National Institute for Health and Care Excellence

Draft for consultation

# Stroke (update)

## Evidence review E: Maintenance of homeostasis

*NICE guideline*

*Intervention evidence review*

*November 2018*

*Draft for consultation*

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

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# Contents

# 1 Restoration or maintenance of homeostasis

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

## 1.2 Introduction

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

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

## 1.3 PICO table

For full details see the review protocol in appendix A.

**Table 1: PICO characteristics of review question**

| | |
|---|---|
| **Population** | People aged over 16 with acute intracerebral haemorrhage and high blood pressure at the time of assessment |
| **Interventions** | Intensive blood pressure reduction within 48 hours<br>• Calcium antagonists (e.g. intravenous isradipine, oral nimodipine, oral and intravenous nimodipine, urapidil, flunarizine, nicardipine and oral PY108-608)<br>• Intravenous or transdermal glyceryl trinitrate (GTN)<br>• Angiotensin II antagonist (e.g. cilextil)<br>• Beta-blockers (e.g. atenolol, propranolol and labetalol) |
| **Comparisons** | Standard care or no treatment/placebo |
| **Outcomes** | Critical<br>Mortality at 24 hours/90 days<br>Modified Rankin scale (mRS) score at 90 days and 1 year |

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

## 1.4 Methods and process

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

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

## 1.5 Clinical evidence

### 1.5.1 Included studies

Seven studies were included in the review[1, 3, 15, 32, 33, 41, 62] and evidence from these studies is summarised in the clinical evidence summary below Table 2. The studies all compare intensive blood pressure therapy with standard blood pressure therapy; although some of the blood pressure lowering protocols had different targets. One study[33] was a subgroup analysis of those with intracerebral haemorrhage within a randomised trial.[11] Stroke type (ischaemic or haemorrhagic) was a pre-speicfied subgroup that was used a a stratification variable before intial randomisation; therefore, randomisation was not lost and the subgroup data were eligible for inclusion.

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

### 1.5.2 Excluded studies

See the excluded studies list in appendix H.

### 1.5.3 Summary of clinical studies included in the evidence review

**Table 2: Summary of studies included in the evidence review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| ATACH-2 2016, Qureshi et al[41]<br><br>China, Germany, Japan, South Korea, Taiwan, USA | Intensive blood pressure therapy using intravenours nicardipine to target blood pressure vs standard blood pressure therapy using intravenours nicardipine<br><br>Therapy started within 4.5 hours of presentation and continued for 24 hours<br>Target to be acheived within 2 hours of randomisation | Acute intracerebral haemorrhage and systolic blood pressure ≥170 mmHg to ≤200 mmHg within 4.5 hours<br><br>n=1000 | 90 day:<br>Mortality<br>mRS score<br>EQ-5D utility index score<br>EQ-5D visual analogue scale<br>Renal failure<br><br>24 hour:<br>Haematoma expansion (≥33% at baseline)<br>Neurological deterioration (Glasgow coma scale [GCS] decrease ≤2 from baseline or NIHSS increase ≥4) | Intensive systolic blood pressure target: 110 to 139 mmHg<br>Target achieved: 87.8%<br><br>Comparison systolic blood pressure target: 140 to 179 mmHg<br>Target achieved: 99.2%<br><br>Mean (SD) minimum systolic blood pressure during the first 2 hours was 128.9 (16) mmHg in the intensive treatment group and 141.1 (14.8) mmHg in the standard treatment group |
| ENOS-ICH 2016, Krishnan et al[33]<br><br>Australia, Canada, China, Denmark, Egypt, Georgia, Greece, Hong Kong, India, Ireland, Italy, Malaysia, New Zealand, Norway, Philippines, Poland, Romania, Singapore, | Transdermal glyceryl trinitrate (5 mg per day) vs no glyceryl trinitrate continued for 7 days | Acute intracerebral haemorrhage and systolic blood pressure ≥140 mm Hg within 48 hours of presentation<br><br>n=629 | 90 day:<br>Mortality<br>mRS score<br>Recurrent stroke<br>Myocardial infarction | Pre-specified subgroup analysis of ENOS 2015[11]<br><br>Following first dose of transdermal glyceryl trinitrate vs no treatment, blood pressure fell by 7.5/4.2 mmHg |

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

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Austria, Belgian, Brazil, China, China Shanghai, China Hong, Chile, Finland, France, Germany, India, Italy, The Netherlands, Norway, Pakistan, Portugal, Spain, Switzerland, UK, US | The majority of participants in both groups received the following: alpha-adrenergic antagonist, such as urapidil, calcium-channel blocker, such as nicardipine or nimodipine, combined alpha- and beta-blocker, such as labetalol, nitroglycerin | presentation<br><br>n=2839 | 24 hour:<br>Substantial haematoma expansion<br>Neurological deterioration (GCS decrease ≤2 from baseline or NIHSS increase ≥4) | Comparison systolic blood pressure target of <180 mmHg within 1 hour of randomisation<br><br>At 1 hour the mean systolic blood pressure in the intensive group was 150 mmHg and 164 mmHg in the standard group (difference 14 mmHg, 95%CI 9 to 18 mmHg) |
| Koch 2008[32]<br><br>USA | Intensive blood pressure therapy vs standard blood pressure therapy continued for 48 hours<br><br>The majority of participants in both groups received intravenours nicardipine | Acute intracerebral haemorrhage and mean arterial pressure ≥110 mmHg randomised within 8 hours of symptom onset<br><br>n=42 | 90 day:<br>Mortality<br>mRS score<br>Renal failure<br><br>24 hour:<br>Haematoma expansion (≥30% at baseline) | Intensive mean arterial pressure target of <110 mmHg<br>Target achieved after 3 hours of treatment: 67%<br><br>Comparison mean arterial pressure target of 110-130 mmHg<br>Target achieved after 3 hours of treatment: 90%<br><br>Between 0 to 3 hours, mean (SD) arterial pressure in the intensive group was 113.8 (30) mmHg and 124.1 (12.8) in the standard group |
| PATICH 2017, Zheng et al[62]<br><br>China | Intensive blood pressure therapy vs standard blood pressure therapy continued for 7 days<br><br>Details of specific | Acute intracerebral haemorrhage undergoing surgical hematoma evacuation within 1 hour of randomisation and | 90 day:<br>Mortality<br>Renal failure<br>EQ-5D utility index score | Intensive systolic blood pressure at the end of the first hour after randomization was between 140 and 160 mm Hg, at time of surgery was between 120 and 140 mm Hg, after the operation, the antihypertensive treatment began when the SBP became |

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

1 See appendix D for full evidence tables.

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## 1.5.4 Quality assessment of clinical studies included in the evidence review

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

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

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

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

1 See appendix F for full GRADE tables.

2 **Table 4: Data not suitable for meta-analysis**

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

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# 1.6 Economic evidence

## 1.6.1 Included studies

No relevant health economic studies were identified.

## 1.6.2 Excluded studies

Two economic studies relating to this review question were identified but were excluded as they were not applicable. [39, 52, 57] These are listed in appendix H, with reasons for exclusion given.

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

## 1.6.3 Unit costs

**Table 5: UK costs of drugs to lower blood pressure**

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

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

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

*(a) Dosages for adults*
*(b) Depending on number of units taken*
*(c) Cost of 5 day course*
*(d) Cost of 2 day course*

**Table 6: UK costs of blood pressure lowering with labetalol**

| Drug | Assumed daily dose[a] | Cost per unit (£) | Cost per 2-day course | Number needed to treat (mRS 0-2) | Total cost |
|---|---|---|---|---|---|
| Labetalol 100mg/20ml solution for injection ampoules | 50mg per hour [For hypertension following MI: 15mg/hour, then increased to up to 120 mg/hour, dose to be increased gradually] | £10.44[a] | £250.66 | 40 | £9,641 |

*(a) Source: British National Formulary*

The clinical review found that 40 people with haemorrhagic stroke would need to be treated to yield one additional person with an mRS 0-2. At a total cost of £250.66 per person, the cost of treating 40 people with haemorrhagic stroke is £9,641 (Table 6). According to published literature, the cost saving between mRS 0-2 and mRS 3-5 is £7,813 within three months of stroke onset and £10,182 over the first year after stroke [23]. Over a lifetime time horizon, further cost savings are therefore likely to be accrued. The committee therefore considered that the cost of treating 40 people with intravenous labetalol (£9,641) would be recuperated over a year and cost saving over a lifetime time horizon.

## 1.7 Resource costs

The recommendation made by the committee based on this review (see section 1.9) that rapid blood pressure lowering should be offered in people with acute intracerebral haemorrhage and systolic blood pressure between 150 and 220 mmHg and presenting within 6 hours of symptom onset is not expected to have a substantial impact on resources to the NHS in England. The committee also made a recommendation based on this review (see section 1.9) that controlled blood pressure lowering should be 'considered' for people with acute intracerebral haemorrhage who present beyond 6 hours of symptom onset or have a systolic blood pressure greater than 220 mmHg. Unlike for stronger recommendations stating

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

## 1.8 Evidence statements

### 1.8.1 Clinical evidence statements

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

### 1.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

# 1.9 Recommendations

E1. Offer rapid blood pressure lowering to people with acute intracerebral haemorrhage who:

- present within 6 hours of symptom onset, and
- have a systolic blood pressure of between 150 and 220 mmHg.

Aim for a systolic blood pressure target of below 140 mmHg within 2 hours of starting treatment and maintain the blood pressure at that level for at least 7 days. [2019]

E2. Consider controlled blood pressure lowering for people with acute intracerebral haemorrhage who:

- present beyond 6 hours of symptom onset, or
- have a systolic blood pressure greater than 220 mmHg.

Aim for a systolic blood pressure target of below 140 mmHg and maintain the blood pressure at that level for at least 7 days. [2019]

# 1.10 Rationale and impact

## 1.10.1 Why the committee made the recommendations

Good quality evidence from a large number of trial participants showed no clear harm associated with rapidly lower blood pressure to a target of 140 mmHg systolic blood pressure compared with standard blood pressure lowering . Specifically, no clinically relevant increase in the risk of increased neurological deterioration caused by reduced blood flow to the brain or renal failure caused by rapid lowering of systolic blood pressure was found. There was also no clinical diference found for mortality and haematoma growth The intervention achieved a good functional outcome (defined as a modified Rankin Score [mRS] of 0-2), and the potential to improve quality of life, which was agreed to be clinically meaningful. The mortality rate without interventions is thought to be around 40% at 1 month, and up to 60% of people who do survive have moderate or severe disability. Therefor any intervention to reduce this is important. It is also important to standardise care in this area where much inconsistency is known to exist. The committee noted that one trial used an even more aggressive blood pressure lowering strategy withtreatment started within 4.5 hours of symptom onset and a target for systolic blood pressure of 110–139 mmHg. This showed an increased incidence of renal failure compared with standard treatment, and so this regimen has not been recommended.

There was little or no evidence on people presenting beyond 6 hours and those with a systolic blood pressure over 220 mmHg. However, the committee agreed that guidance is needed on treating hypertension in these groups and that it is logical to extrapolate from the available data to these groups. Therefore, they made a consensus recommendation to consider controlled systolic blood pressure reduction in these groups. A research recommendation was not made as the population of people presenting to services 6 hours after the index intracerebral haemorrhage with high blood pressure is likely to be small.

## 1.10.2 Impact of the recommendations on practice

The recommendations reflect current best practice but might require a change in some settings as practice is currently variable. Although there is variation in current practice, this

protocol is already being widely implemented in most trusts and so is not expected to result in a substantial resource impact to the NHS in England.

# 1.11 The committee's discussion of the evidence

## 1.11.1 Interpreting the evidence

### 1.11.1.1 The outcomes that matter most

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

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

### 1.11.1.2 The quality of the evidence

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

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

### 1.11.1.3 Benefits and harms

The committee noted that for the recommended strategy there was no evidence of blood pressure lowering causing harm in people after intracerebral haemorrhage with high blood pressure, with no signal of increased neurological deterioration due to reduced blood flow to the brain. Rapid blood pressure lowering did not adversely affect renal function in the majority of trials except in one which used a more aggressive blood pressure reduction protocol, with a target for systolic blood pressure of 110-139 mmHg and treatment started within 4.5 hours of onset, where there was evidence of increased renal failure with 19 more cases per 1000 compared to the control rate of 14 per 1000. The committee agreed that rapid lowering of systolic blood pressure is safe when using less aggressive protocols, and so have included detail on the blood pressure target and time window in the recommendation. While there was no clear difference in the pooled common odds ratio from the mRS ordinal shift analysis, the committee considered the absolute benefit demonstrated for the dichotomous outcome of mRS 0 to 2 to be sufficiently clinically meaningful to recommend systolic blood pressure lowering. These outcomes were supported by the evidence for quality of life at 90 days from the INTERACT2 trial and haematoma growth at 24 hours, which also favoured rapid treatment with no indication of harm. In accordance with evidence from the trials where rapid systolic blood pressure lowering was found to be safe it was recommended that treatment should start within 6 hours and continue for 7 days, and that the target should be below 140 mmHg. It was noted that this should be a strong recommendation because:

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

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

Similarly, although the majority of the evidence was from trials that did not include people with a systolic blood pressure over 220 mmHg the committee agreed that current practice is to implement controlled systolic blood pressure reduction as part of initiating secondary prevention as soon as possible. The committee also believed that this should not pose any greater harm than rapid systolic blood pressure reduction in those with a systolic blood pressure below 220 mmHg.

Overall, it was agreed that although there was little or no evidence for those presenting beyond 6 hours and those with a systolic blood pressure over 220 mmHg, it is logical to extrapolate from the available data to these groups and that guidance on how to manage these patients is required. In those with BP over 220 mmHg, rapid lowering to a target of 140mmHg within 2 hours has not been shown to be safe. In those presenting more than 6 hours from symptoms, rapid lowering to a target of 140mmHg within 2 hours has not been shown to be effective. However, in the absence of direct evidence for this group it was agreed not to recommend a change to current practice, and so systolic blood pressure reduction should be controlled rather than rapid.

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

### 1.1.13.2 Cost effectiveness and resource use

No relevant economic evaluations were identified which addressed the cost effectiveness of measures to manipulate systolic blood pressure versus treatment as usual in people with acute intracerebral haemorrhage. The committee expressed that there is variation between centres and consultants in current practice of systolic blood pressure lowering. Intravenous labetalol is commonly used as the first-line treatment for systolic blood pressure lowering in the UK. In the absence of relevant economic evaluations, the committee considered the unit costs of systolic blood pressure lowering agents. Labetalol 100mg/20ml solution for injection ampoules currently have a unit cost of £10.44. For a two-day course of 50 mg/hour intravenous labetalol, the current total cost per person is £250.66.

Upon considering the cost of treatment with intravenous labetalol, the committee considered that the clinical evidence indicated that treatment of approximately 40 people within 6 hours of acute intracerebral haemorrhage would yield an additional person with an mRS score of 0-2 at 90 days. At a total cost of £250.66 per person, the total cost of treating 40 people with haemorrhagic stroke is £9,641. In addition, the clinical evidence associated with rapid blood pressure lowering, found an absence of harm and a higher quality of life at 90 days in the intervention group than in the control. The committee noted, however, that very aggressive systolic blood pressure lowering (e.g. from a high baseline to a low target, as in ATACH2)

could have deleterious effects on renal function and consequently impact long term costs and quality of life.

The cost of treating 40 people with haemorrhagic stroke was interpreted in light of the costs, obtained from the literature, of being in mRS 0-2 compared with mRS 3-5. A cost utility analysis from the UK NHS perspective obtained annual costs (adjusted to 2013/2014 UK pounds) of being in the independent and dependent health states from a second study. This study applied UK NHS reference costs to the resource use from a UK, single centre randomised controlled trial to calculate the costs of stroke. It did not differentiate between haemorrhagic and ischaemic strokes and excluded very mild and very severe strokes, as defined by the Barthel Index. The study assumed that mild and moderate strokes correspond to independent stroke survivors and severe stroke described the cost of dependent stroke survivors. These studies indicate that estimated cost savings of £7,813 within three months of stroke onset and £10,182 over the first year after stroke could be made by shifting one person from mRS 3-5 to mRS 0-2. Over a lifetime time horizon, further cost savings are therefore likely to be accrued. The committee therefore considered that the cost of treating 40 people with intravenous labetalol (£9,641) would be recuperated over a year and cost saving over a lifetime time horizon.

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

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

The committee noted that the unit costs of oral systolic blood pressure lowering agents are currently significantly lower than those of intravenous systolic blood pressure lowering agents. The committee stressed that after an intravenous course with an approximate duration of up to two days, people with haemorrhagic stroke should be maintained on oral systolic blood pressure drugs when possible. Oral systolic blood pressure medicines should be introduced as soon as possible to prevent rebound of systolic blood pressure when the intravenous course is discontinued and maintain smooth blood pressure control beyond the hyperacute phase.

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

### 1.11.3 Other factors the committee took into account

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

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

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# 1 Appendices

# 2 Appendix A: Review protocols

3 **Table 7: Review protocol: Maintenance or restoration of homeostasis**

| Field | Content |
|---|---|
| Review question | What is the safety and efficacy of measures to lower blood pressure versus standard treatment in people with acute intracerebral haemorrhage? |
| Type of review question | Intervention<br>A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline. |
| Objective of the review | To identify if there is a benefit to lowering blood pressure in intracranial haemorrhage |
| Eligibility criteria – population / disease / condition / issue / domain | People aged over 16 with acute intracerebral haemorrhage and high blood pressure at the time of assessment |
| Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s) | Intensive blood pressure reduction (for example to a target of <140 mmHg systolic) within 48 hours with:<br>• Calcium antagonists (e.g. intravenous isradipine, oral nimodipine, oral and intravenous nimodipine, urapidil, flunarizine, nicardipine and oral PY108-608)<br>• Intravenous or transdermal glyceryl trinitrate (GTN)<br>• Angiotensin II antagonist (e.g. cilextil)<br>• Beta-blockers (e.g. atenolol, propranolol and labetalol)<br>All drug classes to be pooled for analysis |
| Eligibility criteria – comparator(s) / control or reference (gold) standard | Standard care (for example standard blood pressure lowering to a target of 140-180 mmHg systolic)<br>Placebo or no treatment |
| Outcomes and prioritisation | <u>Critical</u><br>Mortality at 24 hours and 90 days<br>mRS score at 90 days and 1 year<br><br><u>Important</u><br>Symptomatic cerebral ischemia at 24 hours<br>Haemorrhage expansion at 24 hours<br>Neurological deterioration at 24 hours<br>Adverse events (renal failure, cord infarction, myocardial infarction) at 90 days<br>Quality of life (both health- and social-related quality) at 90 days<br>Percentage achieving blood pressure target |
| Eligibility criteria – study design | Randomised controlled trials<br>Systematic reviews and meta-analyses of the above |
| Other inclusion exclusion criteria | Inclusion<br><br>Settings: Emergency department, critical care, hyper acute stroke unit |
| Proposed sensitivity / subgroup analysis, | <u>Subgroups to investigate if heterogeneity is present</u><br>Lobar vs deep (haematoma location)<br>Time to treatment (within 6 hours vs >6 hours of stroke onset) |

| | |
|---|---|
| or meta-regression | Age <80/>80 years<br>Volume of haemorrhage (< 15, 15 – 30, >30 $ml^3$)<br>NIHSS <15/ >15 |
| Selection process – duplicate screening / selection / analysis | Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol. |
| Data management (software) | • EndNote will be used for reference management, sifting, citations and bibliographies.<br>• EviBASE will be used for data extraction and quality assessment for clinical studies.<br>• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).<br>• GRADEpro will be used to assess the quality of evidence for each outcome. |
| Information sources – databases and dates | Databases: Medline, Embase, Cochrane Library,<br>Language: Restrict to English only<br>Date restriction: 2007<br><br>Key papers<br>1. Potter J, Mistri A, Brodie F et al. (2009) Controlling hypertension and hypotension immediately post stroke (CHHIPS)--a randomised controlled trial. Health Technology Assessment (Winchester, England) 13:iii-ixi.<br>2. Wilson EC, Ford GA, Robinson T et al. (2010) Controlling hypertension immediately post stroke: a cost utility analysis of a pilot randomised controlled trial. Cost Effectiveness & Resource Allocation 8:3.<br>3. Geeganage C and Bath PM. (2008) Interventions for deliberately altering blood pressure in acute stroke. [Review] [92 refs][Update of Cochrane Database Syst Rev. 2001;(3):CD000039; PMID: 11686949]. Cochrane Database of Systematic Reviews CD000039.<br>4. Geeganage C and Bath PM. (2010) Vasoactive drugs for acute stroke. [Review] [183 refs][Update of Cochrane Database Syst Rev. 2000;(4):CD002839; PMID: 11034772]. Cochrane Database of Systematic Reviews CD002839.<br>5. Anderson CS, Huang Y, Wang JG et al. (2008) Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurology 7:391-399.<br>6. Anderson CS, Huang Y, Arima H et al. (2010) Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). Stroke 41:307-312.<br>7. Koch S, Romano JG, Forteza AM et al. (2008) Rapid blood pressure reduction in acute intracerebral hemorrhage: feasibility and safety. Neurocritical Care 8:316-321.<br>8. Jusufovic M, Sandset EC, Bath PM et al. (2014) Blood pressure-lowering treatment with candesartan in patients with acute hemorrhagic stroke. Stroke 45:3440-3442. |
| Identify if an update | Yes<br>Question in CG68: What is the safety and efficacy of measures to manipulate blood pressure versus treatment as usual in patients with acute stroke?<br><br>Recommendations from CG68<br>1.5.3.1 Anti-hypertensive treatment in people with acute stroke is recommended only if there is a hypertensive emergency with one or more of the following serious concomitant medical issues: |

| | |
|---|---|
| | • hypertensive encephalopathy<br>• hypertensive nephropathy<br>• hypertensive cardiac failure/myocardial infarction<br>• aortic dissection<br>• pre-eclampsia/eclampsia<br>• intracerebral haemorrhage with systolic blood pressure over 200 mmHg.<br>1.5.3.2 Blood pressure reduction to 185/110 mmHg or lower should be considered in<br>people who are candidates for thrombolysis. |
| Author contacts | https://www.nice.org.uk/guidance/indevelopment/gid-ng10071 |
| Highlight if amendment to previous protocol | For details please see section 4.5 of Developing NICE guidelines: the manual. |
| Search strategy – for one database | For details please see appendix B |
| Data collection process – forms / duplicate | A standardised evidence table format will be used, and published as appendix D of the evidence report. |
| Data items – define all variables to be collected | For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables). |
| Methods for assessing bias at outcome / study level | Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual<br>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/<br>[Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.] |
| Criteria for quantitative synthesis | For details please see section 6.4 of Developing NICE guidelines: the manual. |
| Methods for quantitative analysis – combining studies and exploring (in)consistency | For details please see the separate Methods report for this guideline. |
| Meta-bias assessment – publication bias, selective reporting bias | For details please see section 6.2 of Developing NICE guidelines: the manual. |
| Confidence in cumulative evidence | For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual. |
| Rationale / context – what is known | For details please see the introduction to the evidence review. |
| Describe contributions of authors and guarantor | A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual.<br>Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where |

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

1

2 **Table 8: Health economic review protocol**

| Review question | All questions – health economic evidence |
|---|---|
| **Objectives** | To identify health economic studies relevant to any of the review questions. |
| **Search criteria** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.<br>• Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).<br>• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• Studies must be in English. |
| **Search strategy** | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant. |
| **Review strategy** | Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br><br>Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.<br>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[37]<br><br>**Inclusion and exclusion criteria**<br>• If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.<br>• If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. |

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

**Where there is discretion**

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

The health economist will be guided by the following hierarchies.

*Setting:*

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

*Health economic study type:*

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

*Year of analysis:*

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

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

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

1
2

# Appendix B: Literature search strategies

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

*For more detailed information, please see the Methodology Review*. [Add cross reference]

## B.1 Clinical search literature search strategy

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

**Table 9: Database date parameters and filters used**

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

**Medline (Ovid) search terms**

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

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

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

1 **Embase (Ovid) search terms**

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

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

**Cochrane Library (Wiley) search terms**

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

# B.2 Health Economics literature search strategy

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

**Table 10: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 01 January 2007 – 06 August 2018 | Exclusions<br>Health economics studies |

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

1 **Medline (Ovid) search terms**

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

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

1 **Embase (Ovid) search terms**

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

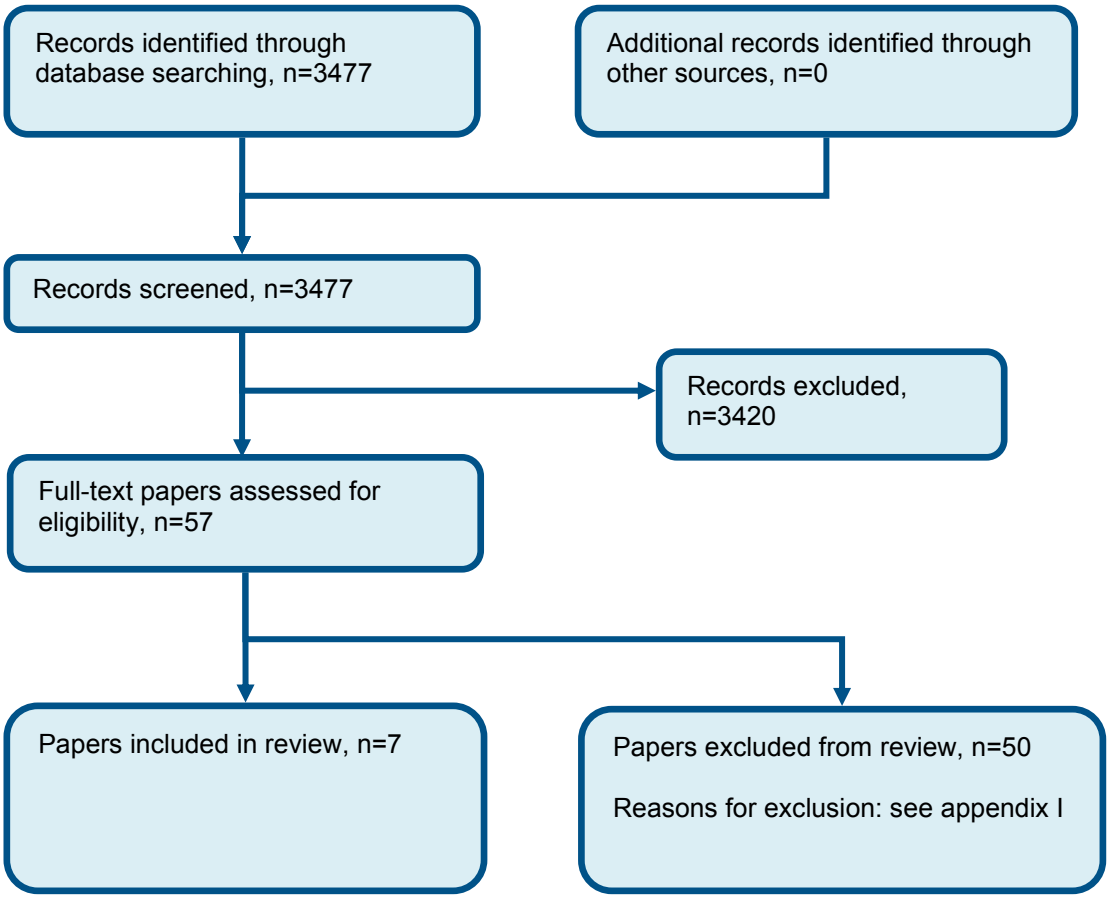
| | |
|---|---|
| 12. | ((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab. |
| 13.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

## NHS EED and HTA (CRD) search terms

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

# Appendix C: Clinical evidence selection

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



# Appendix D: Clinical evidence tables

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

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| Further population details | 1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable |
| Indirectness of population | No indirectness |
| Interventions | (n=500) Intervention 1: Intensive therapy. Reduce and maintain the hourly minimum systolic blood pressure in range of 110 to 139 mmHg. Duration 24 hours. Concurrent medication/care: Standard therapy. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours<br><br>(n=500) Intervention 2: Conservative therapy. Reduce and maintain the hourly minimum systolic blood pressure in range of 140 to 179 mmHg. Duration 24 hour. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours |
| Funding | Academic or government funding (National Institute of Neurological Disorders and Stroke, Intramural Research Fund for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center.<br><br>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.<br>) |

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

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 33/481, Group 2: 34/480
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19; Group 2 Number missing: 20

Protocol outcome 2: EQ-5D utility index score at 90 days
- Actual outcome: EQ-5D utility index score at 90 days; Group 1: median (IQR): 0.7 (-0.1 to 1.0); group 2: median (IQR): 0.7 (0 to 1.0).

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| Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19; Group 2 Number missing: 20<br><br>Protocol outcome 3: EQ-5D visual analogue scale at 90 days<br>- Actual outcome: EQ-5D visual analogue scale at 90 days; ; Group 1: median (IQR): 62.5 (0 to 100); group 2: median (IQR): 70 (0 to 100).<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19; Group 2 Number missing: 20<br><br>Protocol outcome 4: Neurological decline at 24 hours<br>- Actual outcome: Neurological decline at 90 days; Group 1: 55/500, Group 2: 40/500<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 5: Haematoma growth at 24 hours<br>- Actual outcome: Haematoma growth at 90 days; Group 1: 85/450, Group 2: 104/426<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP at presentation in ED Mean (SD) intensive 200 (27.1), conservative 201 (26.9); Group 1 Number missing: 19, Reason: No CT; Group 2 Number missing: 20, Reason: No CT | |
| Protocol outcomes not reported by the study | Mortality at 24 hours; mRS score at 90 days; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; mRS score at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS score 0-3 vs 4-6 at 90 days; Renal failure at 90 days; Myocardial infarction at 90 days; Neurological decline at 90 days; Barthel index at 90 days; mRS score at 1 year; EQ-5D at 90 days |

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

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

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

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 42/310, Group 2: 47/319
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: mRS score at 90 days
- Actual outcome: mRS score at 90 days; ; Adjusted common OR: 1.04 (0.78 to 1.38), p=0.81;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Myocardial infarction at 90 days
- Actual outcome: Myocardial infarction at 90 days; Group 1: 1/310, Group 2: 2/319
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD) intensive 172.1 (19.4) versus conservative 172.3 (19.9), diastolic blood pressure mmHg, mean (SD) intensive 93.4 (13.9) versus conservative 94.0 (13.1), Treated hypertension intensive 40.2% versus 39.0%; Group 1 Number missing: ;

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

| Study | ICH-ADAPT trial: Butcher 2013[15] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=78) |
| Countries and setting | Conducted in Canada; Setting: ED, Secondary care |
| Line of therapy | 1st line |
| Duration of study | Intervention + follow up: 24 hours, follow-up 90 days |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: CT |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | ≥18 years of age, with spontaneous cerebral haemorrhage diagnosed on noncontrast computed tomography (CT) <24 hours after onset. SBP was ≥150 mm Hg (≥2 readings ≥5 minutes apart) |
| Exclusion criteria | evidence of secondary cerebral haemorrhage (vascular malformation), planned surgical resection, or contraindications to CT perfusion (CTP; eg, contrast allergy or renal impairment) |
| Recruitment/selection of patients | ED |
| Age, gender and ethnicity | Age - Mean (SD): Intensive 70.7 (12.5), conservative therapy 68.7 (11.1). Gender (M:F): Intensive 67% male, conservative therapy 78%. Ethnicity: Not reported |
| Further population details | 1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable |
| Indirectness of population | No indirectness |

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| Interventions | (n=39) Intervention 1: Intensive therapy. Intensive therapy. Duration 24 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable<br><br>(n=36) Intervention 2: Conservative therapy. Conservative care. Duration 24 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable |
| Funding | Academic or government funding (Alberta Innovates Health Solutions, Heart and Stroke Foundation of Canada) |

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

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 7/37, Group 2: 4/39
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Very serious indirectness, Comments: Mortality at 30 days not 90 days; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated

Protocol outcome 2: mRS score at 90 days
- Actual outcome: mRS score at 90 days; 0 to 6 Top=High is poor outcome;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated

Protocol outcome 3: Neurological decline at 24 hours
- Actual outcome: Neurological decline at 2 hours; Group 1: 3/37, Group 2: 2/36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Decline at 2 hours not 24 hours; Baseline details: Systolic BP mmHg, mean (SD) intensive 182 (20), conservative 184 (25), diastolic , BP mmHg, mean (SD) intensive 93 (19), conservative 97 (23), Prior hypertension intensive 67%, conservative 27%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: Not stated

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

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

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

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

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 166/1394, Group 2: 170/1421
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4% conservative 72.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 2: Recurrent and /or extended stroke at 90 days
- Actual outcome: Recurrent stroke at 90 days; Group 1: 12/1399, Group 2: 12/1430
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 72.5%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: EQ-5D at 90 days
- Actual outcome: EQ-5D at 90 days; Group 1: mean 0.6 (SD 0.39); n=1394, Group 2: mean 0.55 (SD 0.4); n=1421
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 72.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 4: mRS score 0-2 vs 3-6 at 90 days
- Actual outcome: mRS score 0-2 vs 3-6 at 90 days; Group 1: 663/1382, Group 2: 627/1412; ordinal analysis: pooled OR: 0.87 (0.77 to 1.00)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 5: mRS score 0-3 vs 4-6 at 90 days
- Actual outcome: mRS score 0-3 vs 4-6 at 90 days; Group 1: 883/1382, Group 2: 861/1412
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 6: Neurological decline at 24 hours
- Actual outcome: Neurological decline at 90 days; Group 1: 198/1369, Group 2: 211/1395
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mean (SD) intensive 19 (17), conservative 179 (17), diastolic blood pressure mean (SD) intensive 101 (15), conservative 101 (15), history of hypertension intensive 72.4 %, conservative 77.5%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 9, Reason: Not stated

Protocol outcome 7: Haematoma growth at 24 hours

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

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

| | |
|---|---|
| Further population details | 1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not applicable 4. Volume of haemorrhage: Not applicable |
| Indirectness of population | No indirectness |
| Interventions | (n=201) Intervention 1: Conservative therapy. Conservative therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable<br><br>(n=203) Intervention 2: Intensive therapy. Intensive therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours |
| Funding | Academic or government funding (National Health and Medical Research Council of Australia) |

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

Protocol outcome 1: Recurrent and /or extended stroke at 90 days
- Actual outcome: Recurrent stroke at 90 days; Group 1: 2/203, Group 2: 3/201
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 2: mRS score at 90 days
- Actual outcome: mRS score at 90 days; 0 to 6 Top=High is poor outcome; median (IQR) Group 1: 2 (1-4); group 2: 2 (1-4)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 2: EQ-5D at 90 days
- Actual outcome: EQ-5D at 90 days; OR; Median (range) intensive: 0.75 (0.52 to 1.00), conservative: 0.78 (0.59 to 1.00);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 3: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 21/202, Group 2: 25/200
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 4: Renal failure at 90 days
- Actual outcome: Renal failure at 90 days; Group 1: 4/203, Group 2: 2/201
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 5: Neurological decline at 24 hours
- Actual outcome: Neurological decline at 72 hours; Group 1: 31/203, Group 2: 30/201
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: Serious indirectness, Comments: 72 hours not 24 hours; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 1, Reason: Loss to follow-up; Group 2 Number missing: 1, Reason: Loss to follow-up

Protocol outcome 6: Haematoma growth at 24 hours
- Actual outcome: Haematoma growth at 24 hours; Group 1: 26/174, Group 2: 40/172
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Previous ischaemic stroke intensive versus conservative: 13% vs 19%, Previous ICH intensive versus conservative: 9% vs 13%, hypertension intensive versus conservative: 74% vs 74%; Group 1 Number missing: 27, Reason: Loss to follow-up; Group 2 Number missing: 29, Reason: Loss to follow-up

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

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

| | |
|---|---|
| Interventions | (n=21) Intervention 1: Intensive therapy. Intensive therapy. Duration 48 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): >6 hours (Within 8 hours).<br><br>(n=21) Intervention 2: Conservative therapy. Conservative therapy. Duration 48 hours. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): >6 hours (Within 8 hours). |
| Funding | Funding not stated |

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

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 3/21, Group 2: 3/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: mRS score at 90 days
- Actual outcome: mRS score at 90 days; Group 1: 10/21, Group 2: 8/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Renal failure at 90 days
- Actual outcome: Renal failure at 90 days; Group 1: 1/21, Group 2: 1/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Arrival MAP mmHg mean (SD) intensive 144.3 (15.8), conservative 150.7 (20.1), Prior hypertension intensive 18%, conservative 19%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Neurological decline at 90 days
- Actual outcome: Neurological decline at 48 hours; Group 1: 2/21, Group 2: 1/21
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

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

| Study | PATICH trial: Zheng 2017[62] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=201) |
| Countries and setting | Conducted in China; Setting: ED, Secondary care |
| Line of therapy | 1st line |
| Duration of study | Intervention + follow up: 7 days + 90 days |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: CT / MRI |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Aged ≥18 years, had computed tomography- or magnetic resonance imaging–confirmed sICH with elevated systolic BP between 150 and 220 mm Hg (at least 2 measurements) and were able to receive surgery within 24 hours after ictus |
| Exclusion criteria | Definite indication or contraindications to antihypertensives, secondary intracerebral hemorrhage, a Glasgow Coma Scale score between 3 and 5, a definite contraindication to operation, advanced dementia or disability before ICH onset, or comorbidities that would interfere with the outcome assessment and follow-up. |
| Recruitment/selection of patients | ED |
| Age, gender and ethnicity | Age - Mean (SD): Intensive 54 (14), conservative 55 (12). Gender (M:F): Male sex intensive 75%, conservative 69%. Ethnicity: Chinese |
| Further population details | 1. Age <80 vs >/=80 years: Not applicable 2. Lobar vs deep haematoma location: Not stated / Unclear 3. NIHSS: Not stated / Unclear 4. Volume of haemorrhage: Not stated / Unclear |

| | |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (n=101) Intervention 1: Intensive therapy. Intensive therapy. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Within 6 hours<br><br>(n=101) Intervention 2: Conservative therapy. Conservative care. Duration 7 days. Concurrent medication/care: Standard care. Indirectness: No indirectness<br>Further details: 1. Time to treatment (within 6 hours vs >6 hours): Not applicable |
| Funding | Academic or government funding (The National Key Technology R&D Program for the 12th Five-year Plan of P.R. China ) |

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

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 13/96, Group 2: 18/99
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD), intensive 181 (16), conservative 183 (19), diastolic blood pressure mmHg, mean (SD) intensive 103 (12), conservative 104 (13), Prior hypertension intensive 51% conservative 59%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 2, Reason: Not stated

Protocol outcome 2: EQ-5D utility index score at 90 days
- Actual outcome: EQ-5D utility score at 90 days; Group 1: mean 0.54 (SD 0.23); n=96, Group 2: mean 0.56 (SD 0.23); n=99
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systolic blood pressure mmHg, mean (SD), intensive 181 (16), conservative 183 (19), diastolic blood pressure mmHg, mean (SD) intensive 103 (12), conservative 104 (13), Prior hypertension intensive 51% conservative 59%; Group 1 Number missing: 5, Reason: Not stated; Group 2 Number missing: 2, Reason: Not stated

| | |
|---|---|
| Protocol outcomes not reported by the study | Mortality at 24 hours; mRS score at 90 days; Recurrent and /or extended stroke at 24 hours; Recurrent and /or extended stroke at 90 days; Adverse events at 24 hours; Adverse events at 90 days; Quality of life at 90 days; Quality of life at 24 hours; EQ-5D visual analogue scale at 90 days; mRS score at 90 days; mRS score 0-2 vs 3-6 at 90 days; mRS |

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

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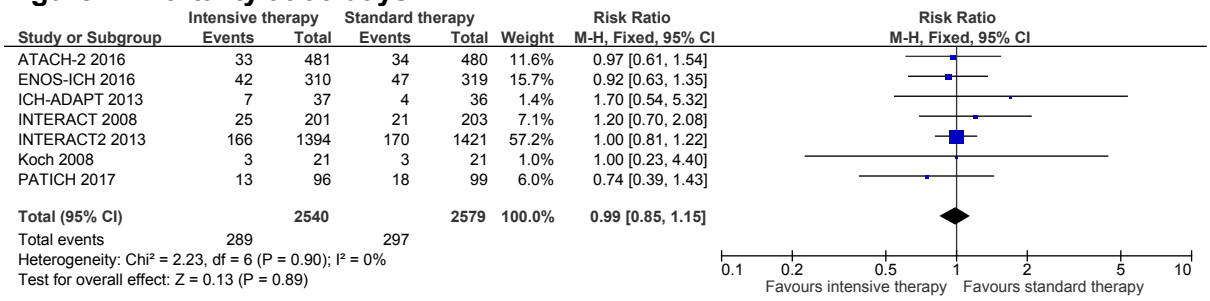
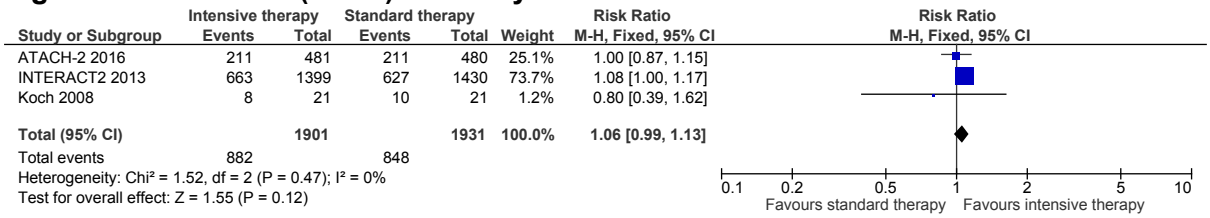
# Appendix E: Forest plots

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

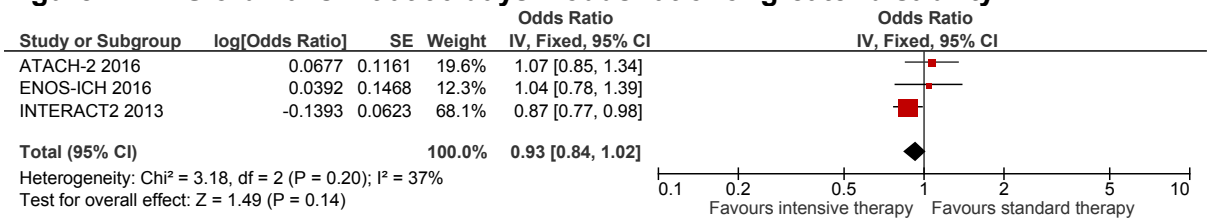
### Figure 2: Mortality at 90 days



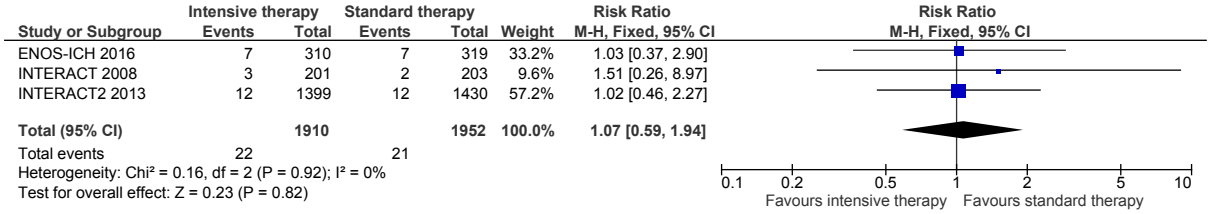

### Figure 3: mRS score (0 to 2) at 90 days




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



## Figure 5: Recurrent stroke at 90 days

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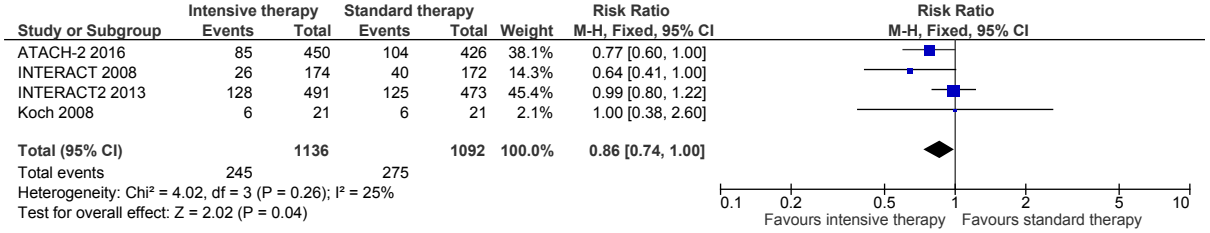
## Figure 6: Haematoma growth at 24 hours

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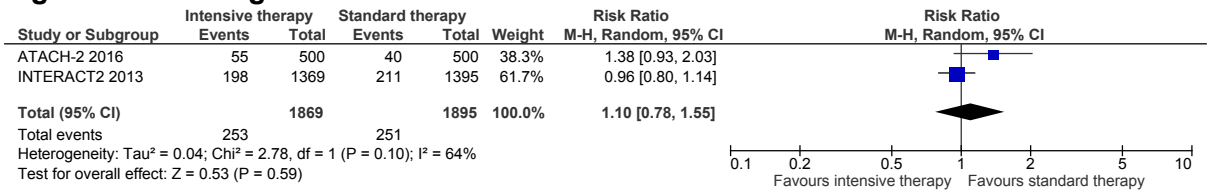
## Figure 7: Neurological deterioration at 24 hours

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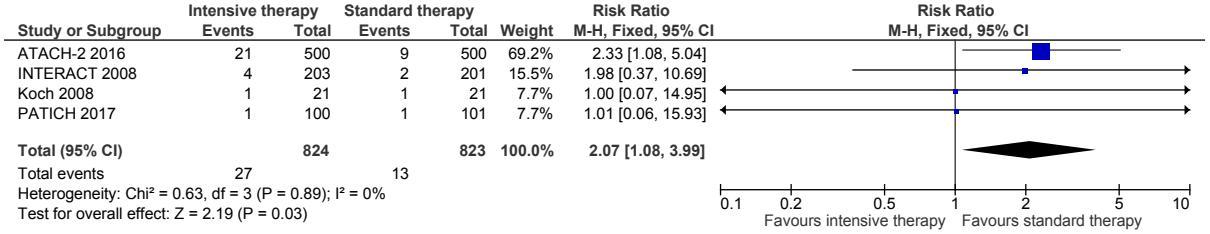
## Figure 8: Renal failure at 90 days

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## Figure 9: Myocardial infarction at 90 days

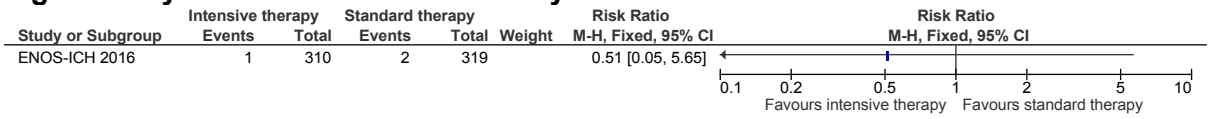

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**Figure 10: EQ-5D utility score at 90 days**

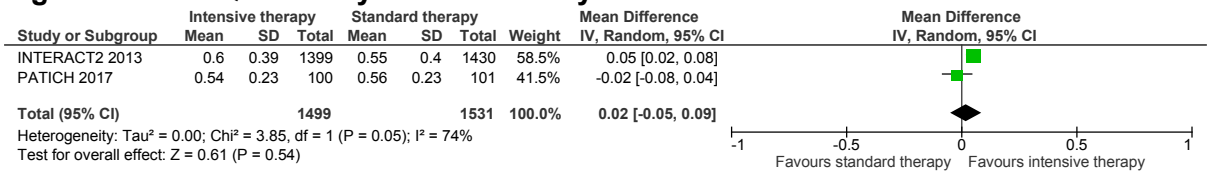


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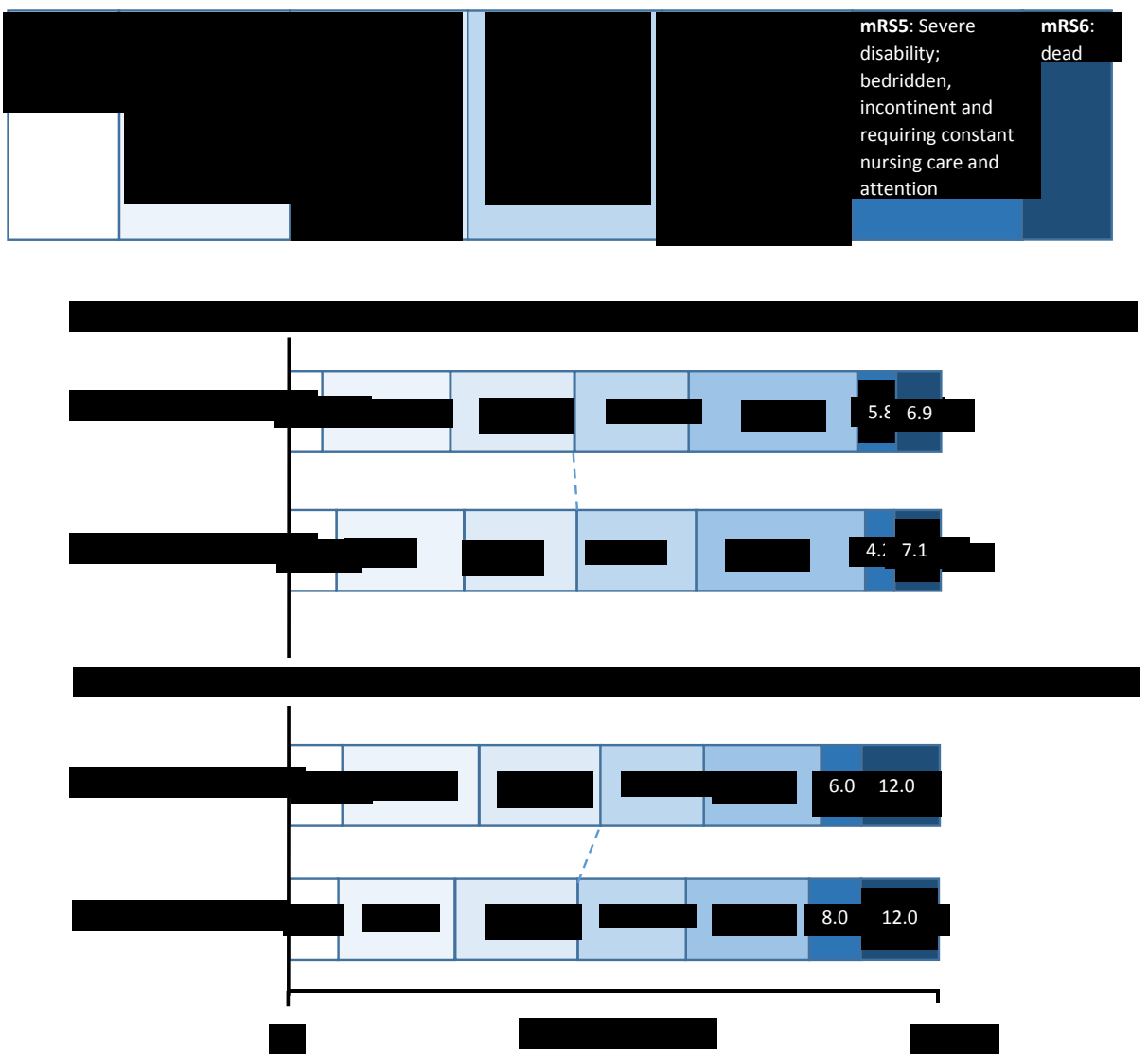
**Figure 11: mRS ordinal shift at 90 days**

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# Appendix F: GRADE tables

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

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

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

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Heterogeneity I2=63% not explained by subgroup analysis because only 2 studies included in the analysis
[4] Heterogeneity I2=74% not explained by subgroup analysis because only 2 studies included in the analysis

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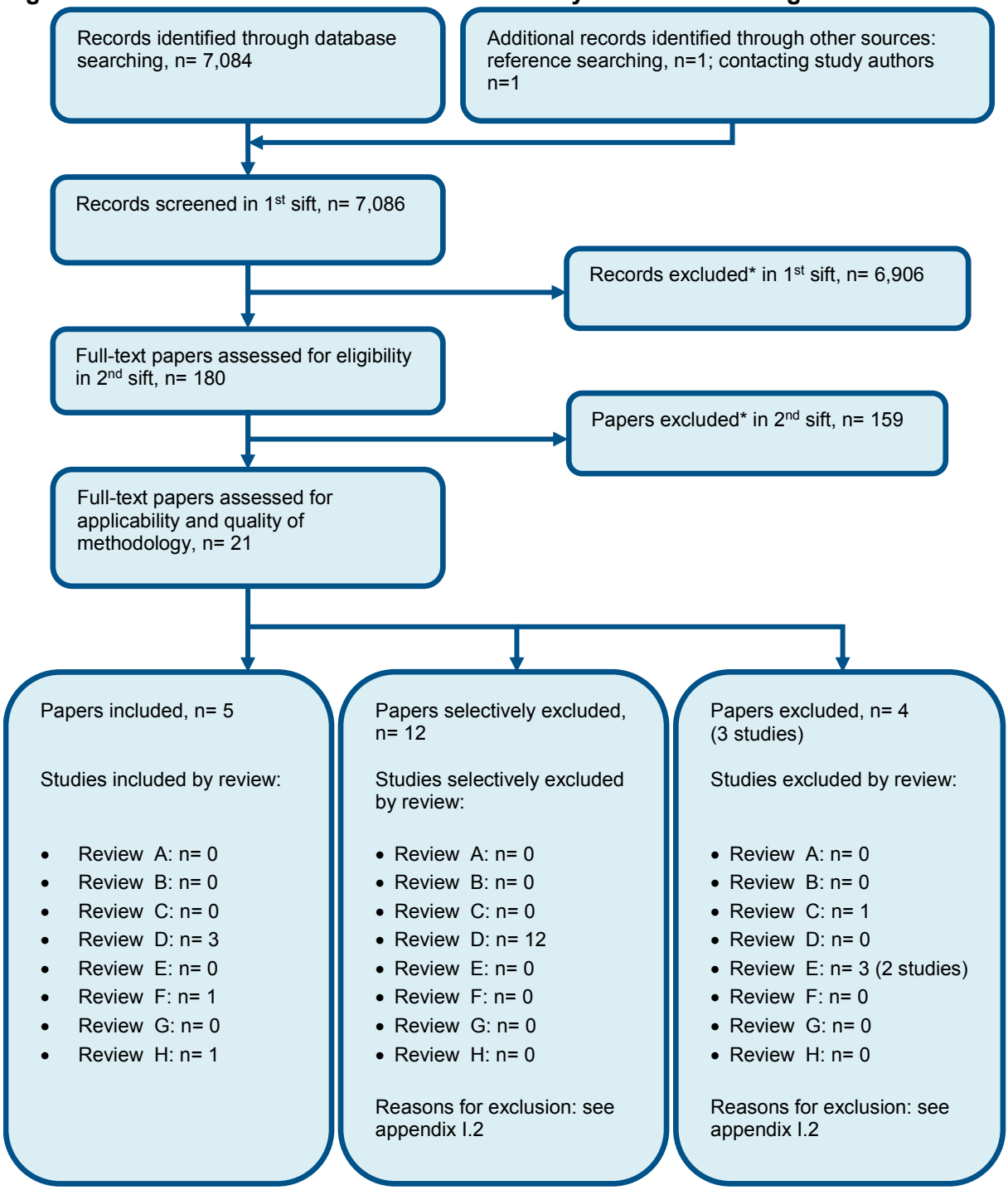
# Appendix G: Health economic evidence selection

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




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

# Appendix H: Excluded studies

## H.1 Excluded clinical studies

**Table 12: Studies excluded from the clinical review**

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

| Study | Exclusion reason |
|---|---|
| Sandset 2011[45] | Mixed ischaemic and intracerebral haemorrhage stroke population |
| Sandset 2012[46] | Mixed ischaemic and intracerebral haemorrhage stroke population |
| Sato 2014[47] | No outcomes of interest |
| Schrader 2003[48] | Not review population |
| Shi 2017[49] | SR did not identify one study |
| Song 2016[50] | Post-hoc analysis |
| Starke 2016[51] | Not RCT, narrative review |
| Tsivgoulis 2014[53] | Systematic review: quality assessment is inadequate |
| Wang 2014[54] | Mixed ischaemic and intracerebral haemorrhage stroke population |
| Willmot 2004[56] | SR on mixed ischaemic and intracerebral haemorrhage stroke population |
| Willmot 2006[55] | Mixed ischaemic and intracerebral haemorrhage stroke population |
| Woodhouse 2017[58] | Mixed ischaemic and intracerebral haemorrhage stroke population |
| Xu 2011[59] | Not English language, Chinese |
| Ye 2017[60] | Not RCT, study protocol |
| Zhang 2017[61] | Not review population |

## H.2 Excluded health economic studies

**Table 13: Studies excluded from the health economic review**

| Reference | Reason for exclusion |
|---|---|
| Tavakoli 2009 [52] | This study was assessed as not applicable as the intervention was not delivered within 48 hours of stroke onset. |
| Potter 2009, Wilson 2010 [39, 57] | This study was assessed as not applicable as the population was mixed ischaemic stroke and haemorrhagic stroke. The intervention was also not delivered in the hyper-acute phase post-stroke. |

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