preferred method of administering drugs because this allows a greater level of control on titration, given there is often large variability on the dosage needed between patients. The duration of treatment using IV medications will vary greatly based on how well blood pressure is being controlled. Many patients have difficulty swallowing oral tablets, however these may still be used if a patient has a nasogastric (NG) tube, for this reason oral treatments have still been included within the list of treatments. Treatment is usually transitioned to alternative oral medications as soon the blood pressure is controlled. Whilst the committee discussed the unit costs of the treatments used, these did not inform the decision making because this guidance is not covering which treatments should be used and these costs were presented for reference only in the absence of any cost effectiveness evidence.

Upon considering the evidence, there was no statistically significant difference between the 120-130 mg Hg threshold and the 130-140 mg Hg threshold for both mRS scores 0-2 and safety. The committee discussed that it is possible an increased dosage of medication may be used to achieve a larger decrease in blood pressure which would come about as a result of relaxing the lower bound of the threshold for those patients in which a lower blood pressure is achievable and appropriate. The committee highlighted it is possible relaxing the lower bound may increase the likelihood that medication will need to be administered by infusion. The resource impact is expected to be limited because medication is usually administered intravenously at the current blood pressure threshold and any change in medication dosage is expected to be small given the upper bound of the threshold has remained the same.

Cardiorenal harms would be reduced by avoiding a drop in the systolic blood pressure of more than 60mmHg. The committee discussed that whilst it is possible additional planning and close monitoring of the patient will be needed in the first hour of treatment, this may not necessarily translate into a change in the protocols of managing blood pressure, given intensive management protocols are already in place for the first hour of treatment. The committee agreed there would not be an increase in medication dosage or inpatient stay because of this limit in the magnitude of the drop in blood pressure. The committee discussed this would be likely to lead to cost savings because of the reduced harms.

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 the consistency of the evidence between the 120-130mg Hg threshold and the 130-140mg Hg threshold for both mRS 0-2 at 90 days and safety outcomes following rapid systolic blood pressure reduction. The committee was confident in recommending that restricting the drop in systolic blood pressure to 60mg Hg would reduce the harms and subsequently the associated costs.

1,1,10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.4 – 1.5.8 and research recommendations 1 and 2 in the NG128 guideline.

1.1.11 References – included studies

1.1.11.1 Effectiveness

Anderson CS, Heeley E, Huang Y et al. (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. The New England journal of medicine 368(25): 2355-2365

Anderson CS, Huang Y, Wang JG et al. (2008) Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. The Lancet. Neurology 7(5): 391-399

Butcher KS, Jeerakathil T, Hill M et al. (2013) The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial. Stroke 44(3): 620-626

Koch S, Romano JG, Forteza AM et al. (2008) Rapid blood pressure reduction in acute intracerebral hemorrhage: feasibility and safety. Neurocritical care 8(3): 316-321

Krishnan K, Scutt P, Woodhouse L et al. (2016) Glyceryl Trinitrate for Acute Intracerebral Hemorrhage: Results From the Efficacy of Nitric Oxide in Stroke (ENOS) Trial, a Subgroup Analysis. Stroke 47(1): 44-52

Moullaali, Tom J, Wang, Xia, Martin, Renee H et al. (2019) Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. The Lancet. Neurology 18(9): 857-864

Qureshi AI, Palesch YY, Barsan WG et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. The New England journal of medicine 375(11): 1033-1043

Qureshi, Adnan I, Foster, Lydia D, Lobanova, Iryna et al. (2020) Intensive Blood Pressure Lowering in Patients with Moderate to Severe Grade Acute Cerebral Hemorrhage: Post Hoc Analysis of Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 Trial. Cerebrovascular diseases (Basel, Switzerland) 49(3): 244-252

Qureshi, Adnan I, Huang, Wei, Lobanova, Iryna et al. (2020) Outcomes of Intensive Systolic Blood Pressure Reduction in Patients With Intracerebral Hemorrhage and Excessively High Initial Systolic Blood Pressure: Post Hoc Analysis of a Randomized Clinical Trial. JAMA neurology 77(11): 1355-1365

Toyoda, Kazunori, Koga, Masatoshi, Sato, Shoichiro et al. (2019) Clinical Outcomes Depending on Acute Blood Pressure After Cerebral Hemorrhage. Annals of Neurology 85(1): 105-113

Zheng J, Li H, Lin S et al. (2017) Perioperative Antihypertensive Treatment in Patients With Spontaneous Intracerebral Hemorrhage. Stroke 48(1): 216-218

1.1.11.2 Economic

National Institute for Health and care Excellence. British National Formulatory. Published 2021. Accessed October 25, 2021. https://bnf.nice.org.uk/

Appendices

Appendix A – Review protocols

Review protocol for What is the safety and efficacy of intensive interventions to lower blood pressure versus less intensive interventions in people with acute intracerebral haemorrhage?

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Intensive interventions to lower blood pressure in people with intracerebral haemorrhage.
2.	Review question	What is the safety and efficacy of intensive interventions to lower blood pressure versus less intensive interventions in people with acute intracerebral haemorrhage?
3.	Objective	• To identify if there is a benefit to intensive lowering blood pressure in intracerebral haemorrhage • To identify the limits within which blood pressure should be lowered in people with acute intracerebral haemorrhage.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR)

		• Embase • MEDLINE Searches will be restricted by: • 2018 onwards • English language Other searches: • Inclusion lists of systematic reviews The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Stroke, Blood pressure, intracerebral haemorrhage.
6.	Population	Inclusion: People aged over 16 with acute intracerebral haemorrhage and high systolic blood pressure between 150 and 220 mmHg and over 220 mmHg at the time of assessment Exclusion: Children under the age of 16

7.	Intervention/Exposure/Test	Intensive blood pressure reduction within 24 hours of admission: • Calcium channel blocker • Intravenous or transdermal glyceryl trinitrate (GTN) • Angiotensin II antagonist • Beta-blockers All drug classes to be pooled (IV and oral if the data allows) for analysis
8.	Comparator/Reference standard/Confounding factors	Less intensive blood pressure lowering treatment • Calcium channel blocker • Intravenous or transdermal glyceryl trinitrate (GTN) • Angiotensin II antagonist • Beta-blockers All drug classes (IV and oral if the data allows) to be pooled for analysis
9.	Types of study to be included	• Randomised controlled trials • Systematic reviews and meta-analyses of the above
10.	Other exclusion criteria	• All other study designs

11.	Context	People with intracerebral haemorrhage have a mortality of around 40% with 60-70% of those who survive having moderate or severe disability Currently NICE an intensive blood pressure reduction protocol with a systolic blood pressure target of 130 to 140 mmHg for people with intracerebral haemorrhage that present within 6 hours of symptom onset and have a systolic blood pressure between 150 and 220 mmHg. If intensive lowering blood pressure is safe and effective, this may provide the opportunity improve the outcome in this type of stroke. The 2019 NICE guideline – NG128, provides blood pressure lowering thresholds of 130 to 140 mmHg for people with acute intracerebral haemorrhage (based on benefits seen with this target in INTERACT2), however new evidence from a pooled analysis of individual patient-level data from INTERACT2 and ATACH-2 showed that these thresholds may be harmful, and that a very large reduction (>60 mmHg) in blood pressure within the first hour may be harmful, hence the need for this review update.
12.	Primary outcomes (critical outcomes)	• Mortality at 24 hours and 90 days • Functional status as measures by the modified Rankin Scale mRS score at 90 days and 1 year
13.	Secondary outcomes (important outcomes)	• Symptomatic cerebral ischemia at 24 hours • Haemorrhage expansion at 24 hours

		• Neurological deterioration at 24 hours • Adverse events (renal failure, cord infarction, symptomatic hypotension, myocardial infarction) up to 90 days • Quality of life (both health- and social-related quality) up to 90 days • Quality of life up to 6 months/ 12 months • Mortality up to 30 days • Percentage achieving blood pressure target
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. This review will not make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.

		Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. Where data is available sensitivity analyses will be conducted using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random effects. GRADE will be used to assess the quality of each outcome, considering individual study quality and the meta-analysis results. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. Network meta-analysis is not planned for this review. The cost effectiveness of intensive interventions to lower blood pressure in people with acute intracerebral haemorrhage will also be considered.
17.	Analysis of sub-groups	The following groups will be considered for subgroup analysis if heterogeneity is present:

		• People who are frail • Time of treatment/presentation (within 6 hours/ >6 hours) • Location of Haematoma • NIH Stroke Scale
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	November 2021

22.	Anticipated completion date	January 2022		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE Guideline Updates Team **5b Named contact e-mail** strokeandtia@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and NICE Guideline Updates Team		
25.	Review team members	From the NICE Guideline Updates Team • Caroline Mulvihill • Ahmed Yosef • Lindsay Claxton • Kirsty Hounsell • Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the NICE Guideline Updates Team which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10244
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Blood pressure, intracerebral haemorrhage, stroke, transient ischaemic disease

33.	Details of existing review of same topic by same authors	N/ A
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/ A
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Scoping search strategies

Scoping searches

A scoping search was not undertaken for this update.

Main searches

Bibliographic databases searched for the guideline

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- EMBASE (Ovid)
- Epistemonikos
- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence for review question

The search was conducted in November 2021 for 1 review question (RQ).

Where appropriate, in-house study design filters were used to limit the retrieval to, for example, randomised controlled trials. Details of the study design filters used can be found in section 3.

A date limit was applied from June 2018 to November 2021.

The search was limited to the English language. Animal studies were removed from results

Review question search strategy

Search strategy review question

RQ1: What is the safety and efficacy of intensive interventions to lower blood pressure versus less intensive interventions in people with acute intracerebral haemorrhage?

Table 1: search strategy

Medline Strategy, searched 3rd November 2021 **Database: Ovid MEDLINE(R) 1946 to November 02, 2021** **Search Strategy:**	
1	exp Stroke/
2	(stroke or strokes).tw.
3	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).tw.
4	(CVA or poststroke or poststrokes).tw.
5	exp Intracranial Hemorrhages/
6	(brain adj2 (attack* or hemorrhag* or haemorrhag* or bleed* or infarct*)).tw.

Medline Strategy, searched 3rd November 2021 Database: Ovid MEDLINE(R) 1946 to November 02, 2021 Search Strategy:
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*)).tw. 8 exp "Intracranial Embolism and Thrombosis"/ 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* or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).tw. 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* or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).tw. 13 (isch?emi* adj2 attack*).tw. 14 TIA*.tw. 15 or/1-14 16 exp Hypotension/ 17 hypotensi*.tw. 18 ((low* or depress* or decreas* or reduc* or drop* or diminish* or control* or regulat* or down) adj3 (blood pressure* or BP)).tw. 19 or/16-18 20 15 and 19 21 limit 20 to english language 22 Animals/ not Humans/ 23 21 not 22 24 limit 23 to ed=20180601-20211103

Note: *In-house RCT and systematic review filters were appended*.

Study Design Filters

Table 2: Study design filters

The study filters used as part of the literature searches are presented below.
RCT 1 randomized controlled trial.pt. 2 randomi?ed.mp. 3 placebo.mp. 4 or/1-3
Systematic Review 1 MEDLINE or pubmed).tw. 2 systematic review.tw. 3 systematic review.pt. 4 meta-analysis.pt. 5 intervention$.ti. 6 or/1-5

Health economics search strategies

Economic evaluations and quality of life data

Sources searched to identify economic evaluations

- Econlit (Ovid)
- Embase (Ovid)
- HTA (CRD)
- INAHTA
- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- MEDLINE In-Process (Ovid)
- NHS EED (CRD)

Search filters to retrieve economic evaluations and quality of life papers were appended to the search strategy for RQ1. The search was conducted in November 2021.

A date limit was applied from June 2018 to November 2021.

The search was limited to those in the English language. Animal studies were removed from results.

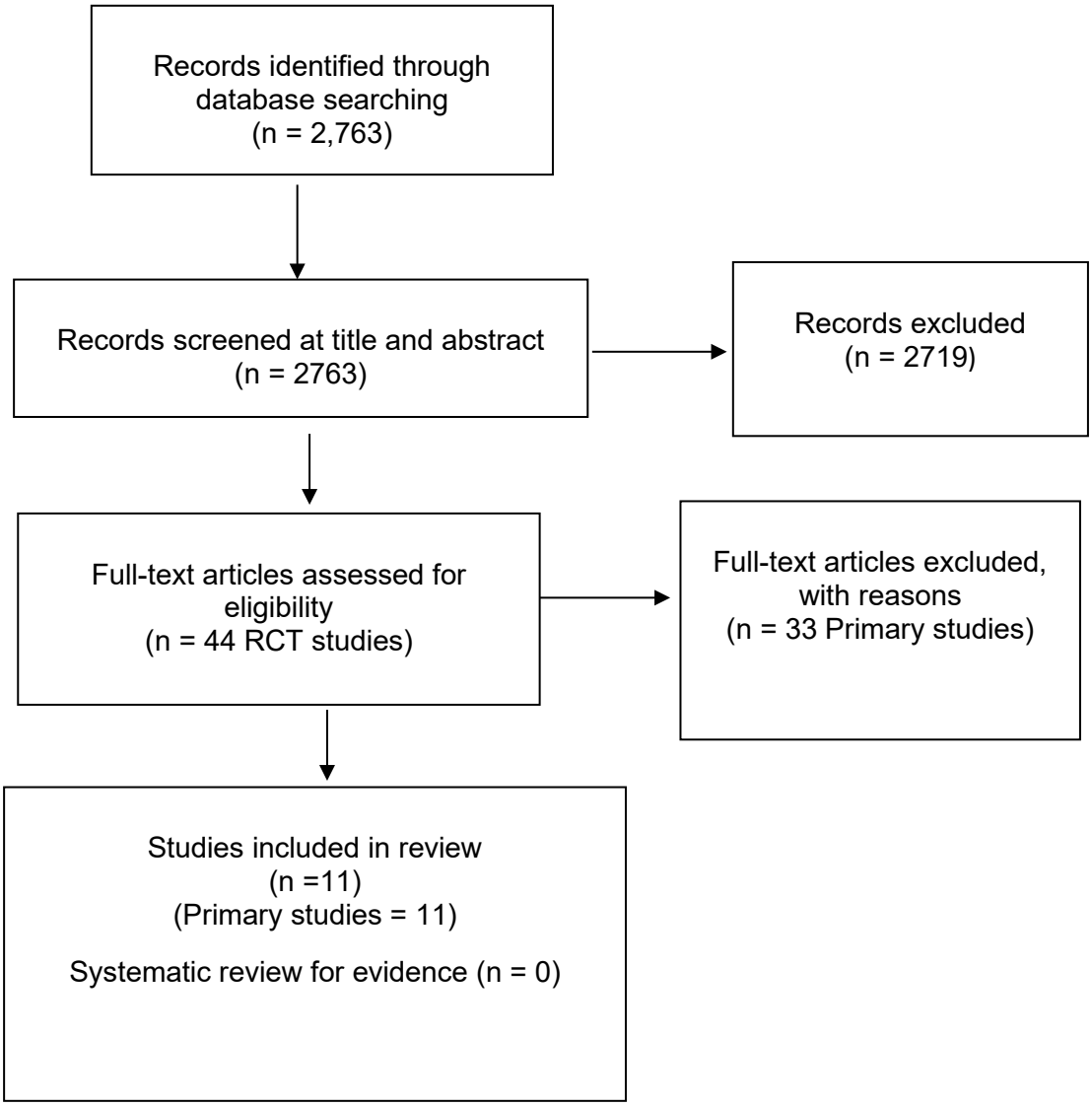
Table 3: Economic evaluation and quality of life filters

Medline Strategy	
Economic evaluations	
1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/
9	exp Models, Economic/
10	Markov Chains/
11	Monte Carlo Method/
12	Decision Trees/
13	econom$.tw.
14	cba.tw.
15	cea.tw.
16	cua.tw.
17	markov$.tw.
18	(monte adj carlo).tw.
19	(decision adj3 (tree$ or analys$)).tw.
20	(cost or costs or costing$ or costly or costed).tw.
21	(price$ or pricing$).tw.
22	budget$.tw.

Medline Strategy
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix C – Effectiveness evidence study selection

Study selection



Appendix D – Effectiveness evidence

Anderson, 2013

Study location	144 hospitals in 21 countries; from Asia, Europe, and other regions of the world.
Study setting	Secondary care, ED
Study dates	From October 2008 through August 2012,
Sources of funding	INTERACT2 is supported by a project grant from the NHMRC of Australia.
Inclusion criteria	People who had a systolic blood pressure between 150- and 220-mm Hg and who did not have a definite indication for or contraindication to blood-pressure–lowering treatment that could be commenced within 6 hours after the onset of spontaneous intracranial haemorrhage; the diagnosis of intracranial haemorrhage was confirmed by means of computed tomography (CT) or magnetic resonance imaging (MRI)
Exclusion criteria	Patients were excluded if there was a structural cerebral cause for the intracerebral haemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale [GCS], if they had a massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned.
Intervention(s)	Intensive BP lowering - patients allocated to the intensive BP lowering group started on a standardised treatment regime commencing with intravenous and then changed when feasible to oral (or via a nasogastric tube) agent(s). The treatment goal was to achieve a systolic BP goal (<140 mmHg) within one hour of commencing the randomised treatment. The second goal was to maintain the systolic BP to 140 mmHg or less or at least 7 days in hospital, and subsequently on discharge and for 90 days post randomisation. Specific treatment protocols are developed for each participating region/centre based on the availability of BP lowering agents for routine use.

Comparator	BP lowering - patients allocated to this group received BP management that is based on American Heart Association (AHA) guidelines. In this group, the threshold to be considered for the initiation of treatment was a systolic BP ≥180 mmHg.
Outcome measures	Mortality at 90 days EQ-5D utility index score at 90 days Neurological decline at 24 hours Recurrent stroke at 90 days Modified Rankin Scale at 90 days Haematoma growth at 90 days;
Number of participants	2839 participants
Duration of follow-up	Participants were followed up in person or by telephone at 28 days and at 90 days by trained local staff who were unaware of the group assignments
Loss to follow-up	Primary outcome was determined for 1382 of the participants (98.5%) in the intensive-treatment group and for 1412 (98.3%) in the standard-treatment group. Intensive group: 5 lost to follow up, 4 withdrew consent, 9 Alive at 90 days but missing data on mRS Standard treatment group 2 Were lost to follow up, 3 Withdrew consent, 12 Alive at 90 days but missing data on mRS
Methods of analysis	Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analyse according to the intention-to-treat principle.

Study arms **Intensive Treatment (N = 1399)**	In participants who were assigned to receive intensive treatment to lower their blood pressure (intensive-treatment group), intravenous treatment and therapy with oral agents were to be initiated according to prespecified treatment protocols that were based on the local availability of agents, with the goal of achieving a systolic blood-pressure level of less than 140 mm Hg within 1 hour after randomization and of maintaining this level for7 days
Standard Treatment (N = 1430)	In participants who were assigned to receive guideline-recommended treatment (standard-treatment group), blood-pressure–lowering treatment was to be administered if their systolic blood pressure was higher than 180 mm Hg; no lower level was stipulated.

Study-level characteristics

Characteristic	**Study (N = 2839)**
% Female Sample size	n = 1059; % = 37.3
Mean age (SD) Mean (SD)	63.5 (empty data)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Patients were randomised via a 24-hour central internet-based randomisation system (or IVRS system, currently in development) to either (a) intensive or (b) conservative management of BP. Treatment is to start as soon as possible after randomisation (e.g., in the emergency department) and will be continued in a monitored facility (i.e., intensive care unit, high dependency unit, or stroke unit) for all randomised patients.)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes (Treatment allocations are stored securely in a separate location for that purpose., two independent statisticians, and two other investigators, who are blind to the treatment allocations and study results.)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (There were no significant differences between the groups in any of the characteristics)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no (For both groups, patients must be on an oral anti-hypertensive agent by day 7 or discharge from acute care hospital, with a long-term target systolic BP of 140 mmHg, as per secondary stroke prevention guidelines.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
intended interventions (effect of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes (The sample size of 2,800 provides at least 90% power (alpha=0.05) to detect a beneficial effect of early treatment on the primary outcome, which equates to one or more cases of death or dependency prevented among every 14 patients treated. This assumes primary outcome event rates of about 50% in the control group and 43% in the active group, a 14% difference in)
Domain 2b: Risk of bias due to deviations from the	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
intended interventions (effect of adhering to intervention)		
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Yes
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No (The clinical assessments were undertaken by a person who was not involved in the initial treatment of the patient and kept blind to the treatment allocation. Data collection and trial management will be

Section	Question	Answer
		facilitated by an established internet-based system. Endpoint assessment blinded to treatment.)
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable (some outcome measurements assessed at different time points to protocol outcomes e.g. Haematoma growth at 90 days; instead of 24hrs)

Anderson, 2008

Study details

Trial registration number and/or trial name	ClinicalTrials.gov, number NCT00226096.
Study location	Australia, China, and South Korea
Study setting	This investigator-initiated, multicentre, open, blinded outcome, randomised trial enrolled patients from 44 hospital sites
Study dates	Between November 2005, and April, 2007
Sources of funding	INTERACT was funded by a grant from the National Health and Medical Research Council of Australia
Inclusion criteria	People 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 h of ICH onset in a suitably monitored environment.
Exclusion criteria	People were excluded for the following reasons: a clear indication for intensive lowering of blood pressure (e.g., systolic blood pressure >220 mm Hg or hypertensive encephalopathy); a clear contraindication to intensive lowering of blood pressure (e.g., severe cerebral artery stenosis or renal failure); clear evidence that the ICH was secondary to a structural cerebral abnormality (e.g., arteriovenous malformation, intracranial aneurysm, or tumour) 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;17 significant pre-stroke disability or medical illness; or early planned decompressive neurosurgical intervention.
Intervention(s)	For patients allocated to the intensive group, the goal was to achieve a systolic blood pressure of 140 mm Hg within 1 h of randomisation and to maintain this target blood pressure for the next 7 days or until discharge from hospital if this occurred earlier
Comparator	For patients allocated to the guideline group, treatment was recommended to achieve a target systolic blood pressure of 180 mmHg.
Outcome measures	Mortality at 90 days EQ-5D utility index score at 90 days Neurological decline at 24 hours Haematoma growth at 24 hours Recurrent stroke at 90 days Modified Rankin Scale at 90 days Renal failure at 90 days
Number of participants	404
Duration of follow-up	Intervention + follow up: 7 days intervention, 90 days follow-up
Loss to follow-up	Intensive Group Number missing: 1 Reason: Loss to follow-up Standard treatment Group Number missing: 1Reason: Loss to follow-up
Methods of analysis	Analysis was by intention to treat.

Study arms **Intensive Treatment** (N = 203)	The intensive group, were treated to achieve a systolic blood pressure of 140 mm Hg within 1 h of randomisation and to maintain this target blood pressure for the next 7 days or until discharge from hospital if this occurred earlier
Standard Treatment (N = 201)	treatment was to achieve a target systolic blood pressure of 180 mmHg.

Study-level characteristics

Characteristic	**Study (N = 404)**
% Female Sample size	n = 142; % = 35
Mean age (SD) Custom value	62.13

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Randomisation was done with minimisation through a password protected, internet-based system, with patients stratified according to country of residence and time from onset of ICH (<3 h vs ≥3 h).)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No (The risk that biases were introduced by the unblinded administration of intervention was kept to a minimum by documentation of use of ancillary post-

Section	Question	Answer
		randomisation treatments, assessment of the haematoma outcomes in a standardised masked way, measurement of clinical outcomes with established objective scales, and adjudication of serious adverse events by a central, blinded committee.)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (Baseline demographic and clinical characteristics and the median time from ICH onset to randomisation (about 3·5 h) were similar in the treatment groups)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no (In all other respects, both groups received the best practice standard of care for acute stroke. An oral treatment plan to lower blood pressure was provided in the study protocol, with continuation of antihypertensive therapy recommended for patients who had been taking such treatment before enrolment. The combination of a diuretic and an angiotensin converting enzyme (ACE) inhibitor was recommended to achieve a systolic blood pressure of

Section	Question	Answer
		140 mm Hg after discharge from hospital for secondary stroke prevention.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Yes
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Butcher, 2013

Study details

Trial registration number and/or trial name	(ClinicalTrials.gov registration number NCT00963976).
Study location	Canada
Study setting	ED/secondary care
Study dates	Between January 28, 2007, and December 6, 2011
Sources of funding	This trial was funded by grant-in-aid support from Alberta Innovates Health Solutions (G513000128) and the Heart and Stroke Foundation of Canada (G220170180). Dr Butcher holds a Canada Research Chair in Cerebrovascular Disease, a Heart and Stroke Foundation of Alberta (HSFA) Professorship in Stroke Medicine and a New Investigator Award from Alberta Innovates Health Solutions (AIHS). Dr Hill holds an HSFA Professorship in Stroke Medicine. Dr Demchuk holds a Chair in Stroke Medicine (HSFA). Dr Coutts holds an AIHS New Investigator award. B. Gould and R. McCourt were supported by AIHS studentships
Inclusion criteria	Eligible patients were ≥18 years of age, with spontaneous ICH diagnosed on non-contrast computed tomography (CT) & 24 hours after onset. SBP was ≥150 mmHg (≥2 readings ≥5 minutes apart).
Exclusion criteria	Patients with evidence of secondary ICH (e.g., vascular malformation), planned surgical resection, or contraindications to CT perfusion (CTP), e.g., contrast allergy or renal impairment) were excluded.

Intervention(s)	Patients with spontaneous ICH <24 hours after onset and systolic BP > 150 mmHg were randomly assigned to an intravenous antihypertensive treatment protocol targeting a systolic BP of <150 mmHg (n=39)
Comparator	Patients with spontaneous ICH <24 hours after onset and systolic BP > 150 mmHg were randomly assigned to an intravenous antihypertensive treatment protocol targeting a systolic BP of<180 mmHg (n=36).
Outcome measures	Mortality at 90 days Modified Rankin Scale at 90 days Haematoma growth at 2 hours. Neurological decline at 2 hours 30-day mortality 90-day Barthel Index
Number of participants	A total of 456 patients were screened and 75 patients were randomized.
Duration of follow-up	intervention + follow up: 24 hours, follow-up 90 days
Loss to follow-up	Intensive treatment Group Number missing: 2, Reason: participants did not have an analysable computed tomography perfusion standard treatment Group Number missing: 0, Reason: Not stated
Methods of analysis	Intergroup comparisons of normally and non-normally distributed variables were assessed with unpaired t tests and Wilcoxon tests, respectively

Study arms **Intensive Treatment** (N = 39)	Patients with spontaneous ICH <24 hours after onset and systolic BP > 150 mmHg were randomly assigned to an intravenous antihypertensive treatment protocol targeting a systolic BP of <150 mmHg
Standard Treatment (N = 36)	Patients with spontaneous ICH <24 hours after onset and systolic BP > 150 mmHg were randomly assigned to an intravenous antihypertensive treatment protocol targeting a systolic BP of<180 mmHg

Study-level characteristics

Characteristic	**Study (N = 75)**
% Female	n = 21; % = 28
Sample size	

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (A block randomization design (6 patients/block), stratified by onset to treatment time (≤6 and 6–24 hours), was used.)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes (groups were assessed by trained personnel blinded to treatment group allocation)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (The treatment groups were balanced with respect to baseline demographics, including a history of hypertension, treatment with antihypertensive, BP, time to enrolment, and hematoma location)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Yes
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No (Functional outcome was assessed with Barthel Index and modified Rankin Scale at 24 hours, day 30, and day 90 by assessors blinded to BP treatment.)
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Some of the outcome measurements were taken after 2 hours rather than at 24 hours: Neurological decline at 2 hours not 24 hours; Haematoma growth at 2 hours not 24hours)

Koch, 2008

Study details

Study location	USA
Study setting	ED, Secondary care
Study dates	Patients were enrolled between January 2004 and December 2006
Sources of funding	not detailed
Inclusion criteria	People 18 years of age or older with radiologically confirmed acute spontaneous supratentorial ICH within 8 h of symptom onset
Exclusion criteria	People with history of head trauma, coma with signs of herniation, coagulopathy defined as platelet count > 50,000 mm3 110 mmHg at presentation, ICH secondary to arteriovenous malformations, trauma, aneurysms or other secondary causes, surgical hematoma evacuation, or inability to give informed consent.
Intervention(s)	An aggressive BP treatment group with a target MAP < 110 mmHg Agent selection was not strictly standardized and occurred according to routine clinical practice. Patients were typically treated initially with intermittent labetalol infusions (10–20 mg). If this failed to achieve target blood pressure a continuous infusion of nicardipine (5–15 mg/h) was started. More severe cases were treated with intravenous nicardipine from the onset according to manufacturers' recommendations, i.e. initial dose, 5 mg/h followed by titration and increases of 2.5 mg/ h every 5–15 min. No bolus was administered. Most severe cases of hypertension were treated with sodium nitroprusside infusion at 0.3 mcg/kg/min IV infusion and titrated every few minutes to desired effect
Comparator	A standard BP treatment group with a target MAP 110–130 mmHg according to American Heart Association (AHA) guidelines for the management of ICH
Outcome measures	Mortality at 90 days

	Haematoma growth at 24 hours Modified Rankin Scale at 90 days Renal failure at 90 days Neurological decline at 48 hours
Number of participants	42
Duration of follow-up	Functional outcomes were determined 90 days after symptom onset by follow-up examination or phone contact employing the modified Rankin scale (mRS). Favourable functional outcome was defined as a 90-day mRS
Loss to follow-up	unable to reach 3 patients (2 in the standard and 1 in the aggressive treatment groups) for the 90-day follow-up.
Methods of analysis	analysed as nominal variables.

Study arms **Intensive Treatment** N = 21)	Aggressive BP lowering (MAP < 110 mmHg) within 8 h of symptom onset.
Standard Treatment (N = 21)	A standard BP treatment group with a target MAP 110–130 mmHg according to American Heart Association (AHA) guidelines for the management of ICH

Study-level characteristics

Characteristic	**Study (N = 42)**
% Female	n = 19

Characteristic	Study (N = 42)
Sample size	
Mean age (SD) Mean (SD)	60.6 (12.3)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Probably yes (states All patients were randomly assigned to one of two BP management groups: but no information of method of randomisation.)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes (Allocation to treatment was concealed by numbered envelopes in random sequence prior to the onset of the study.)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (There were no significant differences between the standard and aggressive BP treatment groups in baseline clinical variables;)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes (All patients underwent standard glycaemic management. There were no significant differences between admission, 24 and 48-h glucose levels between the standard and aggressive BP treatment groups)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Probably yes

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Probably yes
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Yes (Stroke severity was determined blinded to treatment allocation using the NIH stroke scale (NIHSS) and Glasgow coma scale (GCS) on admission. Patient and treating health care personnel were not blinded to treatment allocation. NIHSS and GCS were repeated blinded to treatment at 24 and 48 h to assess clinical evolution)
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Krishnan, 2016

Study details

Trial registration number and/or trial name	The trial was registered (ISRCTN99414122)
Study location	Conducted in Multiple countries;

Study setting	ED, Secondary care
Study dates	Between July 2001 and October 2013
Sources of funding	Efficacy of Nitric Oxide in Stroke (ENOS) was funded by the Bupa UK Foundation and Medical Research Council (G0501797). Other funders, who supported the trial, were the 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).
Inclusion criteria	People who had a systolic blood pressure between 150- and 220-mm Hg and who did not have a definite indication for or contraindication to blood-pressure–lowering treatment that could be commenced within 6 hours after the onset of spontaneous intracranial haemorrhage; the diagnosis of intracranial haemorrhage was confirmed by means of computed tomography (CT) or magnetic resonance imaging (MRI)
Exclusion criteria	Patients were excluded if there was a structural cerebral cause for the intracerebral haemorrhage, if they were in a deep coma (defined as a score of 3 to 5 on the Glasgow Coma Scale [GCS], if they had a massive hematoma with a poor prognosis, or if early surgery to evacuate the hematoma was planned.
Intervention(s)	Intravenous or transdermal glyceryl trinitrate (GTN). 5 mg/day. Duration 7 days.
Comparator	No GTN. Duration 7 days.
Outcome measures	Mortality at 90 days Recurrent stroke at 90 days Modified Rankin Scale at 90 days Myocardial infarction at 90 days Barthel index at 90 days
Number of participants	A total of 629 participants with ICH
Duration of follow-up	Intervention + follow up: 7 days, 90 days
Loss to follow-up	not detailed

Methods of analysis	Statistical analysis was performed by intention-to-treat and followed the trial's statistical analysis plan and analysis approaches used in the primary publication.

Study arms **Intensive Treatment** (N = 310)	***Transdermal GTN*** transdermal GTN (5 mg daily) for 1 week, in patients with acute stroke (randomization within 48 hours of ictus) and high systolic BP (140–220 mmHg).
Standard Treatment (N = 319)	***No Transdermal GTN*** no GTN, given for 1 week, in patients with acute stroke (randomization within 48 hours of ictus) and high systolic BP (140–220 mmHg).

Study-level characteristics

Characteristic	**Study (N = 629)**
% Female Sample size	% = 33
Mean age (SD) Mean (SD)	67 (empty data)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No information
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Yes
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Probably no
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No information
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Moullaali, 2019

Study details

Trial registration number and/or trial name	INTERACT2/ATACH-II
Study location	Multiple countries
Study setting	ED, secondary care
Study dates	INTERACT2 between Oct 7, 2008, and Aug 30, 2012, and ATACH-II recruited between May 1, 2011, and Sept 14, 2015.
Sources of funding	There was no funding source for this study. The corresponding author had full access to all of the data and final responsibility for the decision to submit for publication

Inclusion criteria	Patients aged 19–99 years with spontaneous(non-traumatic) intracerebral haemorrhage and elevated systolic blood pressure (defined as 150–220 mm Hg in INTERACT2 and ≥180 mm Hg in ATACH-II), without a clear indication or contraindication to treatment.
Exclusion criteria	patients without any systolic blood pressure data and seven with too few data before early death, and we imputed missing systolic blood pressure data (due to early death or another reason) in 23 (1%)
Intervention(s)	INTERACT2 Intervention group: Lowering mean SBP to a target of <140 mmHg within 1 h of randomization Treat with any IV or oral agents available to the treating physician. Mean SBP maintained at target level from 1 h to 7 days. IV treatment was stopped if SBP <130 mmHg at any time point ATACH-II Intervention group: Lowering minimum SBP to a target of 110–139 mmHg within 2 h of randomization. Treat with IV nicardipine only but allow IV rescue medications. Minimum hourly SBP maintained at target level from 2 to 24 h
Comparator	INTERACT2 Control group: Lowering and maintaining mean SBP according to standard guidelines (<180 mmHg), at the discretion of the responsible physician. Stop IV treatment if SBP <130 mmHg at any time point ATACH-II Control group: Lowering minimum SBP to 140–179 mmHg within 2 h of randomization Treat with IV nicardipine only but allow IV rescue meds. Minimum hourly SBP maintained at the target level for 2 to 24 h
Outcome measures	Modified Rankin Scale at 90 days Renal serious adverse events at 90 days Cardiac serious adverse events at 90 days Adverse symptomatic hypotension at 90 days
Number of participants	3829 patients with acute intracerebral haemorrhage were randomly assigned in ATACH-II and INTERACT2,
Duration of follow-up	Patients were followed up to 90 days post-randomisation by trained staff masked to treatment allocation.
Loss to follow-up	Multiple imputation within each trial will be used to impute missing primary outcome data, using PROC

Methods of analysis	Analyses were done in a modified intention-to-treat population, comprising patients with sufficient data on systolic blood pressure.
Additional comments	Key differences in eligibility criteria for INTERACT2 and ATACH-I INTERACT2 Time to treatment <6 h Baseline SBP 150–220 mmHg Excluded those with prior ischemic stroke within 30 days; poor prognosis (likely death < 24 h); known dementia; or concomitant illness that would interfere with follow-up and outcome assessments ATACH-I Time to treatment <4.5 h Baseline SBP 180–240 mmHg Excluded those with IVH where blood completely fills one lateral ventricle or more than half of both ventricles; history of bleeding disorder (including platelet count < 50,000/mm) or recent warfarin use; or those who were pregnant, lactating, or gave birth within the previous 30 days SBP: systolic blood pressure; IVH: intraventricular haemorrhage. International Journal of Stroke

Study arms ***INTERACT2 (N = 2829)***	Intervention group: Lowering mean SBP to a target of <140 mmHg within 1 h of randomization Treat with any IV or oral agents available to the treating physician. Mean SBP maintained at target level from 1 h to 7 days. Stop IV treatment if SBP <130 mmHg at any time points Control group: Lowering and maintaining mean SBP according to standard guidelines (<180 mmHg), at the discretion of the responsible physician. Stop IV treatment if SBP <130 mmHg at any time point
ATACH-II (N = 1000)	Intervention group: Lowering minimum SBP to a target of 110–139 mmHg within 2 h of randomization. Treat with IV nicardipine only but allow IV rescue medications. Minimum hourly SBP maintained at target level from 2 to 24 h Control group: Lowering minimum SBP to 140–179 mmHg within 2 h of randomization Treat with IV nicardipine only but allow IV rescue meds. Minimum hourly SBP maintained at the target level for 2 to 24 h
COMBINED (N = 3829)	A pooled analysis of individual patient-level data acquired from the main phase of (INTERACT2) and (ATACH-II) trial.3829 patients were randomly assigned in INTERACT2 and ATACH-II, with a median neurological impairment defined by scores on the National Institutes of Health Stroke Scale of 11 (IQR 6–16) and median time from the onset of symptoms of intracerebral haemorrhage to randomisation of 3·6

Study-level characteristics

Characteristic	**Study (N = 3829)**
% Female	n = 1429; % = 37

Characteristic	Study (N = 3829)
Sample size	
Mean age (SD) Mean (SD)	63.1 (12.9)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No information
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Qureshi, 2016

Study details

Study location	Studies conducted the trial at 110 sites in the United States, Japan, China, Taiwan, South Korea, and Germany.
Study setting	ED, secondary care
Study dates	The trial enrolled the first patient in May 2011 and the last in September 2015.
Sources of 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
Inclusion criteria	Patients 18 years of age or older with a Glasgow Coma Scale (GCS) score of 5 or more (on a scale from 3 to 15, with lower scores indicating a worse condition) at the time of arrival in the emergency department and with a measurement of the intraparenchymal hematoma of less than 60cm3 on initial computed

	tomographic (CT) scan were eligible for inclusion in the trial if antihypertensive treatment could be initiated within 4.5 hours after symptom onset
Exclusion criteria	People with Ischaemic stroke and patients were not eligible if their systolic blood pressure was lowered to less than 140 mm Hg before randomisation during concurrent treatment
Intervention(s)	Intensive-treatment N=500 Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg initiated within 4.5 hours after symptom onset and continued for 24 hours. Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,
Comparator	Standard-treatment N=500 Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg within 24 hours
Outcome measures	Mortality at 90 days EQ-5D utility index score at 90 days Neurological decline at 24 hours Haematoma growth at 24 hours EQ-5D visual analogue scale at 90 days
Number of participants	1000, participants underwent randomisation; 500 patients were assigned to the intensive-treatment group and 500 to the standard-treatment group
Duration of follow-up	Follow-up after discharge included telephone contact at 1 month and in-person clinical evaluation at 3 months
Loss to follow-up	baseline data were missing or were obtained outside the specified time window for 30 patients in the intensive-treatment group and for 41 in the standard-treatment group and the multiple-imputation method was used for the 39 participants with missing

Methods of analysis	Missing data were imputed with the use of the multiple-imputation method that generated and analysed 100 samples (with the use of a computer simulation) of the trial data, each with a variable imputed value for the missing data, and results were subsequently compiled as described in the statistical analyses. A sample size of 1280 participants was calculated after inflation by a factor of 1.23 as derived from the following calculation: 1/(1−R)2 , where R was the proportion of patients with anticipated nonadherence (e.g., treatment failure or loss to follow-up).is plan
Additional comments	

Study arms **Intensive Treatment** N = 500)	Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg initiated within 4.5 hours after symptom onset and continued for 24 hours. Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,
Standard Treatment (N = 500)	Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg within 24 hours

Study-level characteristics

Characteristic	**Study (N = 1000)**
% Female Sample size	n = 380; % = 38
Mean age (SD) Mean (SD)	61.9 (empty data)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Randomization was performed centrally through the trial website with the use of a minimization algorithm combined with the biased coin method to ensure a balance of treatment assignment within and across clinical sites, baseline GCS score, age (divided into seven strata), and presence or absence of intraventricular haemorrhage at baseline)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No (No effort was made to conceal the treatment assignment from the participants or treating physicians)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (There were no significant differences between the two groups at baseline.)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
of assignment to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	No information

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No (Intensive Treatment Group Number missing: 19; Standard Treatment Group Number missing: 20)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Yes
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Yes
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected,	No/Probably no

Section	Question	Answer
	on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Qureshi, 2020

Study details

Secondary publication of another included study- see primary study for details	The ATACH-2 trial was a randomized, multicentre, 2-group, open-label trial to determine the relative efficacy of intensive versus standard antihypertensive treatment that was initiated within 4.5 h after symptom onset and continued for the next 24 h in patients with spontaneous supratentorial ICH.
Study location	A total of 110 sites in the USA, Japan, China, Taiwan, South Korea, and Germany.
Study setting	Secondary Care/Emergency department

Study dates	May 2011 till September 2015
Sources of funding	This study was funded by the National Institute of Neurological Disorders and Stroke and the National Cerebral and Cardiovascular Center; ATACH-2 ClinicalTrials.gov number: NCT01176565.
Inclusion criteria	Patients aged ≥18 years with a GCS score of 5 or more and with a measurement of the intraparenchymal hematoma of <60 mL on initial computed tomographic (CT) scan were eligible for inclusion.
Exclusion criteria	Patients with intraventricular haemorrhage (IVH) associated with intraparenchymal haemorrhage and blood completely filling one lateral ventricle or more than half of both ventricles on initial CT scan were excluded
Intervention(s)	The treatment was to reduce and maintain the hourly minimum SBP in the range of 110–139 mm Hg in the intensive SBP reduction group throughout the period of 24 h after randomization. Patients with moderate to severe grade ICH were identified based on previously published criteria baseline GCS score <13 or NIHSS score ≥10; baseline intraparenchymal haemorrhage volume ≥30 mL; or presence of IVH.
Comparator	The treatment was to reduce and maintain the hourly minimum SBP in the range of 140–179 mm Hg in the standard SBP reduction group throughout the period of 24 h after randomization. Patients who did not meet any of those criteria were classified as mild grade.
Outcome measures	EQ-5D utility index score at 90 days EQ-5D visual analogue scale at 90 days Modified Rankin Scale at 90 days
Number of participants	(n = 961),
Duration of follow-up	90 Days
Methods of analysis	used the χ2 test, Fisher’s exact test, and ANOVA for categorical and the Wilcoxon 2-sample test for continuous variables. Analyses inclusive of missing data imputed by the multiple-imputation method

Study arms ***Mild Grade ICH Patients (N = 318)***	Patients with moderate to severe grade ICH were identified based on previously published criteria baseline GCS score <13 or NIHSS score ≥10; baseline intraparenchymal haemorrhage volume ≥30 mL; or presence of IVH. Among subjects with moderate to severe grade ICH 336 were assigned to intensive SBP reduction and 346 to standard SBP reduction.
Moderate to Severe Grade ICH Patients (N = 682)	Patients who did not meet any of the moderate to severe grade criteria were classified as mild grade. Among subjects with mild grade ICH. 164 were assigned to intensive treatment and 154 to standard treatment.

Study-level characteristics

Characteristic	**Study (N = 961)**
% Female Sample size	n = 341

Qureshi, 2020

Study details

Study location	Multicentre
Study setting	Secondary care. Emergency department
Study dates	Analysis was performed in November 2019 on data from the multicentre randomized clinical trial, which was conducted between May 2011 to September 2015.

Sources of funding	The study is supported by the National Institute of Neurological Disorders and Stroke (grants U01-NS062091 [Dr Qureshi] and U01-NS056975 [Dr Barsan]) and the Intramural Research Fund for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center (grant H23-4-3 [Dr Toyoda]).
Inclusion criteria	Patients with intracerebral haemorrhage and initial systolic blood pressure of 180 mm Hg or more, randomized within 4.5 hours after symptom onset, were included.
Intervention(s)	
Comparator	
Outcome measures	Neurological decline at 24 hours Haematoma growth at 24 hours Modified Rankin Scale at 90 days Renal failure at 90 days Any serious adverse event at 90 days
Number of participants	228
Duration of follow-up	Neurological deterioration and hematoma expansion within 24 hours and death or severe disability at 90 days, plus kidney adverse events and serious adverse events until day 7 or hospital discharge.
Loss to follow-up	Data were missing for1 patient in the standard treatment group.
Methods of analysis	A post hoc analysis of the Antihypertensive Treatment of Acute Cerebral Haemorrhage-II trials

Study arms ***Intensive SBP reduction (N = 110)***	intensive (goal, 110-139 mm Hg) systolic blood pressure reduction in patients with intracerebral haemorrhage and initial systolic blood pressure of 220 mm Hg or more
Standard SBP reduction (N = 118)	Standard (goal, 140-179 mm Hg) systolic blood pressure reduction in patients with intracerebral haemorrhage and initial systolic blood pressure of 220 mm Hg or more

Study-level characteristics

Characteristic	**Study (N = 220)**
% Female Sample size	n = 83; % = 39.1
Mean age (SD) Mean (SD)	59 (13.2)

Toyoda, 2019

Study details

Secondary publication of another included study- see primary study for details	An exploratory as-treated analysis of the ATACH-2

Other publications associated with this study included in review	ATACH-2
Trial registration number and/or trial name	ClinicalTrials.gov: NCT01176565;
Study type	Randomised controlled trial (RCT)
Study location	The ATACH-2 was an international, randomized, 2-group, open-label trial
Study setting	Secondary Care
Study dates	The trial enrolled the first patient in May 2011 and the last in September 2015.
Sources of funding	Supported by grants (U01-NS062091 to Qureshi; U01-NS061861 and U01-NS059041 to Palesch) from the National Institute of Neurological Disorders and Stroke and by a grant (H28-4-1 to Toyoda) from the Intramural Research Fund for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.
Inclusion criteria	Patients 18 years of age or older with a Glasgow Coma Scale (GCS) score of 5 or more (on a scale from 3 to 15, with lower scores indicating a worse condition) at the time of arrival in the emergency department and with a measurement of the intraparenchymal hematoma of less than 60cm3 on initial computed tomographic (CT) scan were eligible for inclusion in the trial if antihypertensive treatment could be initiated within 4.5 hours after symptom onset
Exclusion criteria	People with Ischaemic stroke and patients were not eligible if their systolic blood pressure was lowered to less than 140 mm Hg before randomisation during concurrent treatment
Intervention(s)	Intensive-treatment N=498 Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg initiated within 4.5 hours after symptom onset and continued for 24 hours. Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,
Comparator	Standard-treatment N=497

	Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg within 24 hours Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,
Outcome measures	Mortality at 90 days Modified Rankin Scale at 90 days Haematoma growth at 90 days. Cardiorenal Adverse Event at 90 days
Number of participants	995
Duration of follow-up	90 days
Loss to follow-up	A total of 1,000 patients were randomized in the ATACH-2. Of these, 5 were excluded from the present analyses because of a lack of available data on their SBPs between 2 and 24 hours
Methods of analysis	Associations between primary and secondary outcomes were estimated using the Wald's chi-square test. The PROC GENMOD procedure of the latest version of SAS software and JMP (version 12.0.1) software (SAS Institute Inc., Cary, NC) were used to obtain test statistics and results. Values of $p < 0.05$ were considered statistically significant
Additional comments	Subjects were divided into 5 groups in 10-mmHg strata of their average hourly minimum SBP, regardless of the randomized treatment. Subjects were also divided into 5 groups based on the average hourly mean SBP between 2 and 24 hours. Concrete SBP levels for grouping were determined to divide subjects as evenly as possible. As additional analyses, subjects were divided into 5 groups in 18-mmHg strata of the absolute reduction of average hourly minimum SBP from the initial SBP at emergent visit, and also divided into 5 groups in 6% strata of their relative reduction of average hourly minimum SBP from the initial SBP at emergent visit.

Study arms Intensive SBP reduction (N = 498)	Intensive-treatment N=498 Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg initiated within 4.5 hours after symptom onset and continued for 24 hours. Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg,
Standard SBP reduction (N = 497)	Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg within 24 hours Concurrent medication/care: Standard therapy. Before randomization, intravenous antihypertensive medication, including nicardipine, was administered to lower the systolic blood pressure to less than 180 mmHg

Study-level characteristics

Characteristic	**Study (N = 995)**
% Female Sample size	n = 379
Mean age (SD) Mean (SD)	62 (13)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Zheng, 2017

Study details

Trial registration number and/or trial name	This study is registered with www.chictr.org (ChiCTR-TRC-13004304).
Study location	Conducted in China;
Study setting	ED, Secondary care
Study dates	period between September 2013 to September 2014
Sources of funding	This study was supported by The National Key Technology R&D Program for the 12th Five-year Plan of P.R. China (no. 2011BAI08B05).
Inclusion criteria	Eligible patients were aged ≥ 18 years, had computed tomography- or magnetic resonance imaging–confirmed sICH with elevated systolic BP (SBP) between 150 and 220 mmHg (at least 2 measurements) and were able to receive surgery within 24 hours after ictus.
Exclusion criteria	Patients were excluded for having a definite indication or contraindications to antihypertensive, second intracerebral haemorrhage, 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
Intervention(s)	In the intensive group, the target SBP at the end of the first hour after randomization was between 140 and 160 mmHg and that at the time of surgery was between 120 and 140 mmHg using intravenous drugs. After the operation, the antihypertensive treatment began when the SBP became elevated to >140 mmHg. The target postoperative SBP was between 120 and 140 mmHg. The target SBP was maintained for 7 days after randomization or until hospital discharge within 7 days. The oral antihypertensive drugs were administered as soon as possible.
Comparator	In the conservative group, the target perioperative SBP was between 140 and 180 mmHg
Outcome measures	Mortality at 90 days

	EQ-5D utility index score at 90 days Modified Rankin Scale at 90 days 30-day mortality
Number of participants	201
Duration of follow-up	Patients were followed up at 7 days, 30 days and 90 days. The primary outcome of this study was the incidence of re-haemorrhage within 7 days after randomization Secondary outcomes included neurological function at 90 days; 7-, 30-, and 90-day mortality; health-related quality of life at 90 days; and incidence of complications
Loss to follow-up	Intensive Treatment Group Number missing: 5, Reason: 4 patients lost to follow up Standard Treatment Group Number missing: 2, Reason: lost to follow up
Methods of analysis	The “intension to treat” analysis was applied in this study. Categorical data of the primary and secondary outcomes were analyzed by chi-square test. The continuous outcomes were expressed as mean and standard deviation (SD).

Study arms Intensive SBP reduction (N = 100)	In the intensive group, the target SBP at the end of the first hour after randomization was between 140 and 160 mmHg and that at the time of surgery was between 120 and 140 mmHg using intravenous drugs. After the operation, the antihypertensive treatment began when the SBP became elevated to >140 mmHg. The target postoperative SBP was between 120 and 140 mmHg. The target SBP was maintained for 7 days after randomization or until hospital discharge within 7 days. The oral antihypertensive drugs were administered as soon as possible.
Standard SBP reduction (N = 101)	In the conservative group, the target perioperative SBP was between 140 and 180 mmHg

Study-level characteristics

Characteristic	Study (N = 201)
% Female Sample size	n = 57; % = 56.44

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Eligible patients were allocated to an intensive treatment or conservative treatment group randomly by the method of minimization within 1 hour after admission. A special researcher conducted the randomization of patients using the Minimpy program (version 0.3) with stratified factors including age, time since ICH onset, time to surgery, admission Glasgow Coma Scale, and location of hematomas.)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Probably yes (both the patients and doctors could not be blinded in this trial;the assessor was blinded)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes (The baseline characteristics of the patients were well matched)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2b: Risk of bias due to deviations from the	2.2. Were carers and people delivering the interventions aware of	Yes

Section	Question	Answer
intended interventions (effect of adhering to intervention)	participants' assigned intervention during the trial?	
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Yes (The intraoperative SBP was maintained at between 90 and 140 mmHg by anaesthesiologists for both groups. In this study, the operations were conducted by well-trained neurosurgeons, and guideline-recommended medical treatments were performed during hospitalization.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Probably no
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Probably no
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	No
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the	Yes

Section	Question	Answer
	intervention received by study participants?	
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No/Probably no

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

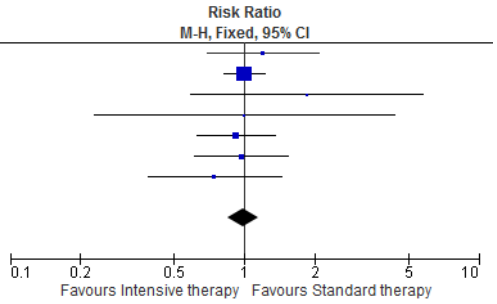
Appendix E – Forest plots

Primary outcomes

Mortality at 90 days.

Study or Subgroup	Intensive BP reduction Events	Total	Standard BP reduction Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anderson 2008	25	200	21	202	7.1%	1.20 [0.70, 2.08]
Anderson,2013	166	1382	170	1412	57.2%	1.00 [0.82, 1.22]
Butcher 2013	7	37	4	39	1.3%	1.84 [0.59, 5.79]
Koch, 2008	3	21	3	21	1.0%	1.00 [0.23, 4.40]
Krishnan 2016	42	310	47	319	15.8%	0.92 [0.63, 1.35]
Qureshi,2016	33	481	34	480	11.6%	0.97 [0.61, 1.54]
Zheng 2017	13	96	18	99	6.0%	0.74 [0.39, 1.43]
Total (95% CI)		**2527**		**2572**	**100.0%**	**0.99 [0.85, 1.16]**
Total events	289		297			

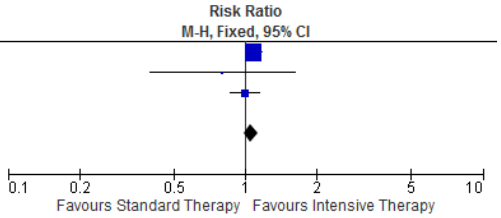
Heterogeneity: Chi² = 2.50, df = 6 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)



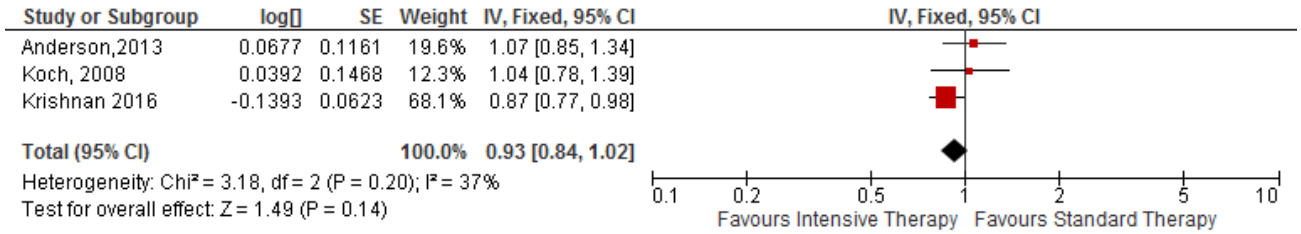
Modified Rankin Scale at 90 days (a score of 0 to 2).

Study or Subgroup	Intensive BP reduction Events	Total	Standard BP reduction Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anderson,2013	663	1399	627	1430	73.7%	1.08 [1.00, 1.17]
Koch, 2008	8	21	10	21	1.2%	0.80 [0.39, 1.62]
Qureshi,2016	211	481	211	480	25.1%	1.00 [0.87, 1.15]
Total (95% CI)		**1901**		**1931**	**100.0%**	**1.06 [0.99, 1.13]**
Total events	882		848			

Heterogeneity: Chi² = 1.52, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)

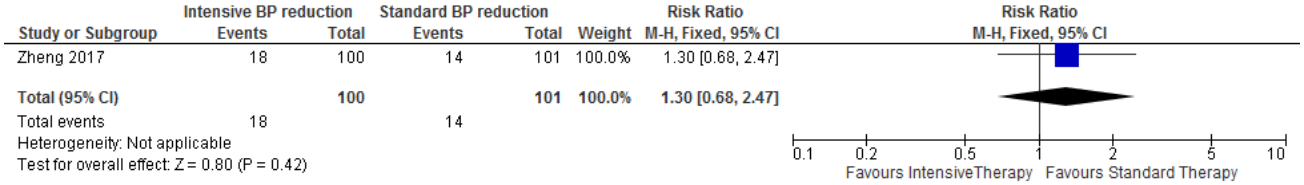


Modified Rankin Scale at 90 days (a score of 4 to 6).

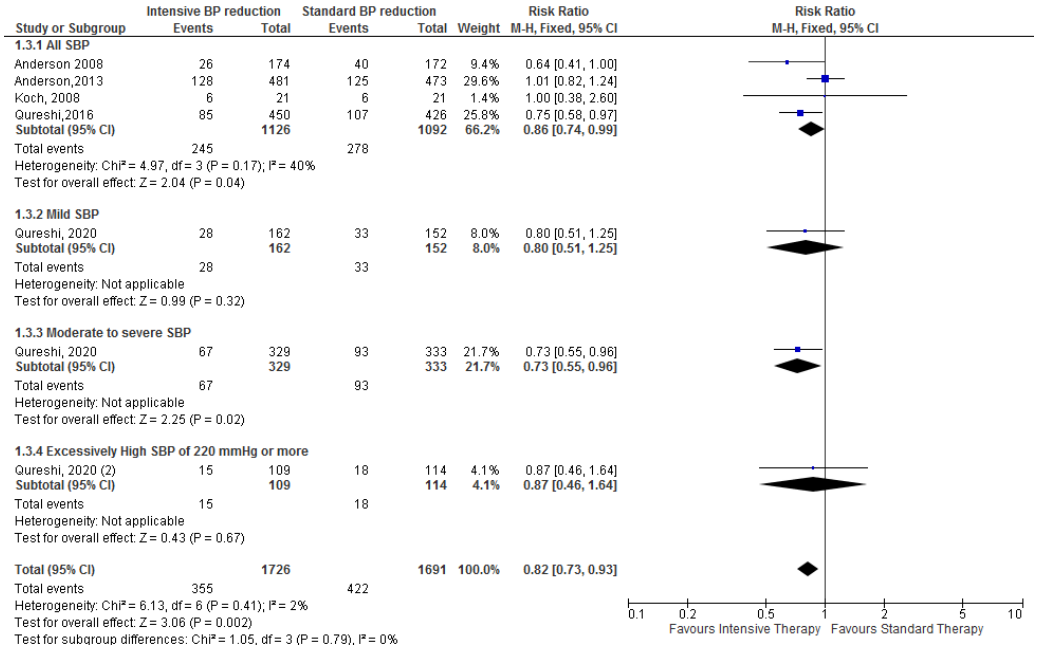


Secondary outcomes

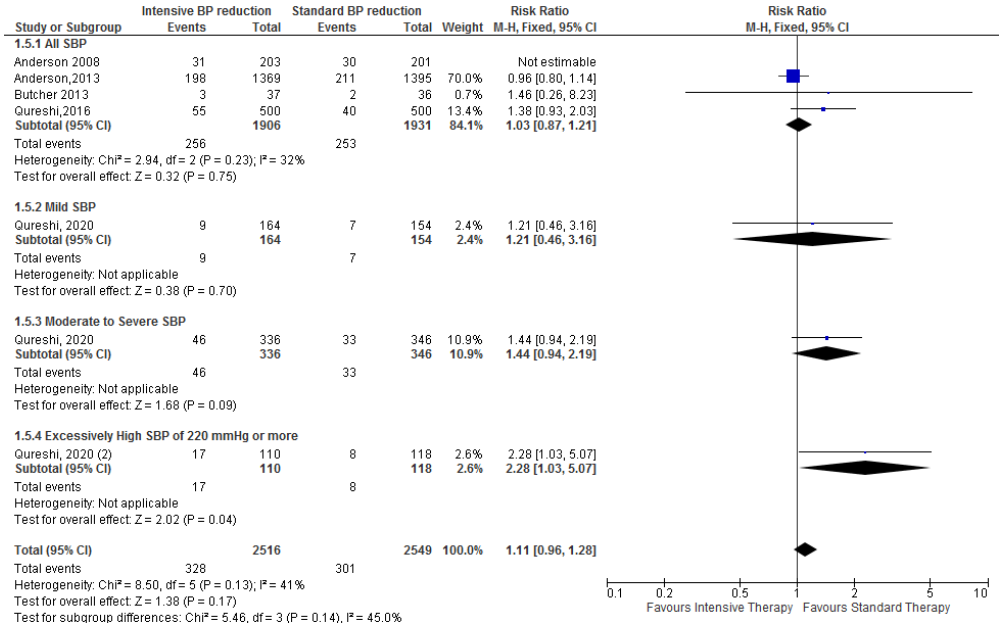
Symptomatic cerebral ischemia at 24 hours



Haemorrhage expansion at 24 hours



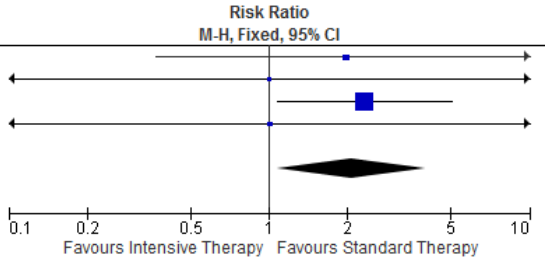
Neurological deterioration at 24 hours



Adverse events (renal failure) up to 90 days

Study or Subgroup	Intensive BP reduction Events	Total	Standard BP reduction Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anderson 2008	4	203	2	201	15.5%	1.98 [0.37, 10.69]
Koch, 2008	1	21	1	21	7.7%	1.00 [0.07, 14.95]
Qureshi,2016	21	500	9	500	69.2%	2.33 [1.08, 5.04]
Zheng 2017	1	100	1	101	7.7%	1.01 [0.06, 15.93]
Total (95% CI)		**824**		**823**	**100.0%**	**2.07 [1.08, 3.99]**
Total events	27		13			

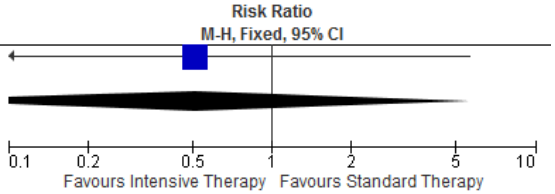
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)



Adverse events (myocardial infarction) up to 90 days

Study or Subgroup	Intensive BP reduction Events	Total	Standard BP reduction Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krishnan 2016	1	310	2	319	100.0%	0.51 [0.05, 5.65]
Total (95% CI)		**310**		**319**	**100.0%**	**0.51 [0.05, 5.65]**
Total events	1		2			

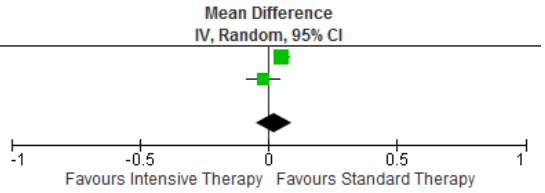
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



Quality of life (health-and social-related quality) up to 90 days

Study or Subgroup	Intensive BP reduction Mean	SD	Total	Standard BP reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anderson,2013	0.6	0.39	1399	0.55	0.4	1430	58.5%	0.05 [0.02, 0.08]
Zheng 2017	0.54	0.23	100	0.56	0.23	101	41.5%	-0.02 [-0.08, 0.04]
Total (95% CI)			**1499**			**1531**	**100.0%**	**0.02 [-0.05, 0.09]**

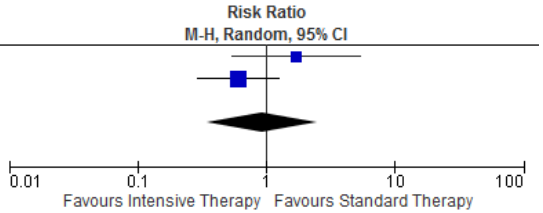
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.61 (P = 0.54)



Mortality up to 30 days

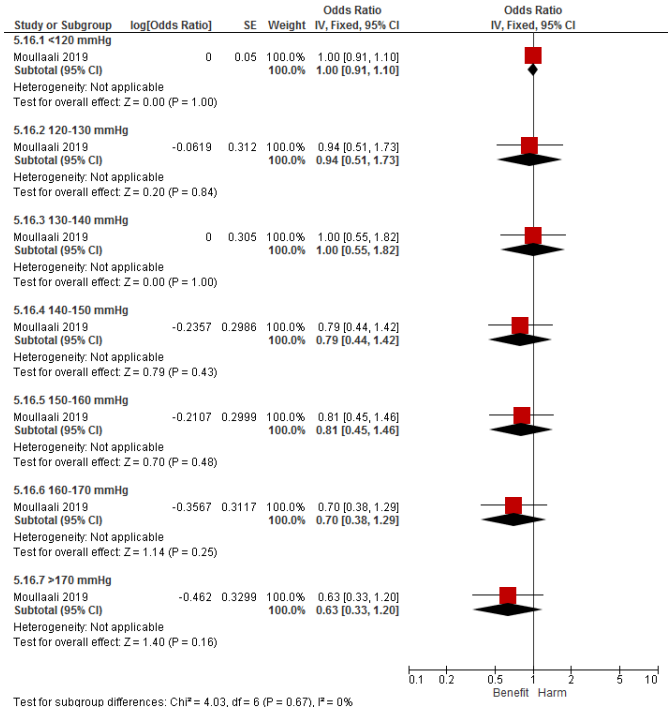
Study or Subgroup	Intensive BP reduction Events	Total	Standard BP reduction Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Butcher 2013	7	37	4	36	40.6%	1.70 [0.54, 5.32]
Zheng 2017	10	96	17	99	59.4%	0.61 [0.29, 1.26]
Total (95% CI)		**133**		**135**	**100.0%**	**0.92 [0.34, 2.49]**
Total events	17		21			

Heterogeneity: Tau² = 0.29; Chi² = 2.24, df = 1 (P = 0.13); I² = 55%
Test for overall effect: Z = 0.16 (P = 0.87)

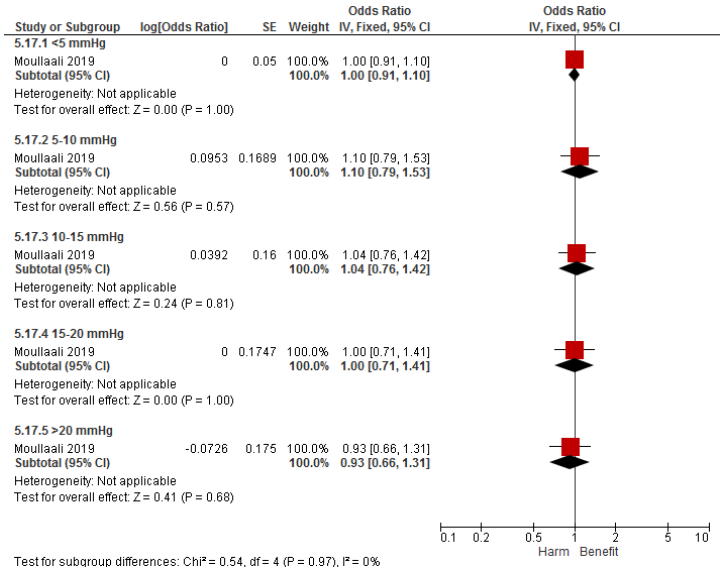


Associations of categorised systolic blood pressure summary measures and with 90-day functional independence (scores 0-2 on the mRS) (Pooled Analysis – Meta analysis not appropriate)

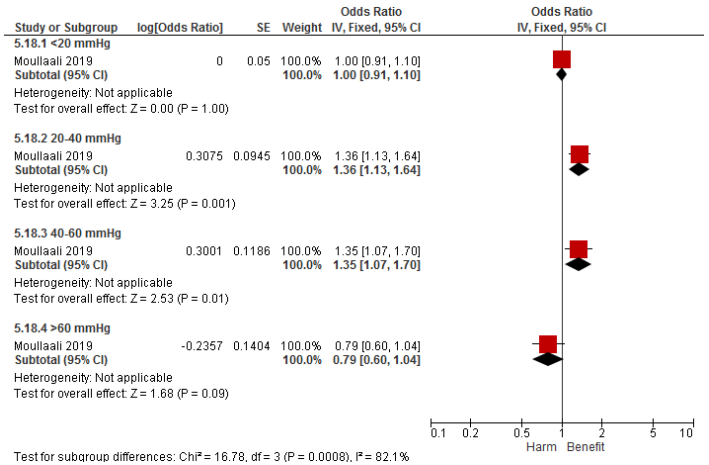
Achieved, mean SBP 1-24 hour



Variability, SD of SBP 1-24 hours

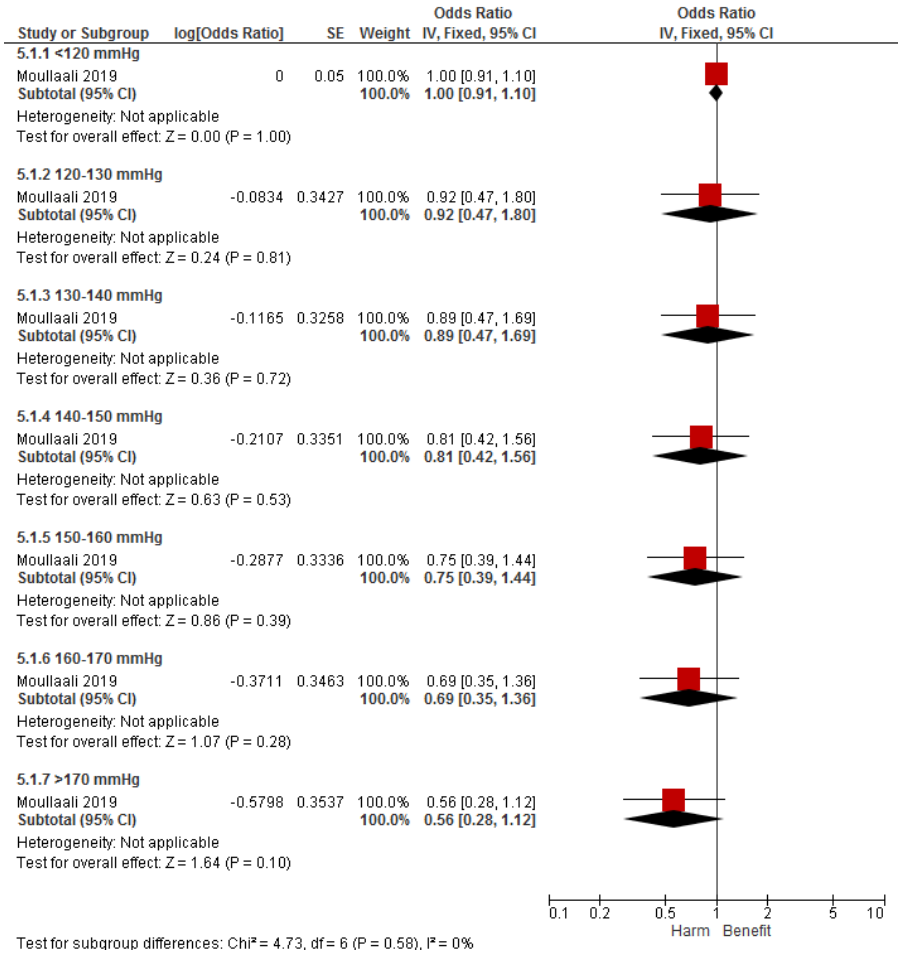


Magnitude, baseline - minimum ≤1 hr post-randomisation

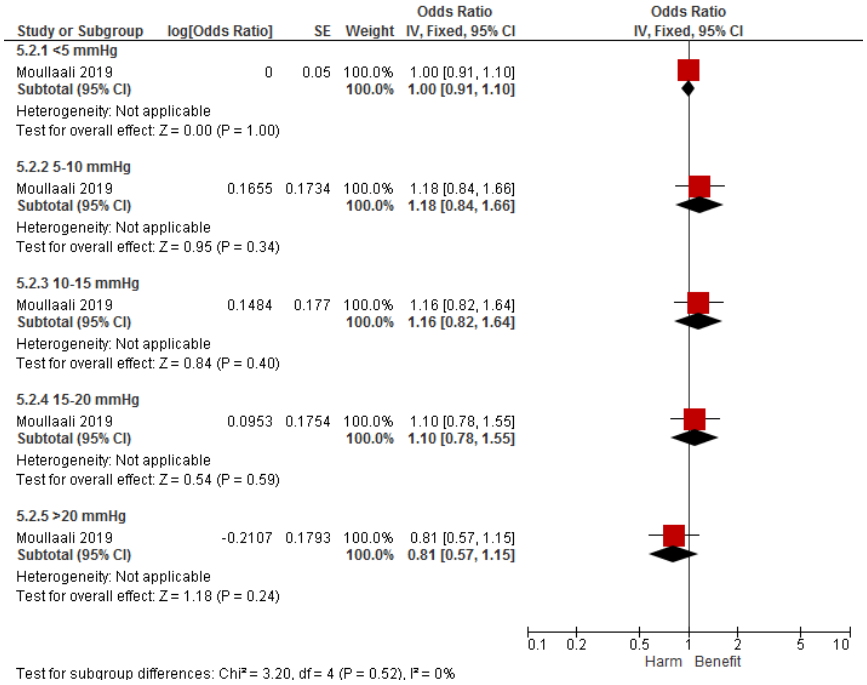


Associations of categorised systolic blood pressure summary measures and with 90-day good outcome (scores 0-3 on the mRS)

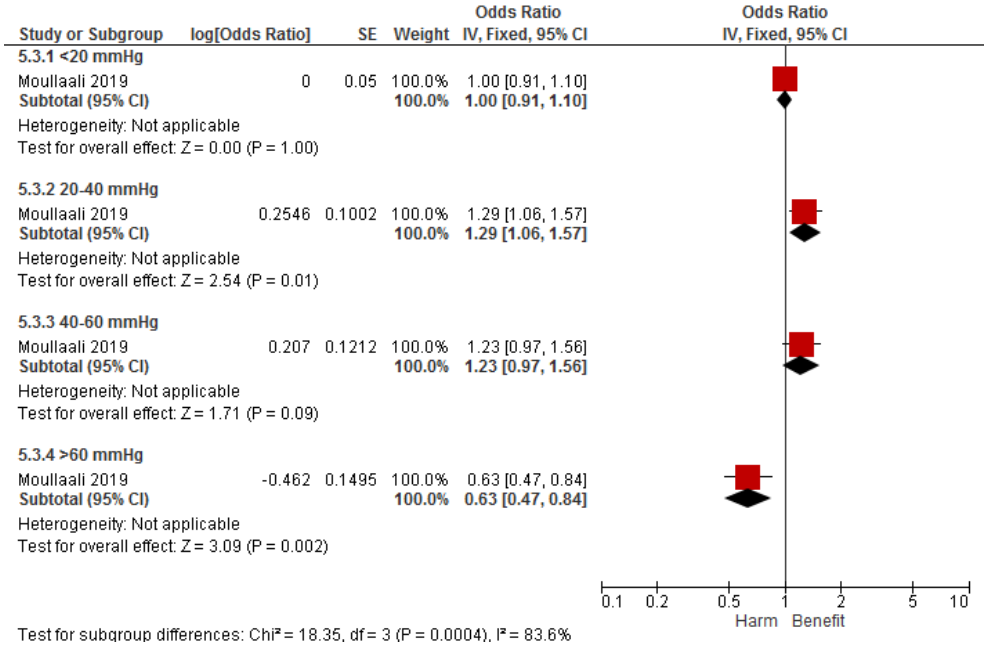
Achieved, mean SBP 1-24 hours



Variability, SD of SBP 1-24 hours

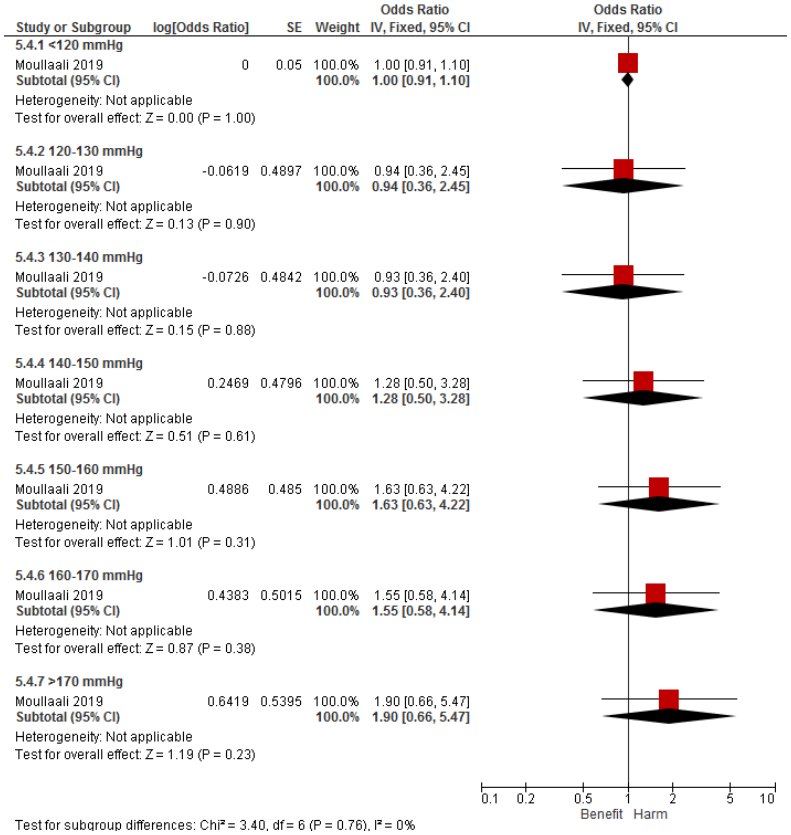


Magnitude, baseline - minimum ≤1 hr post-randomisation

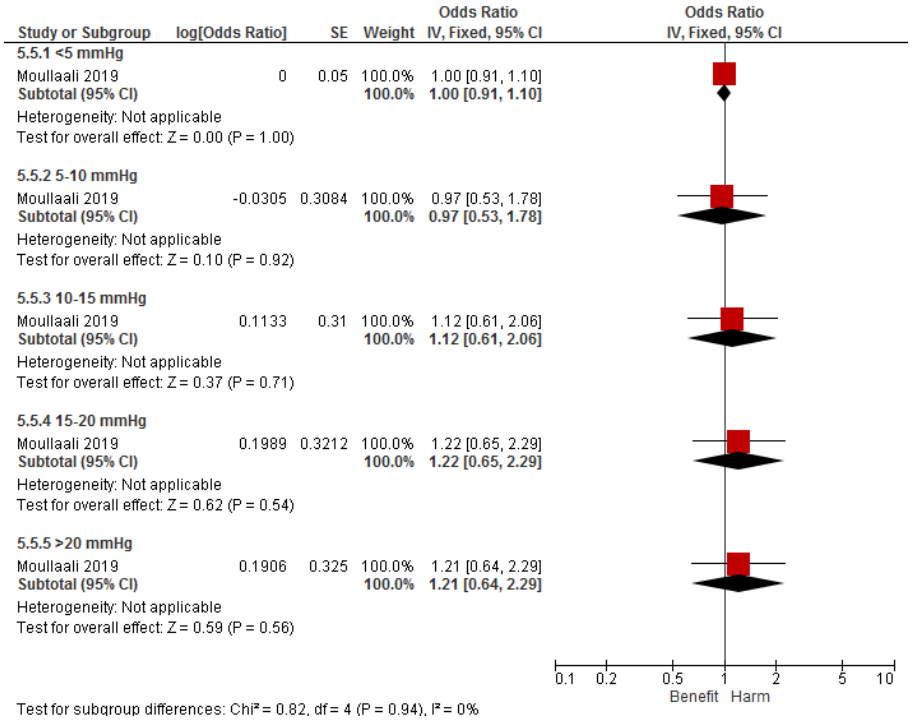


Associations of categorised systolic blood pressure summary measures and haematoma expansion >6mL at 24 hours

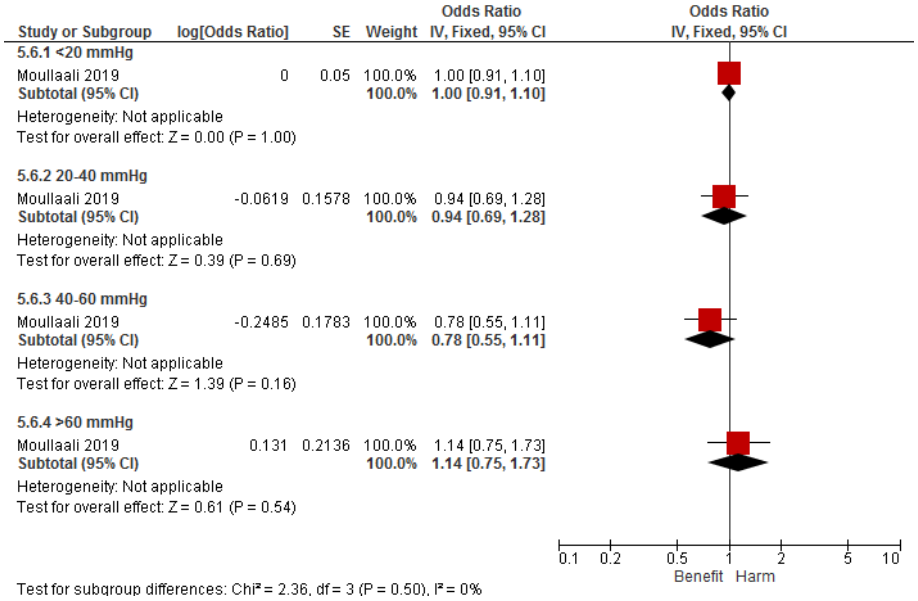
Achieved, mean SBP 1-24 hours



Variability, SD of SBP 1-24 hours

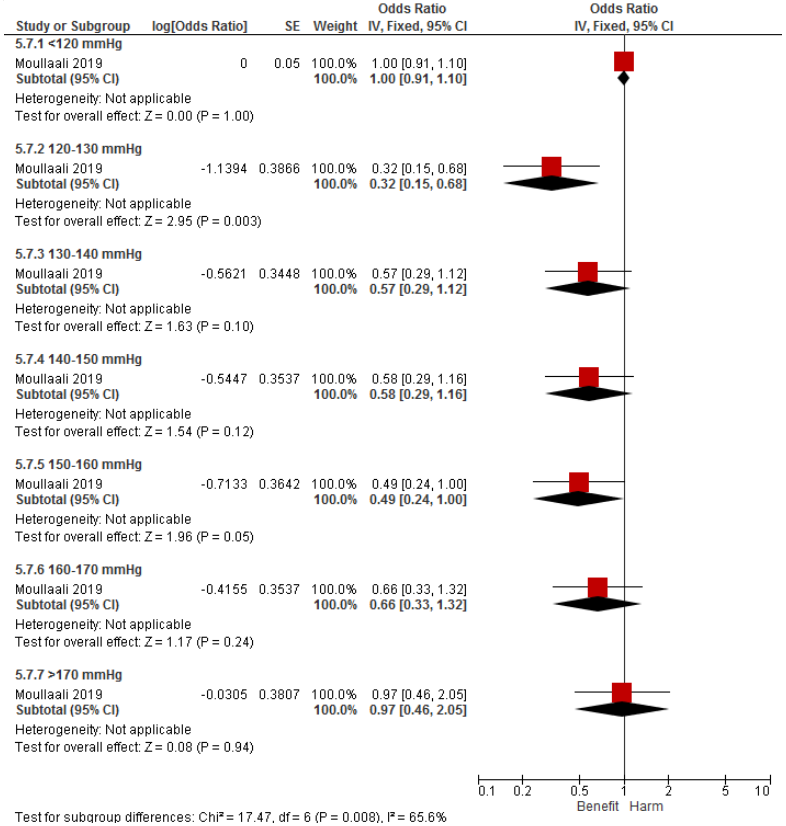


Magnitude, baseline - minimum ≤1 hr post-randomisation

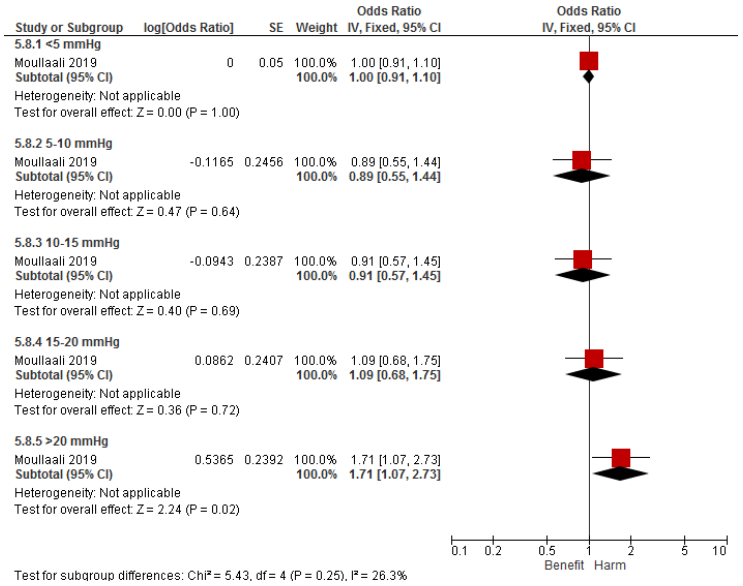


Associations of categorised systolic blood pressure summary measures and neurological deterioration at 24 hours

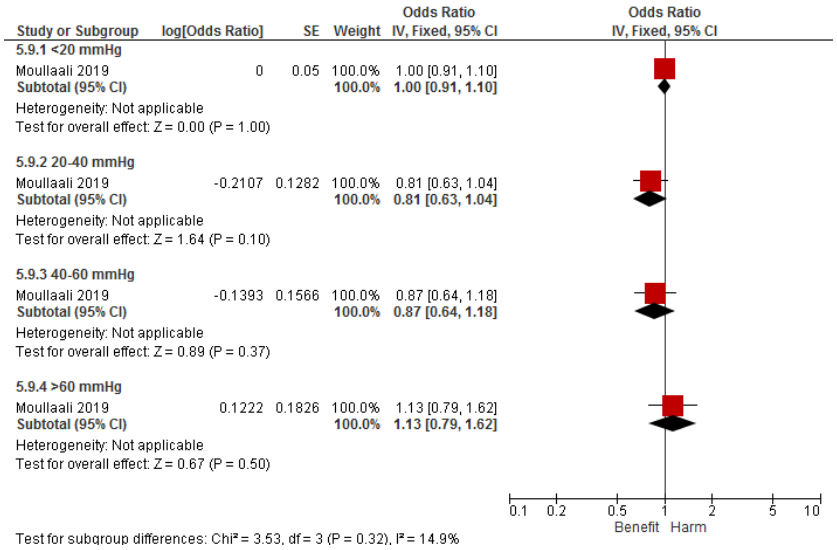
Achieved, mean SBP 1-24 hours



Variability, SD of SBP 1-24 hours

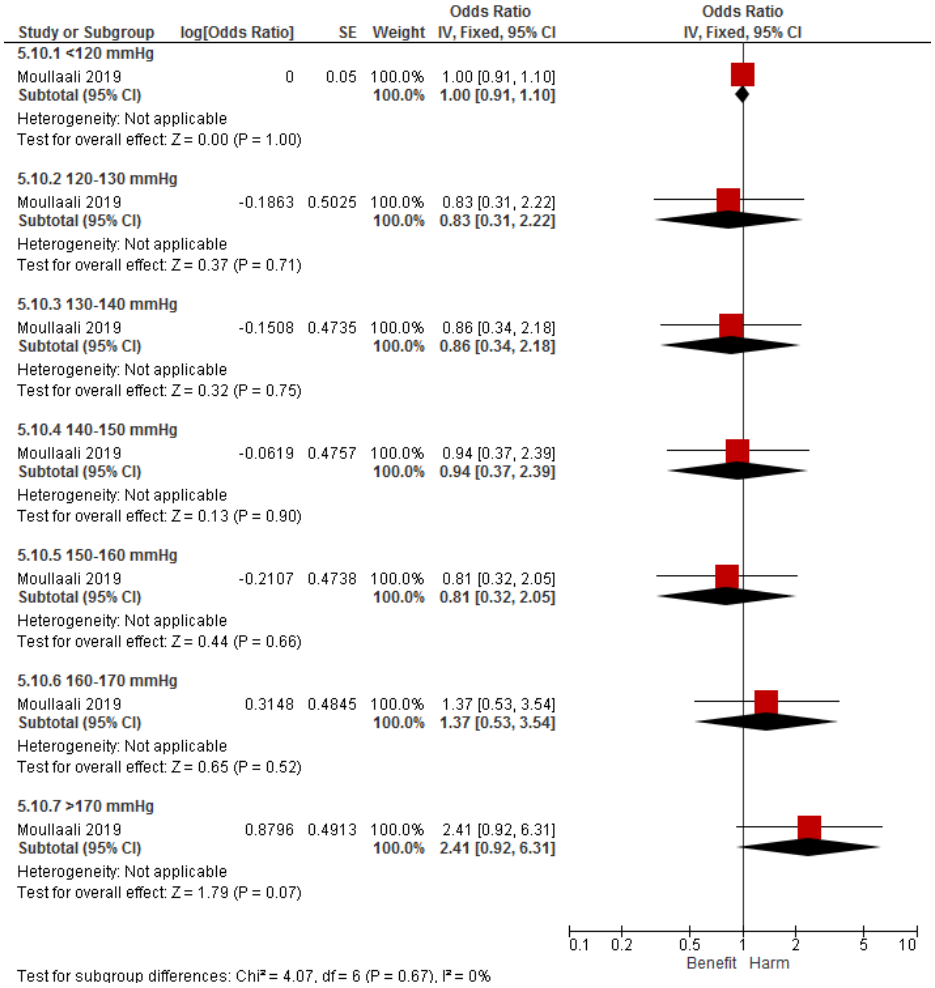


Magnitude, baseline - minimum ≤1 hr post-randomisation

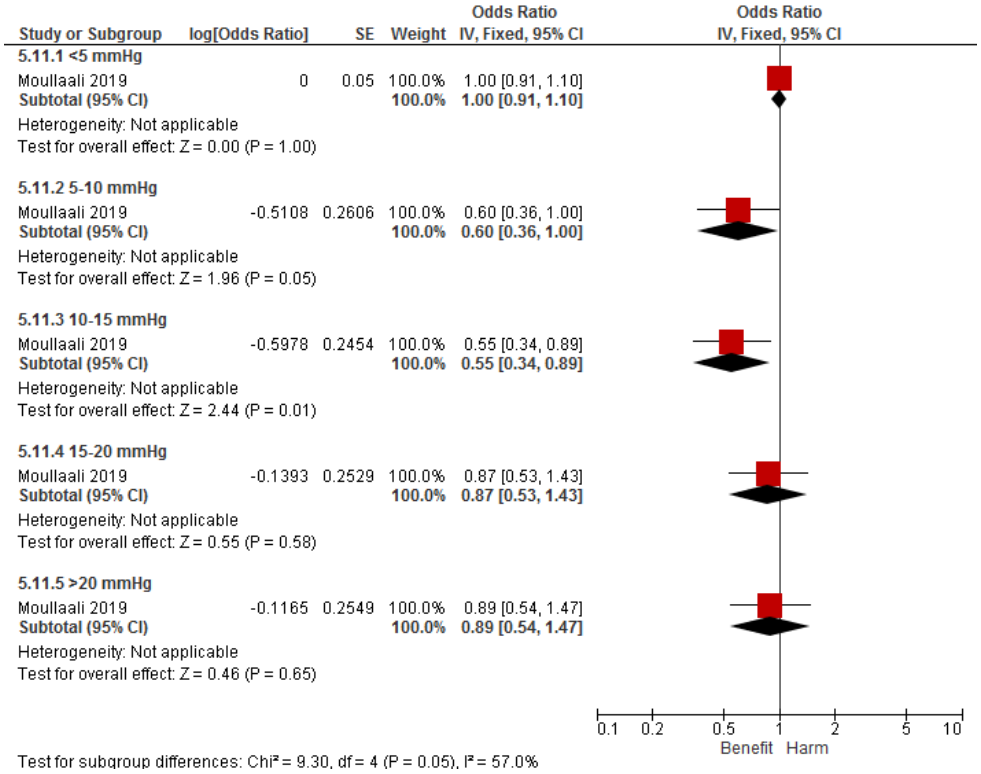


Associations of categorised systolic blood pressure summary measures and death at 90 days

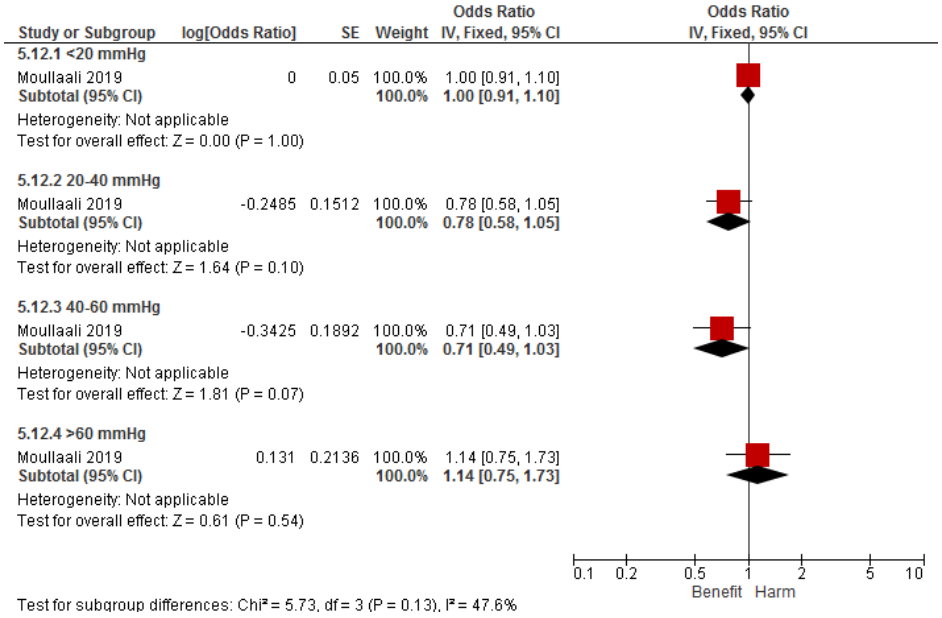
Achieved, mean SBP 1-24 hours



Variability, SD of SBP 1-24 hours

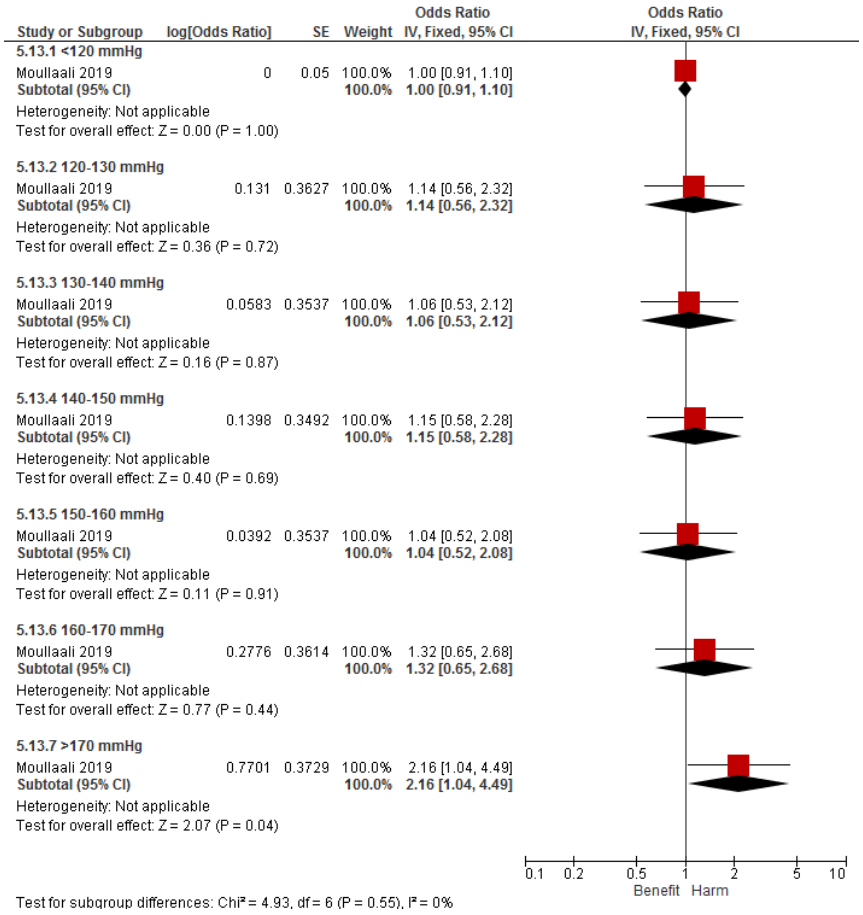


Magnitude, baseline - minimum ≤1 hr post-randomisation

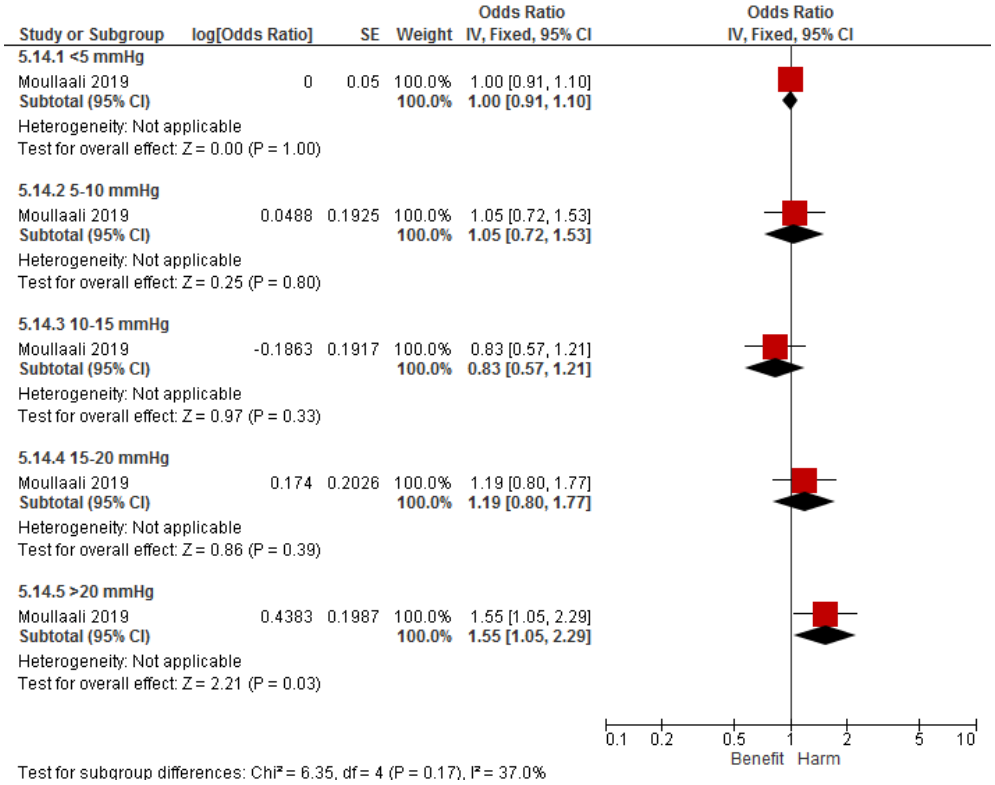


Associations of categorised systolic blood pressure summary measures and any serious adverse events at 90 days

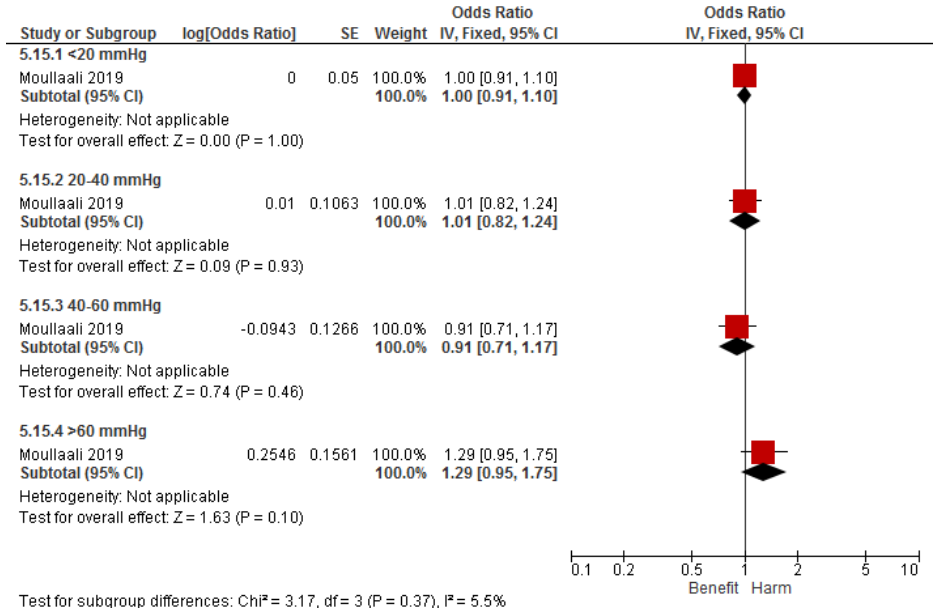
Achieved, mean SBP 1-24 hours



Variability, SD of SBP 1-24 hours

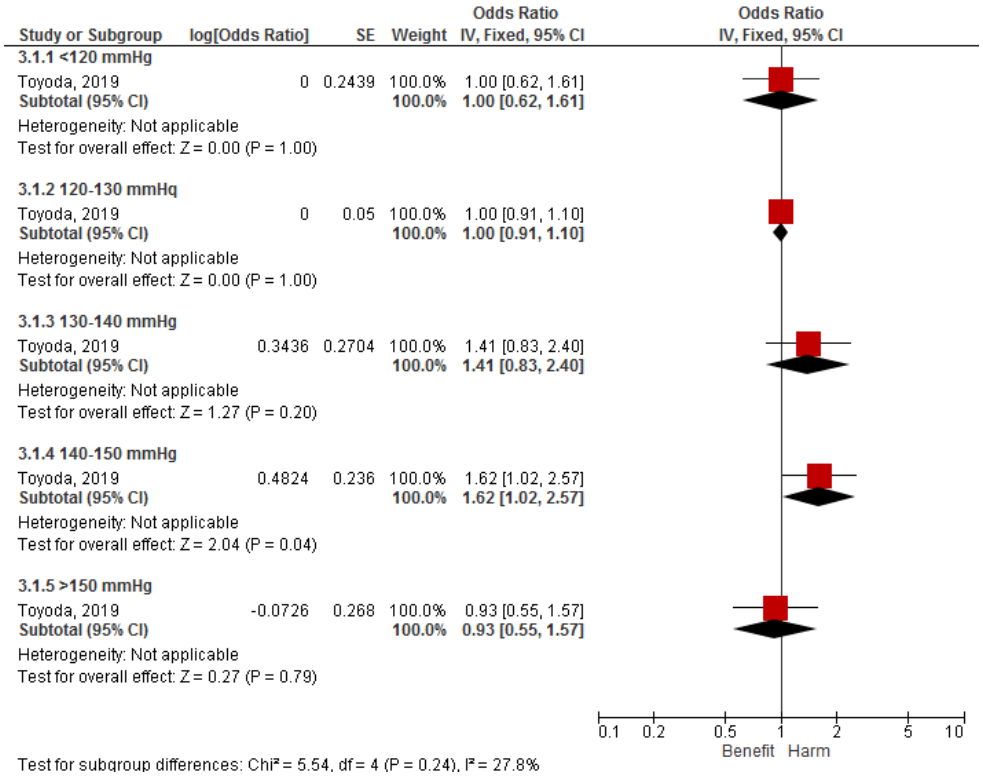


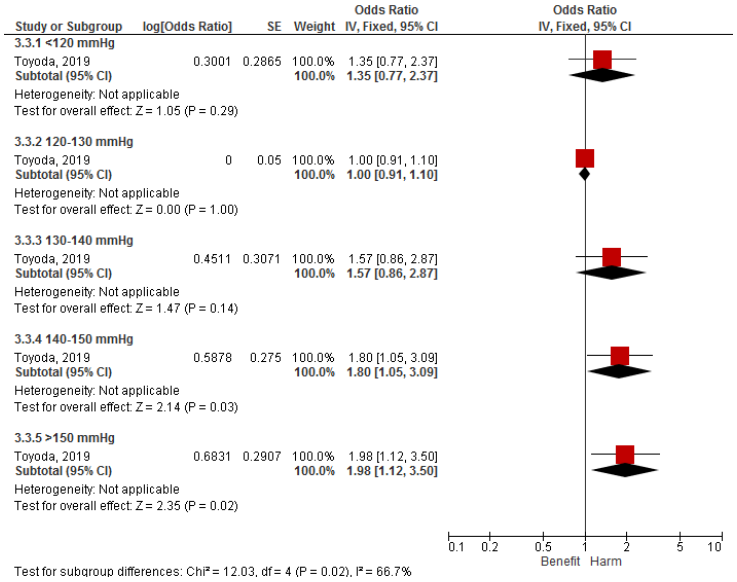
Magnitude, baseline - minimum ≤1 hr post-randomisation



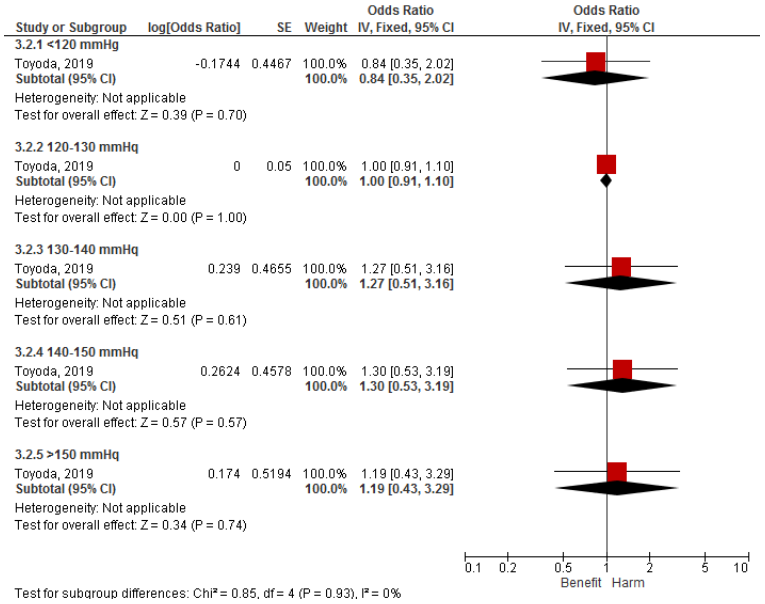
Outcomes by Average Hourly Minimum Systolic Blood Pressure Intensive Blood pressure reduction VS Standard Blood pressure reduction

mRS 4 to 6 at 90 days.

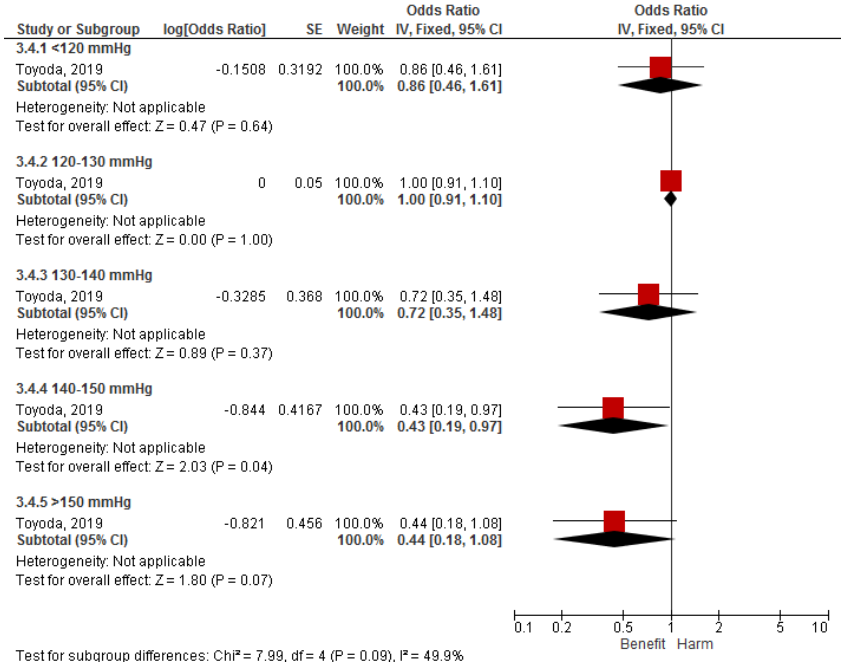



Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
3.3.1 <120 mmHg
Toyoda, 2019 0.3001 0.2865 100.0% 1.35 [0.77, 2.37]
Subtotal (95% CI) 100.0% 1.35 [0.77, 2.37]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
3.3.2 120-130 mmHg
Toyoda, 2019 0 0.05 100.0% 1.00 [0.91, 1.10]
Subtotal (95% CI) 100.0% 1.00 [0.91, 1.10]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
3.3.3 130-140 mmHg
Toyoda, 2019 0.4511 0.3071 100.0% 1.57 [0.86, 2.87]
Subtotal (95% CI) 100.0% 1.57 [0.86, 2.87]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)
3.3.4 140-150 mmHg
Toyoda, 2019 0.5878 0.275 100.0% 1.80 [1.05, 3.09]
Subtotal (95% CI) 100.0% 1.80 [1.05, 3.09]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
3.3.5 >150 mmHg
Toyoda, 2019 0.6831 0.2907 100.0% 1.98 [1.12, 3.50]
Subtotal (95% CI) 100.0% 1.98 [1.12, 3.50]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)
0.1 0.2 0.5 1 2 5 10
Benefit Harm
Test for subgroup differences: Chi² = 12.03, df = 4 (P = 0.02), I² = 66.7%

Hematoma expansion at 24 hours

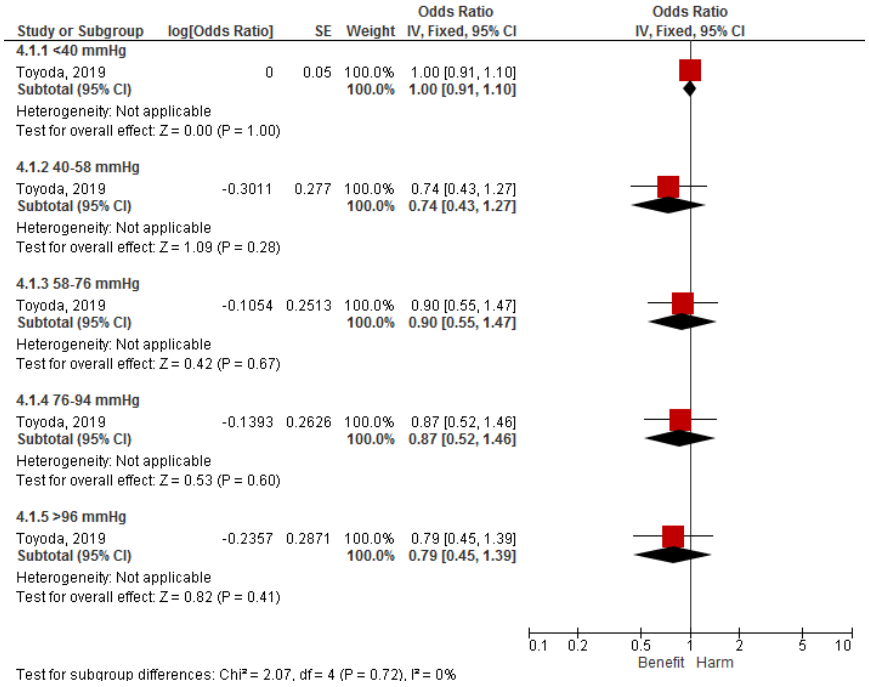


Cardiorenal Adverse Events.

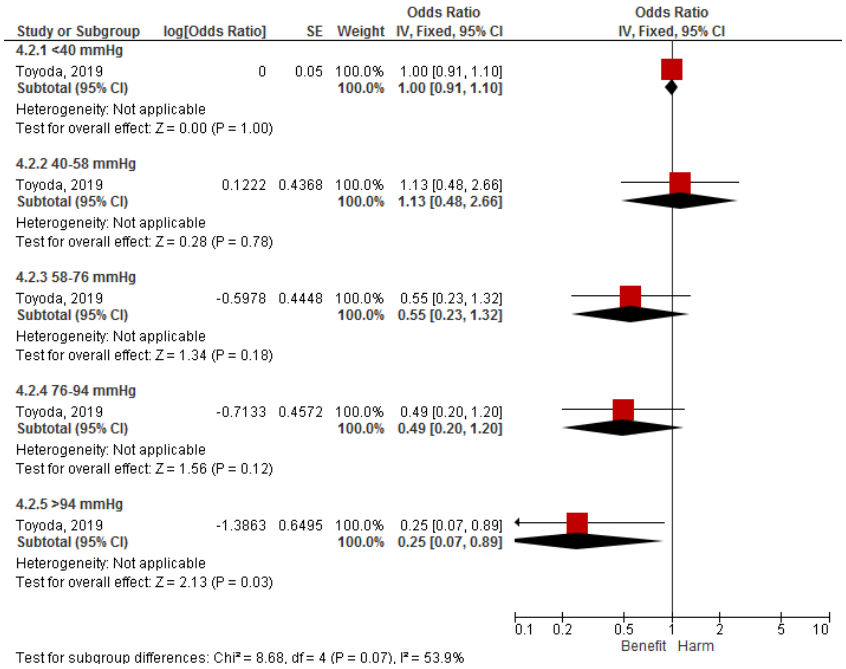


Outcomes by Absolute Reduction of Average Hourly Minimum Systolic Blood Pressure (SBP) From the Initial SBP

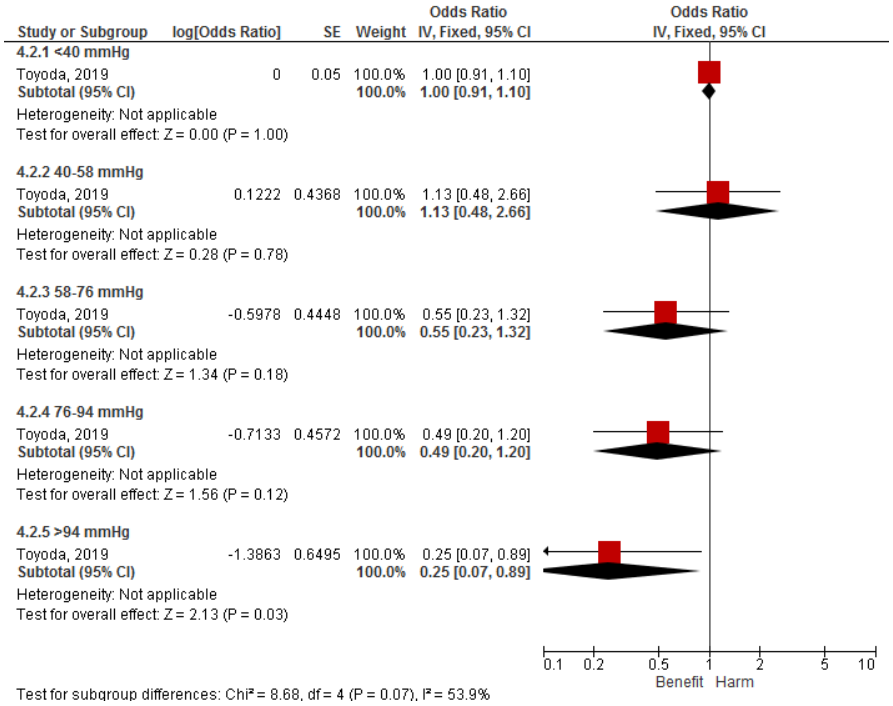
mRS 4 to 6 at 90 days.



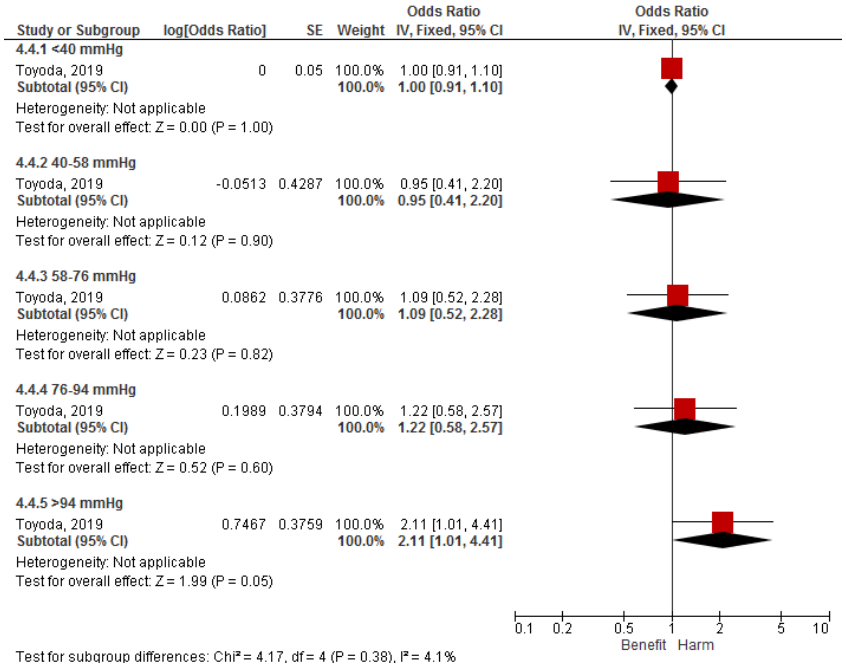
Mortality at 90 days



Hematoma expansion at 24 hours



Cardiorenal Adverse Events.



Appendix F – GRADE tables

Primary outcomes

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Mortality at 90 days										
7	RCT	5099	RR 0.99 [0.85, 1.16]	12 per 100 people	11 per 100 people (10 fewer to 13 more)	No serious risk of bias	No serious Indirectness	No serious Inconsistency	No serious imprecision	High
Modified Rankin Scale at 90 days (a score of 0 to 2) – functional status as defined by the distribution of scores (0 indicates no symptoms, 1 indicates symptoms without disability, 2 indicates disability but independent function)										
3	RCT	3832	RR 1.06 [0.99, 1.13]	44 per 100 people	47 per 100 people (43 fewer to 50 more)	Serious risk of bias[1]	No serious Indirectness	No serious Inconsistency	No serious imprecision	Moderate
Modified Rankin Scale at 90 days (a score of 4 to 6) - functional status as defined by the distribution of scores (4 indicates disability with moderate assistance, 5 indicates bedridden, full dependency, and 6 indicates death)										
3	RCT	3832	OR 0.93 [0.84, 1.02]	-	-	Serious risk of bias[1]	No serious Indirectness	Serious Inconsistency[4]	No Serious imprecision	Very Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcomes measurement)
2. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
3. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval
4. Downgraded by one level for serious inconsistency, if i-squared >33.3%

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

5. Downgraded by two levels for very serious inconsistency, if i-squared >66.7%
6. Inconsistency not applicable for single study Outcome reported from one study
7. Derived by taking the overall number of event/ total number of participants and multiplying by 100

Secondary outcomes

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Symptomatic cerebral ischemia at 24 hours – according to standard definitions										
1	RCT	201	RR 1.30 [0.68, 2.47]	14 per 100 people	18 per 100 people (9 fewer to 34 more)	No serious risk of bias	No serious Indirectness	N/A[6]	Very serious imprecision[3]	Low
Haemorrhage expansion at 24 hours – (>6 mL) from baseline to 24 h)										
6	RCT	3417	RR 0.82 [0.73, 0.93]	25 per 100 people	22 per 100 people (19 fewer to 25 more)	No serious risk of bias	No serious Indirectness	No serious Inconsistency	Serious imprecision[2]	Moderate
Neurological deterioration at 24 hours – Neurological deterioration defined as an increase of 4 points or more on the NIHSS or a decline of 2 points or more on the Glasgow Coma Scale)										
5	RCT	5065	RR 1.11 [0.96, 1.28]	13 per 100 people	13 per 100 people (1 fewer to 2 more)	No serious risk of bias	No serious Indirectness	Serious Inconsistency[4]	Serious imprecision[2]	Low
Adverse events (myocardial infarction) up to 90 days– according to standard definitions,										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1	RCT	629	RR 0.51 [0.05, 5.65]	1 per 100 people	0 per 100 people (0 fewer to 4 more)	No serious risk of bias	No serious Indirectness	N/A[6]	Very serious imprecision[3]	Low
Adverse events (Renal failure) up to 90 days– according to standard definitions,										
4	RCT	1647	RR 2.07 [1.08, 3.99]	2 per 100 people	3 per 100 people (2 fewer to 3 more)	No serious risk of bias	No serious Indirectness	No serious Inconsistency	Serious imprecision[2]	Moderate
Mortality up to 30 days										
2	RCT	268	RR 0.82 [0.45, 1.49]	16 per 100 people	13 per 100 people (7 fewer to 23 more)	No serious risk of bias	No serious Indirectness	Serious Inconsistency[4]	Very serious imprecision[3]	Very Low
The EQ-5D utility index score up to 90 days – (with scores ranging from 0-100 [least favourable health state] to 100 [most favourable health state],										
2	RCT	3030	MD 0.02 [-0.05, 0.09]	-	-	Serious risk of bias[1]	No serious Indirectness	Very serious Inconsistency[5]	No serious imprecision	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcomes measurement)
2. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
3. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval
4. Downgraded by one level for serious inconsistency, if i-squared >33.3%
5. Downgraded by two levels for very serious inconsistency, if i-squared >66.7%
6. Inconsistency not applicable for single study Outcome reported from one study
7. Derived by taking the overall number of event/ total number of participants and multiplying by 100

Grade tables for evidence where meta-analysis was not possible

Associations of categorised systolic blood pressure summary measures and with 90-day functional independence (scores 0-2 on the mRS)

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
2	RCT	(n=74)	OR: 1·00 (reference)	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	N/A	Moderate
120-130 mmHg										
2	RCT	(n=429)	OR 0.94 [0.51, 1.73]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low
130–140 mmHg										
2	RCT	(n=854)	OR 1·00 (0.55, 1.82]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low
140–150 mmHg										
2	RCT	(n=895)	OR: 0·79 [0.44, 1.42]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low
150–160 mmHg										
2	RCT	(n=806)	OR 0.81 [0.45, 1.46]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low
160–170 mmHg										
2	RCT	(n=474)	OR: 0.70 [0.38, 1.29]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low
≥170 mmHg										
2	RCT	(n=284)	OR: 0.63 [0.33, 1.20]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<5 mmHg										
2	RCT	(n=281)	OR: 1·00 (reference)	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	N/A	Moderate
5-10 mmHg										
2	RCT	(n=1005)	OR: 1.10 [0.79, 1.53]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
10-15 mmHg										
2	RCT	(n=1103)	OR 1.04 [0.76, 1.42]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
15-20 mmHg										
2	RCT	(n=735)	OR 1.00 [0.71, 1.41]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low
≥*20* mmHg										
2	RCT	(n=685)	OR 0.93 [0.66, 1.31]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control		Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<20 mmHg											
2	RCT	(n=1354)	OR: 1·00 (reference)	-	-	Serious risk of bias[1]	No serious indirectness		N/A[2]	N/A	Moderate
20-40 mmHg											
2	RCT	(n=1350)	OR: 1.36 [1.13, 1.64]	-	-	Serious risk of bias[1]	No serious indirectness		N/A[2]	Serious Imprecision[3]	Low
40-60 mmHg											
2	RCT	(n=731)	OR 1.35 [1.07, 1.70]	-	-	Serious risk of bias[1]	No serious indirectness		N/A[2]	Serious Imprecision[3]	Low
≥60 mmHg											
2	RCT	(n=381)	OR 0.79 [0.60, 1.04]	-	-	Serious risk of bias[1]	No serious indirectness		N/A[2]	Serious Imprecision[3]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Associations of categorised systolic blood pressure summary measures and with 90-day good outcome (scores 0-3 on the mRS)

Achieved, mean SBP 1-24 hours

No. of	Study	Sample	Effect size (95%	Absolute risk:	Absolute risk: intervention	Risk of				
<120 mmHg										
2	RCT	(n=74)	OR: 1·00 (reference)	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	N/A	Moderate
120-130 mmHg										
2	RCT	(n=429)	OR: 0.92 [0.47, 1.80]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very Low
130–140 mmHg										
2	RCT	(n=854)	OR: 0.89 [0.47, 1.69]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very Low
140–150 mmHg										
2	RCT	(n=895)	OR: 0.81 [0.42, 1.56]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very Low
150–160 mmHg										

<120 mmHg										
2	RCT	(n=74)	OR: 1·00 (reference)	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	N/A	Moderate
2	RCT	(n=806)	OR: 0.75 [0.39, 1.44]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very Low
160–170 mm Hg										
2	RCT	(n=474)	OR: 0.69 [0.35, 1.36]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Very Low
≥170 mm Hg										
2	RCT	(n=284)	OR: 0.56 [0.28, 1.12]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<5 mmHg										
2	RCT	(n=281)	OR: 1·00 (reference)	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	N/A	Moderate
5-10 mmHg										
2	RCT	(n=1005)	OR: 1.18 [0.84, 1.66]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
10-15 mmHg										
2	RCT	(n=1103)	OR: 1.16 [0.82, 1.64]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
15-20 mmHg										
2	RCT	(n=735)	OR: 1.10 [0.78, 1.55]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
≥*20* mmHg										
2	RCT	*(n=685)*	OR: 0.81 [0.57, 1.15]	-	-	Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval										

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<20 mmHg										
2	RCT	(n=1354)	OR: 1·00 (reference)			Serious risk of bias[1]	No serious indirectness	N/A[2]	N/A	Moderate
20-40 mmHg										
2	RCT	(n=1350)	OR: 1.29 [1.06, 1.57]			Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
40-60 mmHg										
2	RCT	(n=731)	OR 1.23 [0.97, 1.56]			Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low
≥60 mmHg										
2	RCT	(n=381)	OR 0.63 [0.47, 0.84]			Serious risk of bias[1]	No serious indirectness	N/A[2]	Serious Imprecision[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Associations of categorised systolic blood pressure summary measures and haematoma expansion >6mL at 24 hours

Achieved, mean SBP 1-24 hours

No. of studies	**Study design**	**Sample size**	**Effect size (95% CI)**	**Absolute risk: control**	**Absolute risk: intervention (95% CI)**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Quality**
<120 mmHg										
2	RCT	(n=45)	OR 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
120-130 mmHg										
2	RCT	(n=295)	OR 0.94 [0.36, 2.45]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
130–140 mmHg										
2	RCT	(n=464)	OR: 0.93 [0.36, 2.40]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
140–150 mmHg										
2	RCT	(n=436)	OR: 1.28 [0.50, 3.28]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
150–160 mmHg										
2	RCT	(n=399)	OR: 1.63 [0.63, 4.22]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
160–170 mmHg										
2	RCT	(n=213)	OR: 1.55 [0.58, 4.14]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥170 mmHg										
2	RCT	(n=84)	OR: 1.90 [0.66, 5.47]			No serious	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
						risk of bias				

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<5 mmHg										
2	RCT	(n=109)	0R: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
5-10 mmHg										
2	RCT	(n=547)	OR: 0.97 [0.53, 1.78]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
10-15 mmHg										
2	RCT	(n=565)	OR: 1.12 [0.61, 2.06]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
15-20 mmHg										
2	RCT	(n=383)	OR: 1.22 [0.65, 2.29]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥*20* mmHg										
2	RCT	*(n=332)*	OR: 1.21 [0.64, 2.29]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<20 mmHg										
2	RCT	(n=646)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
20-40 mmHg										
2	RCT	(n=637)	OR: 0.94 [0.69, 1.28]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
40-60 mmHg										
2	RCT	(n=419)	OR: 0.78 [0.55, 1.11			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[4]	Low
≥60 mmHg										
2	RCT	(n=234)	OR: 1.14 [0.75, 1.73]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval										

Associations of categorised systolic blood pressure summary measures and neurological deterioration at 24 hours

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
2	RCT	(n=73)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	High
120-130 mmHg										
2	RCT	(n=424)	OR 0.32 [0.15, 0.68]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[4]	Moderate
130–140 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2	RCT	(n=845)	OR: 0.57 [0.29, 1.12]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[4]	Moderate
140–150 mmHg										
2	RCT	(n=886)	OR: 0.58 [0.29, 1.16]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[4]	Moderate
150–160 mmHg										
2	RCT	(n=797)	OR: 0.49 [0.24, 1.00]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[4]	Moderate
160–170 mmHg										
2	RCT	(n=466)	OR: 0.66 [0.33, 1.32]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥170 mmHg										
2	RCT	(n=261)	OR: 0.97 [0.46, 2.05]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement)) 2. Inconsistency not applicable for single study Outcome reported from one study 3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval 4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval										

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<5 mmHg										
2	RCT	(n=267)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	low
5-10 mmHg										
2	RCT	(n=1000)	OR: 0.89 [0.55, 1.44]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
10-15 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2	RCT	(n=1097)	OR 0.91 [0.57, 1.45]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
15-20 mmHg										
2	RCT	(n=719)	OR: 1.09 [0.68, 1.75			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥*20* mmHg										
2	RCT	*(n=668)*	OR: 1.71 [1.07, 2.73]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval
1.

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<20 mmHg										
2	RCT	(n=1322)	OR 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
20-40 mmHg										
2	RCT	(n=1334)	OR 0.81 [0.63, 1.04]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
40-60 mmHg										
2	RCT	(n=721)	OR 0.87 [0.64, 1.18]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
≥60 mmHg										
2	RCT	(n=374)	OR 1.13 [0.79, 1.62			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval										
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval										

Associations of categorised systolic blood pressure summary measures and death at 90 days

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
2	RCT	(n=71)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
120-130 mmHg										
2	RCT	(n=421)	OR 0.83 [0.31, 2.22]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
130–140 mmHg										
2	RCT	(n=836)	OR: 0.86 [0.34, 2.18]			No serious	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
						risk of bias				
140–150 mmHg										
2	RCT	(n=877)	OR: 0.94 [0.37, 2.39]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
150–160 mmHg										
2	RCT	(n=793)	OR: 0.81 [0.32, 2.05]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
160–170 mmHg										
2	RCT	(n=463)	OR 1.37 [0.53, 3.54]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥170 mmHg										
2	RCT	(n=274)	OR 2.41 [0.92, 6.31]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval
1.

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<5 mmHg										
2	RCT	(n=275)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
5-10 mmHg										
2	RCT	(n=983)	OR 0.60 [0.36, 1.00]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
10-15 mmHg										
2	RCT	(n=1087)	OR 0.55 [0.34, 0.89]			No serious	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
						risk of bias				
15-20 mmHg										
2	RCT	(n=720)	OR: 0.87 [0.53, 1.43]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥*20* mmHg										
2	RCT	*(n=671)*	OR: 0.89 [0.54, 1.47]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<20 mmHg										
2	RCT	(n=1329)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
20-40 mmHg										
2	RCT	(n=1323)	OR: 0.78 [0.58, 1.05]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
40-60 mmHg										
2	RCT	(n=711)	OR: 0.71 [0.49, 1.03]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
≥60 mmHg										
2	RCT	(n=373)	OR: 1.14 [0.75, 1.73]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval 4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval										

Associations of categorised systolic blood pressure summary measures and any serious adverse events at 90 days

Achieved, mean SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
2	RCT	(n=74)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Low
120-130 mmHg										
2	RCT	(n=428)	OR 1.14 [0.56, 2.32]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
130–140 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2	RCT	(n=854)	OR: 1.06 [0.53, 2.12]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	low
140–150 mmHg										
2	RCT	(n=895)	OR: 1.15 [0.58, 2.28]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
150–160 mmHg										
2	RCT	(n=806)	OR: 1.04 [0.52, 2.08]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
160–170 mmHg										
2	RCT	(n=474)	OR 1.32 [0.65, 2.68]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
≥170 mmHg										
2	RCT	(n=278)	OR: 2.16 [1.04, 4.49]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Variability, SD of SBP 1-24 hours

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<5 mmHg										
2	RCT	(n=281)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Moderate
5-10 mmHg										
2	RCT	(n=1005)	OR 1.05 [0.72, 1.53]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
10-15 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2	RCT	(n=1103)	OR 0.83 [0.57, 1.21]			No serious risk of bias	No serious indirectness	N/A[2]	Very Serious Imprecision[4]	Low
15-20 mmHg										
2	RCT	(n=735)	OR 1.19 [0.80, 1.77]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
≥*20* mmHg										
2	RCT	*(n=685)*	OR: 1.55 [1.05, 2.29]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Magnitude, baseline - minimum ≤1 hr post-randomisation

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<20 mmHg										
2	RCT	(n=1351)	OR: 1·00 (reference)			No serious risk of bias	No serious indirectness	N/A[2]	N/A	Moderate
20-40 mmHg										
2	RCT	(n=1348)	OR: 1.01 [0.82, 1.24			No serious risk of bias	No serious indirectness	N/A[2]	No serious imprecision	High
40-60 mmHg										
2	RCT	(n=729)	OR 0.91 [0.71, 1.17]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate
≥60 mmHg										
2	RCT	(n=381)	OR: 1.29 [0.95, 1.75]			No serious risk of bias	No serious indirectness	N/A[2]	Serious Imprecision[3]	Moderate

1. 1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval 4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval										

Data not suitable for meta-analysis

No. of studies	Study design	Sample size	control	intervention	Risk of bias	Indirectness	inconsistency	Imprecision	Quality
mRS score at 90 days - median (IQR)									
Anderson 2008	RCT	2815	2 (1-4)	2 (1-4)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
mRS score at 90 days - median (IQR)									
Butcher 2013	RCT	73	4 (2–5)	2.5 (1–5.75)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
mRS score at 90 days - median (IQR)									
Krishnan 2016	RCT		3 [2]	3 [2]	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for subjective outcomes) 2. Inconsistency not applicable for single study Outcome reported from one study									

Data not suitable for meta-analysis

No. of studies	Study design	Sample size	control	intervention	Risk of bias	**Indirectness**	**inconsistency**	Imprecision	Quality
EQ-5D utility index score, median (range) at 90 days									
Anderson 2008	RCT	2815	2 (1-4)	2 (1-4)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
EQ-5D utility index score, median (IQR) at 90 days (-0.1 to 1.0)									
Qureshi,2016	RCT	961	0.7	0.7	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
EQ-5D visual analogue scale at 90 days (0 to 100)									
Qureshi,2016	RCT	961	70	62.5	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
EQ-visual analogue scale at 90 days (0 to 100)									
Krishnan 2016	RCT		55.1 (31.5)	54.6 (31.3)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
Mild ICH group									
EQ-5D utility index score, median (range) (with scores ranging from −0.109 [least favourable health state] to 1 [most favourable health state									
Qureshi 2020	RCT	318	0.8 (0.1–1)	0.8 (0.1–1)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
EQ-5D visual-analog scale score, median (range) (with scores ranging from 0 [least favourable health state] to 100 [most favourable health state									
Qureshi 2020	RCT	318	75 (10–100)	70 (8–100)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate
(Moderate-to-severe ICH group)									
EQ-5D utility index score, median (range) (with scores ranging from −0.109 [least favourable health state] to 1 [most favourable health state									
Qureshi 2020	RCT	682	0.8 (0.1–1)	0.8 (0.1–1)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate

No. of studies	Study design	Sample size	control	intervention	Risk of bias	**Indirectness**	**inconsistency**	Imprecision	Quality
EQ-5D visual-analog scale score, median (range) (with scores ranging from 0 [least favourable health state] to 100 [most favourable health state									
Qureshi 2020	RCT	682	75 (10–100)	70 (8–100)	Serious[1]	No serious Indirectness	N/A[6]	N/A	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Outcomes by Average Hourly Minimum Systolic Blood Pressure Intensive Blood pressure reduction VS Standard Blood pressure reduction

mRS 4 to 6 at 90 days

No. of studies	**Study design**	**Sample size**	**Effect size (95% CI)**	**Absolute risk: control**	**Absolute risk: intervention (95% CI)**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Quality**
<120 mmHg										
Toyoda, 2019	RCT	199	OR 1.00 [0.62, 1.61]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Very Low
120-130 mmHq										
Toyoda, 2019	RCT	301	OR 1 (reference)			Serious risk of bias[1]	No serious Indirectness	N/A[2]	N/A	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
130-140 mmHg										
Toyoda, 2019	RCT	139	OR 1.41 [0.83, 2.40]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Serious imprecision[2]	Low
140-150 mmHg										
Toyoda, 2019	RCT	221	OR 0.62 [1.02, 2.57			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Serious imprecision[2]	Low
150 mmHg										
Toyoda, 2019	RCT	135	OR: 0.93 [0.55, 1.57]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Very Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Death at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
Toyoda, 2019	RCT	199	OR: 0.84 [0.35, 2.02]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
120-130 mmHq										
Toyoda, 2019	RCT	301	OR: 1 (reference)			No serious risk of bias	No serious Indirectness	N/A[2]	N/A	Low
130-140 mmHg										
Toyoda, 2019	RCT	139	OR: 1.27 [0.51, 3.16]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
140-150 mmHg										
Toyoda, 2019	RCT	221	. OR: 1.30 [0.53, 3.19]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
150 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Toyoda, 2019	RCT	135	OR: 1.19 [0.43, 3.29]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Hematoma expansion

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
Toyoda, 2019	RCT	199	OR: 1.35 [0.77, 2.37]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
120-130 mmHq										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Toyoda, 2019	RCT	301	OR: 1 (reference)			No serious risk of bias	No serious Indirectness	N/A[2]	N/A	Low
130-140 mmHg										
Toyoda, 2019	RCT	139	OR: 1.57 [0.86, 2.87]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate
140-150 mmHg										
Toyoda, 2019	RCT	221	OR: 1.80 [1.05, 3.09]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate
150 mmHg										
Toyoda, 2019	RCT	135	OR: 1.98 [1.12, 3.50]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

Cardiorenal Adverse Events

No. of studies	Study design	Sample size	Effect size Odds Ratio (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<120 mmHg										
Toyoda, 2019	RCT	199	OR: 0.86 [0.46, 1.61]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
120-130 mmHq										
Toyoda, 2019	RCT	301	OR: 1 (reference)			No serious risk of bias	No serious Indirectness	N/A[2]	N/A	Moderate
130-140 mmHg										
Toyoda, 2019	RCT	139	OR: 0.72 [0.35, 1.48]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low

No. of studies	Study design	Sample size	Effect size Odds Ratio (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
140-150 mmHg										
Toyoda, 2019	RCT	221	OR: 0.43 [0.19, 0.97]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate
150 mmHg										
Toyoda, 2019	RCT	135	OR: 0.44 [0.18, 1.08]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Outcomes by Absolute Reduction of Average Hourly Minimum Systolic Blood Pressure (SBP) From the Initial SBP

mRS 4 to 6 at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<40 mmHg										
Toyoda, 2019	RCT	164	OR 1 (reference)			Serious risk of bias[1]	No serious Indirectness	N/A[2]	N/A	Low
40-58 mmHg										
Toyoda, 2019	RCT	180	OR: 0.74 [0.43, 1.27]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Serious imprecision[2]	Low
58-76 mmHg										
Toyoda, 2019	RCT	253	OR: 0.90 [0.55, 1.47]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Very Low
76-94 mmHg										
Toyoda, 2019	RCT	200	OR: 0.87 [0.52, 1.46]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Very Low
>96 mmHg										
Toyoda, 2019	RCT	161	OR: 0.79 [0.45, 1.39]			Serious risk of bias[1]	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Very Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Death at 90 days

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<40 mmHg										
Toyoda, 2019	RCT	164	OR 1 (reference)			No serious risk of bias	No serious Indirectness	N/A[2]	N/A	Low
40-58 mmHg										
Toyoda, 2019	RCT	180	OR: 1.13 [0.48, 2.66]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
58-76 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Toyoda, 2019	RCT	253	OR: 0.55 [0.23, 1.32]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
76-94 mmHg										
Toyoda, 2019	RCT	200	OR: 0.49 [0.20, 1.20]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate
>96 mmHg										
Toyoda, 2019	RCT	161	OR: 0.25 [0.07, 0.89]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement))
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Hematoma expansion

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<40 mmHg										
Toyoda, 2019	RCT	164	OR 1 (reference)			No serious risk of bias	No serious Indirectness	N/A[2]	N/A	Low
40-58 mmHg										
Toyoda, 2019	RCT	180	OR: 0.90 [0.52, 1.56]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision3	Low
58-76 mmHg										
Toyoda, 2019	RCT	253	OR: 0.48 [0.28, 0.82]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate
76-94 mmHg										
Toyoda, 2019	RCT	200	OR: 0.36 [0.19, 0.68]			No serious risk of bias	No serious Indirectness	N/A[2]	No serious imprecision	High
>96 mmHg										
Toyoda, 2019	RCT	161	OR: 0.36 [0.19, 0.68]			No serious risk of bias	No serious Indirectness	N/A[2]	No serious imprecision	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement)
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

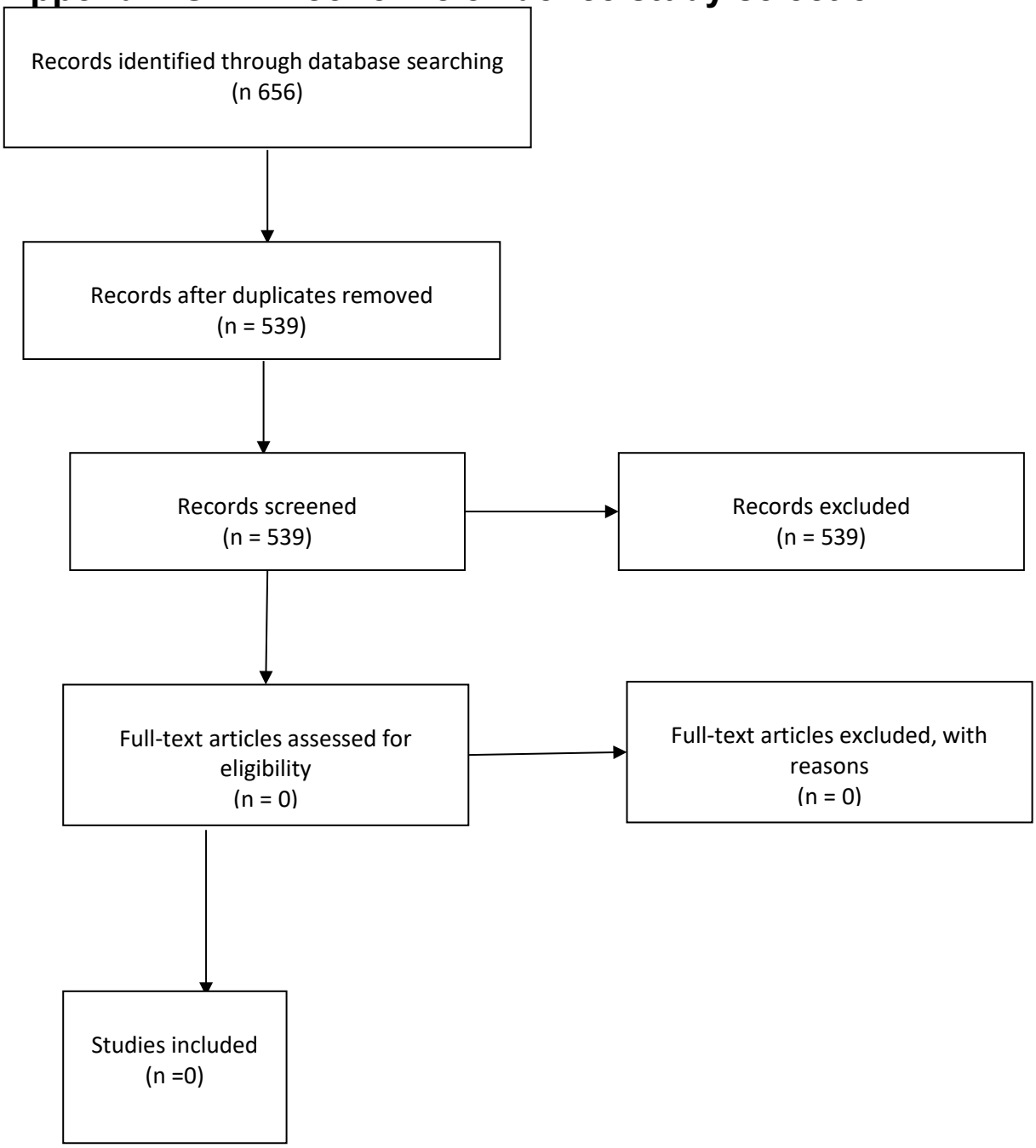
Cardiorenal Adverse Events

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
<40 mmHg										
Toyoda, 2019	RCT	164	OR 1 (reference)			No serious risk of bias	No serious Indirectness	N/A[2]	N/A	Low
40-58 mmHg										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Toyoda, 2019	RCT	180	OR: 0.95 [0.41, 2.20]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision[3]	Low
58-76 mmHg										
Toyoda, 2019	RCT	253	OR: 1.09 [0.52, 2.28]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision3	Low
76-94 mmHg										
Toyoda, 2019	RCT	200	OR: 1.22 [0.58, 2.57]			No serious risk of bias	No serious Indirectness	N/A[2]	Very serious imprecision3	Low
>96 mmHg										
Toyoda, 2019	RCT	161	OR: 2.11 [1.01, 4.41]			No serious risk of bias	No serious Indirectness	N/A[2]	Serious imprecision[2]	Moderate

1. Downgraded by one level if more than 33.3% of weighted data from studies at moderate or high risk of bias (high risk of bias for outcome measurement)
2. Inconsistency not applicable for single study Outcome reported from one study
3. Downgraded by one level for imprecision if 95% confidence interval crosses one end of a defined MID interval
4. Downgraded by two levels for imprecision if 95% confidence interval crosses both ends of a defined MID interval

Appendix G – Economic evidence study selection



Appendix H –Economic evidence tables

There are no included studies in this review question

Appendix I – Health economic model

Appendix J – Excluded studies

Study	Reason
(2021) Associations of an abnormal physiological score with outcomes in acute intracerebral hemorrhage INTERACT2 study. Stroke; a journal of cerebral circulation: 722-725	- Study does not contain a relevant intervention
Anderson, C (2018) The third, intensive care bundle with blood pressure reduction in acute cerebral hemorrhage trial (INTERACT3).	- incomplete clinical trial
Appleton, Jason P, Woodhouse, Lisa J, Bereczki, Daniel et al. (2019) Effect of Glyceryl Trinitrate on Hemodynamics in Acute Stroke. Stroke 50(2): 405-412	- A study plan/ protocol
Bath, Philip M, Scutt, Polly, Appleton, Jason P et al. (2019) Baseline characteristics of the 1149 patients recruited into the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) randomized controlled trial. International journal of stroke : official journal of the International Stroke Society 14(3): 298-305	- incorrect population, includes different types of strokes in inclusion criteria
Bath, PM, Woodhouse, LJ, Krishnan, K et al. (2019) Prehospital Transdermal Glyceryl Trinitrate for Ultra-Acute Intracerebral Hemorrhage: data From the RIGHT-2 Trial. Stroke; a journal of cerebral circulation 50(11): 3064-3071	- incorrect population, includes different types of strokes in inclusion criteria
Engrand, N, Roy-Gash, F, Cantier, M et al. (2021) Intensive blood pressure reduction in patients with intracerebral haemorrhage and extreme initial hypertension: primary target!. Anaesthesia, critical care and pain medicine 40(3)	- Not a relevant study design
Fukuda-Doi, Mayumi, Yamamoto, Haruko, Koga, Masatoshi et al. (2021) Impact of Renal Impairment on Intensive Blood-Pressure-Lowering Therapy and Outcomes in Intracerebral Hemorrhage: Results From ATACH-2. Neurology 97(9): e913-e921	- Secondary publication of an included study that does not provide any additional relevant information
Fukuda-Doi, Mayumi, Yamamoto, Haruko, Koga, Masatoshi et al. (2020) Sex Differences in Blood Pressure-Lowering Therapy and Outcomes Following Intracerebral Hemorrhage: Results From ATACH-2. Stroke 51(8): 2282-2286	- Study does not contain a relevant intervention
Gupta, S, Abbot, AK, Srinath, R et al. (2018) Randomized trial to assess safety and clinical efficacy of intensive blood pressure reduction in acute spontaneous intracerebral haemorrhage. Armed forces medical journal, india 74(2): 120-125	- Study does not contain a relevant intervention

Study	Reason
Kan, Shifeng, Sun, Ran, Chai, Song et al. (2020) A clinical study on the association of clinical outcome and acute systolic blood pressure in cerebral hemorrhage patients. International journal of clinical pharmacology and therapeutics 58(3): 146-154	- Not a relevant study design
Leasure, AC, Qureshi, AI, Murthy, SB et al. (2019) Association of Intensive Blood Pressure Reduction with Risk of Hematoma Expansion in Patients with Deep Intracerebral Hemorrhage. JAMA neurology	- Secondary publication of an included study that does not provide any additional relevant information
Leasure, Audrey C, Qureshi, Adnan I, Murthy, Santosh B et al. (2019) Intensive Blood Pressure Reduction and Perihematomal Edema Expansion in Deep Intracerebral Hemorrhage. Stroke 50(8): 2016-2022	- Secondary publication of an included study that does not provide any additional relevant information
Li, Q, Warren, A, Qureshi, A et al. (2020) Ultra-early intensive blood pressure reduction attenuates hematoma growth and improves functional outcome in patients with acute intracerebral hemorrhage. International journal of stroke 15 (1 SUPPL): 59	- Study does not contain a relevant intervention
Li, Qi, Warren, Andrew D, Qureshi, Adnan I et al. (2020) Ultra-Early Blood Pressure Reduction Attenuates Hematoma Growth and Improves Outcome in Intracerebral Hemorrhage. Annals of neurology 88(2): 388-395	- Study does not contain a relevant intervention
Moullaali, Tom J, Wang, Xia, Martin, Renee' H et al. (2019) Statistical analysis plan for pooled individual patient data from two landmark randomized trials (INTERACT2 and ATACH-II) of intensive blood pressure lowering treatment in acute intracerebral hemorrhage. International journal of stroke : official journal of the International Stroke Society 14(3): 321-328	- Not a relevant study design - study plan/ protocol
Okazaki, S, Yamamoto, H, Foster, L et al. (2019) Late neurological deterioration after intracerebral hemorrhage: an exploratory analysis of ATACH-2. Clinical neurology. Conference: 60th annual meeting of the japanese society of neurology. Japan. 59 (supplement 1) (pp S380), 2019. Date of publication: 2019. conference60thannualmeetingofthejapanesesocietyofneurologyjapan59(supplement1): 380	Outcomes reported in study different from outcomes in protocol
Okazaki, Shuhei, Yamamoto, Haruko, Foster, Lydia D et al. (2020) Late Neurological Deterioration after Acute Intracerebral Hemorrhage: A post hoc Analysis of the ATACH-2 Trial. Cerebrovascular diseases (Basel, Switzerland) 49(1): 26-31	- A post hoc Analysis Secondary publication of an included study that does not provide any additional relevant information
Qureshi, Adnan I, Huang, Wei, Lobanova, Iryna et al. (2020) Systolic Blood Pressure Reduction and Acute	Outcomes reported are irrelevant to protocol

Study	Reason
Kidney Injury in Intracerebral Hemorrhage. Stroke 51(10): 3030-3038	
Qureshi, Adnan I, Lobanova, Iryna, Huang, Wei et al. (2020) Rate and Predictors of Unanticipated Surgical Evacuation in Patients with Intracerebral Hemorrhage: Post Hoc Analysis of ATACH 2 Trial. World neurosurgery 141: e935-e940	- Study does not contain a relevant intervention
Sandset, Else C, Appleton, Jason P, Berge, Eivind et al. (2019) Associations between change in blood pressure and functional outcome, early events and death: results from the Efficacy of Nitric Oxide in Stroke trial. Journal of hypertension 37(10): 2104-2109	- Does contain a mixed population of people with ischaemic stroke or intracerebral haemorrhage
Sandset, Else Charlotte, Wang, Xia, Carcel, Cheryl et al. (2020) Sex differences in treatment, radiological features and outcome after intracerebral haemorrhage: Pooled analysis of Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trials 1 and 2. European Stroke Journal 5(4): 345-350	- outcomes measured are not relevant
Shoamanesh, Ashkan, Morotti, Andrea, Romero, Javier M et al. (2018) Cerebral Microbleeds and the Effect of Intensive Blood Pressure Reduction on Hematoma Expansion and Functional Outcomes: A Secondary Analysis of the ATACH-2 Randomized Clinical Trial. JAMA neurology 75(7): 850-859	- Secondary publication of an included study that does not provide any additional relevant information
Toyoda, Kazunori, Palesch, Yuko Y, Koga, Masatoshi et al. (2021) Regional Differences in the Response to Acute Blood Pressure Lowering After Cerebral Hemorrhage. Neurology 96(5): e740-e751	- Study does not contain a relevant intervention
Toyoda, Kazunori, Yoshimura, Sohei, Inoue, Manabu et al. (2021) Intensive blood pressure lowering with nicardipine and outcomes after intracerebral hemorrhage: An individual participant data systematic review. International Journal of Stroke	- Secondary publication of an included study that does not provide any additional relevant information
van den Berg, Sophie A, Dippel, Diederik W J, Hofmeijer, Jeannette et al. (2019) Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP): study protocol for a randomised controlled trial. Trials 20(1): 383	- Does contain a mixed population of people with ischaemic stroke or intracerebral haemorrhage
Woodhouse, L, Law, Z, Munshi, S et al. (2020) Association between antihypertensive drug class and outcome after acute intracerebral haemorrhage-data from the tranexamic acid for intracerebral haemorrhage 2 (TICH-2) trial. International journal of stroke 15 (1 SUPPL): 61	- Does not contain a population of people with XXX - Study does not contain a relevant intervention - Not a relevant study design - Data not reported in an extractable format

Study	Reason
	- Comparator in study does not match that specified in protocol
You, Shoujiang, Zheng, Danni, Delcourt, Candice et al. (2019) Determinants of Early Versus Delayed Neurological Deterioration in Intracerebral Hemorrhage. Stroke 50(6): 1409-1414	- Study does not contain a relevant intervention
Yuan, Fang, Yang, Fang, Zhao, Jingjing et al. (2021) Controlling Hypertension After Severe Cerebrovascular Event (CHASE): A randomized, multicenter, controlled study. International journal of stroke : official journal of the International Stroke Society 16(4): 456-465	- Does not contain a population of people with ICH
Zang, Yanjing, Zhang, Jing, Feng, Shanshan et al. (2019) Therapeutic effect of early intensive antihypertensive treatment on rebleeding and perihematomal edema in acute intracerebral hemorrhage. Journal of Clinical Hypertension 21(9): 1325-1331	- Secondary publication of an included study that does not provide any additional relevant information
Zhang, Peng; Huang, Hui; Chen, Fujian (2019) Effect of nimodipine injection on the curative effect, overall prognosis and level of serum IL-6, and TNF-alpha in patients with hypertensive intracerebral haemorrhage. Acta Medica Mediterranea 35(2): 715-719	- Not a relevant study design
Zhao, Jingjing, Yuan, Fang, Wang, Xiaomu et al. (2021) Hypertension management in elderly with severe intracerebral haemorrhage. Annals of Clinical and Translational Neurology 8(10): 2059-2069	- Does contain a mixed population of people with ischaemic stroke or intracerebral haemorrhage

Appendix K – Research recommendations – full details

Research recommendation

What is the safety and efficacy of intensive interventions to lower blood pressure versus less intensive interventions in people with acute intracerebral haemorrhage in clinically frail adults?

Why this is important

Expert opinions have highlighted a case for further research to assess whether people living with advanced frailty should have a different stroke pathway. frailty considerations can form part of a holistic baseline assessment may help as an indicator to inform a shared decision-making process in identifying the risk and suitability of people with mild, moderate, or severe frailty for intensive blood pressure reduction treatment.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the long-term outcomes associated with intensive blood pressure reduction therapy clinically vulnerable patients with ICH
Relevance to NICE guidance	Intensive blood reduction therapy has been considered in this guideline and there is a lack of data on long-term safety of intensive blood reduction therapy on the on patients who are more clinically vulnerable The association of frailty with adverse outcomes is an important factor to consider and there is a gap in the data for this proxy at baseline.
Relevance to the NHS	The outcome would affect the types of treatment ICH provided by the NHS and may also be used as a proxy to predict future healthcare needs for patients that present with
National priorities	High
Current evidence base	Minimal long-term data
Equality considerations	None known

Modified PICO table

Population	Adults with ICH and mild, moderate, or severe frailty
Intervention	Intensive blood reduction therapy
Comparator	Less intensive blood pressure therapy
Outcome	Mortality up to 30 days Adverse outcome (renal failure) Neurological deterioration (modified Rankin scale)
Study design	RCT

Timeframe	Long term
Additional information	None

Research recommendation

What are the long-term effects on cognitive function, functional ability, and quality of life of intensive interventions to lower blood pressure compared with standard interventions in people with acute intracerebral haemorrhage?

Why this is important

Epidemiological studies have not been very productive in identifying changes in cognitive function and functional ability. The longer-term changes in cognition following stroke are under researched. Traditional physical/disability indexes are less sensitive to changes in cognitive function and ability. We call for all clinical trials on ICH and blood pressure management to include assessment of cognitive measure including cognitive function functional ability, and quality of life, as primary outcomes.

A cognitive measure can be used to report the effects of intensive blood pressure reductions interventions for subjects. A cognitive function, ability assessment can indicate a general aspect of cognitive function or more specific aspect (s) of cognitive function, such as memory performance or speech. These outcomes are very important to the decision making for the safety and efficacy of intensive blood pressure reduction therapies.

Rationale for research recommendation

Importance to ‘patients’ or the population	Little is known about the long-term cognitive function and overall impact on daily life, particularly in executive function associated with intensive blood pressure reduction therapy patients with ICH
Relevance to NICE guidance	Intensive blood reduction therapy has been considered in this guideline and there is a lack of data on long-term safety of intensive blood reduction therapy on the cognition of patients at 6 months and 12 months.
Relevance to the NHS	The outcome would affect the types of treatment ICH provided by the NHS and may also be used as a proxy to predict future healthcare needs for patients that present with ICH
National priorities	High
Current evidence base	Minimal long-term data
Equality considerations	None known

Modified PICO table

Population	Adults with ICH
Intervention	Intensive blood reduction therapy

Comparator	Less intensive blood pressure therapy
Outcome	Cognitive function, cognitive ability, and Quality of life at 6 months and 12 months
Study design	RCT
Timeframe	Long term
Additional information	None

Appendix L – Methods

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool 2.0. Cohort studies were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.
- Critical risk of bias (ROBINS-I only) - It is very likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are

presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention, or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with $I^2 < 50\%$) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence was identified, only pooled results are presented.

In any meta-analyses where some (but not all) of the data came from studies at critical or high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline.

In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

MIDs found through this process and used to assess imprecision in the guideline are given in **Error! Reference source not found.**. For other continuous outcomes not specified in the table below, no MID was defined.

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 standard deviations was used.

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms

was used (Norman et al. 2003). For dichotomous outcomes, such as relative risks where no other MID was available, default MIDS of 0.8,1.25 were used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from randomised controlled trials, non-randomised controlled trials and cohort studies were initially rated as high quality while data from other study types were originally rated as low quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 6.

Table 6: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies

GRADE criteria	Reasons for downgrading quality
	(heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant). If relative risk could not be estimated (due to zero events in both arms), outcome was downgraded for very serious imprecision as effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Summary of evidence is presented in section 1.1.6. This summarises the effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data.

Evidence was also identified for which GRADE could not be applied as the evidence was presented in the form of median and interquartile range. This evidence is presented in Appendix G. This evidence has been summarised narratively in section 1.1.11.