Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

Maagaard M, Karlsson WK, Ovesen C, Gluud C, Jakobsen JC
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Interventions for altering blood pressure in people with acute subarachnoid haemorrhage

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Editorial group: Cochrane Stroke Group.


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ABSTRACT

Background
Subarachnoid haemorrhage has an incidence of up to nine per 100,000 person-years. It carries a mortality of 30% to 45% and leaves 20% dependent in activities of daily living. The major causes of death or disability after the haemorrhage are delayed cerebral ischaemia and rebleeding. Interventions aimed at lowering blood pressure may reduce the risk of rebleeding, while the induction of hypertension may reduce the risk of delayed cerebral ischaemia. Despite the fact that medical alteration of blood pressure has been clinical practice for more than three decades, no previous systematic reviews have assessed the beneficial and harmful effects of altering blood pressure (induced hypertension or lowered blood pressure) in people with acute subarachnoid haemorrhage.

Objectives
To assess the beneficial and harmful effects of altering arterial blood pressure (induced hypertension or lowered blood pressure) in people with acute subarachnoid haemorrhage.

Search methods
We searched the following from inception to 8 September 2020 (Chinese databases to 27 January 2019): Cochrane Stroke Group Trials register; CENTRAL; MEDLINE; Embase; five other databases, and five trial registries. We screened reference lists of review articles and relevant randomised clinical trials.

Selection criteria
Randomised clinical trials assessing the effects of inducing hypertension or lowering blood pressure in people with acute subarachnoid haemorrhage. We included trials irrespective of publication type, status, date, and language.

Data collection and analysis
Two review authors independently extracted data. We assessed the risk of bias of all included trials to control for the risk of systematic errors. We performed trial sequential analysis to control for the risks of random errors. We also applied GRADE. Our primary outcomes were death from all causes and death or dependency. Our secondary outcomes were serious adverse events, quality of life, rebleeding,
delayed cerebral ischaemia, and hydrocephalus. We assessed all outcomes closest to three months’ follow-up (primary point of interest) and maximum follow-up.

Main results

We included three trials: two trials randomising 61 participants to induced hypertension versus no intervention, and one trial randomising 224 participants to lowered blood pressure versus placebo. All trials were at high risk of bias. The certainty of the evidence was very low for all outcomes.

Induced hypertension versus control

Two trials randomised participants to induced hypertension versus no intervention. Meta-analysis showed no evidence of a difference between induced hypertension versus no intervention on death from all causes (risk ratio (RR) 1.60, 95% confidence interval (CI) 0.57 to 4.42; P = 0.38; I² = 0%; 2 trials, 61 participants; very low-certainty evidence). Trial sequential analyses showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more.

Meta-analysis showed no evidence of a difference between induced hypertension versus no intervention on death or dependency (RR 1.29, 95% CI 0.78 to 2.13; P = 0.33; I² = 0%; 2 trials, 61 participants; very low-certainty evidence). Trial sequential analyses showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more.

One trial (41 participants) reported quality of life using the Stroke Specific Quality of Life Scale. The induced hypertension group had a median of 47 points (interquartile range 35 to 55) and the no-intervention group had a median of 49 points (interquartile range 35 to 55). The certainty of evidence was very low.

One trial (41 participants) reported rebleeding. Fisher’s exact test (P = 1.0) showed no evidence of a difference between induced hypertension and no intervention on rebleeding. The certainty of evidence was very low. Trial sequential analysis showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more.

One trial (20 participants) reported delayed cerebral ischaemia. Fisher’s exact test (P = 1.0) showed no evidence of a difference between induced hypertension and no intervention on delayed cerebral ischaemia. The certainty of the evidence was very low. Trial sequential analysis showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more.

None of the trials randomising participants to induced hypertension versus no intervention reported on hydrocephalus. No subgroup analyses could be conducted for trials randomising participants to induced hypertension versus no intervention.

Lowered blood pressure versus control

One trial randomised 224 participants to lowered blood pressure versus placebo. The trial only reported on death from all causes. Fisher’s exact test (P = 0.058) showed no evidence of a difference between lowered blood pressure versus placebo on death from all causes. The certainty of evidence was very low.

Authors’ conclusions

Based on the current evidence, there is a lack of information needed to confirm or reject minimally important intervention effects on patient-important outcomes for both induced hypertension and lowered blood pressure. There is an urgent need for trials assessing the effects of altering blood pressure in people with acute subarachnoid haemorrhage. Such trials should use the SPIRIT statement for their design and the CONSORT statement for their reporting. Moreover, such trials should use methods allowing for blinded altering of blood pressure and report on patient-important outcomes such as mortality, rebleeding, delayed cerebral ischaemia, quality of life, hydrocephalus, and serious adverse events.

PLAIN LANGUAGE SUMMARY

Assessment of different treatments for altering blood pressure in people with acute subarachnoid haemorrhage

Background

Every year subarachnoid haemorrhage, a type of stroke caused by bleeding into the space surrounding the brain, affects up to nine people per 100,000 population. Mortality (death) of subarachnoid haemorrhage is 30% to 45%, and 20% of survivors are left dependent in activities of daily living. Currently, short-term treatment may involve changing blood pressure and either inducing hypertension (that is, increasing blood pressure), or lowering blood pressure; however, the beneficial and harmful effects of blood pressure alteration in people with acute subarachnoid haemorrhage are unclear.

Review question

Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)
Our aim was to assess the beneficial and harmful effects of altering blood pressure in people with acute subarachnoid haemorrhage.

**Search date**
We searched scientific databases from their inception to September 2020.

**Study characteristics**
We identified three randomised clinical trials (studies where people are randomly put into one of two or more treatment groups) assessing blood pressure alterations in people with acute subarachnoid haemorrhage. Two randomised clinical trials enrolling 61 participants compared induced hypertension with placebo (a pretend treatment) or no treatment. One randomised clinical trial enrolling 224 participants compared lowered blood pressure with placebo. We used trial sequential analysis to estimate the number of participants (amount of information) needed to reject or detect important treatment effects. Trial sequential analysis showed that there was a lack of information for all outcomes. All trials were at high risk of bias and we were very unsure about the results.

**Key results and conclusion**
Our review shows that there is a lack of information about the important treatment effects of induced hypertension or lowered blood pressure in people with acute subarachnoid haemorrhage. Therefore, the beneficial and harmful effects could not be thoroughly assessed. There is an urgent need for randomised trials assessing the effects of altering blood pressure in people with acute subarachnoid haemorrhage, reporting on patient-important outcomes such as mortality, serious side effects, rebleeding, delayed cerebral ischaemia (reduced blood flow to the brain), quality of life, and hydrocephalus.
### SUMMARY OF FINDINGS

**Summary of findings 1. Induced hypertension versus placebo or no intervention for people with acute subarachnoid haemorrhage**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (trials)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Assumed risk (no intervention)</strong></td>
<td><strong>Corresponding risk (induced hypertension)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from all causes (primary outcome)</td>
<td>133 per 1000</td>
<td>225 per 1000</td>
<td>RR 1.60 (0.57 to 4.42)</td>
<td>61 (2 trials)</td>
<td>☢☢☢☢</td>
</tr>
<tr>
<td>Death or dependency (primary outcome)</td>
<td>366 per 1000</td>
<td>483 per 1000</td>
<td>RR 1.29 (0.78 to 2.13)</td>
<td>61 (2 trials)</td>
<td>☢☢☢</td>
</tr>
<tr>
<td>Proportion of participants with ≥ 1 serious adverse events</td>
<td>200 per 1000</td>
<td>451 per 1000</td>
<td>RR 2.24 (1.01 to 4.99)</td>
<td>61 (2 trials)</td>
<td>☢☢☢</td>
</tr>
<tr>
<td>Quality of life</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20 (1 trial)</td>
<td>☢☢☢</td>
</tr>
</tbody>
</table>
insufficient information to confirm or reject our predefined mean difference of the standard deviation divided by '2'. Approximately 11.8% of the required information size was reached with 20 participants in the analyses.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>48 per 1000 vs 100 per 1000</td>
<td>—</td>
<td>41 (1 trial)</td>
<td>☢☢☢</td>
<td>Only 1 study reported rebleeding. Therefore, no meta-analysis was conducted. TSA could not be conducted due to lack of information (only 0.48% of the required information size was reached with 41 participants in the analyses).</td>
</tr>
<tr>
<td>Delayed cerebral ischaemia</td>
<td>100 per 1000 vs 0 per 1000</td>
<td>RR 0.33 (0.02 to 7.32)</td>
<td>20 (1 trials)</td>
<td>☢☢</td>
<td>TSA could not be conducted due to lack of information (only 0.23% of the required information size was reached with 20 participants in the analysis).</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>No studies reported on hydrocephalus.</td>
</tr>
</tbody>
</table>

CI: confidence interval; RR: risk ratio; TSA: trial sequential analysis.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

ाDowngraded one level due to high risk of bias.

bDowngraded two levels due to imprecision.

Summary of findings 2. Lowered blood pressure versus placebo for people with subarachnoid haemorrhage

Lowered blood pressure versus placebo for people with subarachnoid haemorrhage

Patient or population: people with acute subarachnoid haemorrhage
Settings: any setting
Intervention: lowered blood pressure
Comparison: placebo
## Assumed risk and Corresponding risk (lowered blood pressure)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Assumed risk (placebo)</th>
<th>Corresponding risk (lowered blood pressure)</th>
<th>RR (95% CI)</th>
<th>Participants</th>
<th>GRADE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all causes</td>
<td>226 per 1000</td>
<td>117 per 1000</td>
<td>RR <strong>0.52</strong> (0.28 to 0.98)</td>
<td>204 (1 trial)</td>
<td>Very low</td>
<td>TSA showed that we had insufficient information to confirm or reject our predefined relative risk reduction of ≥ 20% (only 7.3% of the required information size was reached with 204 participants in the analysis).</td>
</tr>
<tr>
<td>Death or dependency</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proportion of participants with ≥ 1 serious adverse events</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quality of life</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Delayed cerebral ischaemia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hydrocephalus</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**CI:** confidence interval; **RR:** risk ratio; **TSA:** trial sequential analysis.

**GRADE Working Group grades of evidence**

- **High certainty:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low certainty:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low certainty:** we are very uncertain about the estimate.

**Notes:**

- Downgraded one level due to high risk of bias.
- Downgraded two levels due to imprecision.
**BACKGROUND**

**Description of the condition**

Subarachnoid haemorrhage is an acute condition in which blood extravasates to the subarachnoid space. Subarachnoid haemorrhage is most commonly caused by head trauma, but may also be non-traumatic (spontaneous) (Marder 2014). Spontaneous subarachnoid haemorrhage may occur due to intracranial aneurysm rupture (85%); non-aneurysmal perimesencephalic subarachnoid haemorrhage (10%); or, less commonly, arteriovenous malformation, arterial dissection, cerebral venous sinus thrombosis, and vasculitis (Marder 2014; van Gijn 2007).

The estimated worldwide incidence of aneurysmal subarachnoid haemorrhage is six to nine per 100,000 person-years, but there is regional variability, with markedly higher incidences in Finland and Japan (de Rooij 2007; Ingall 2000; van Gijn 2007). The primary symptom of a spontaneous subarachnoid haemorrhage is a sudden, severe headache; associated symptoms may be nausea, vomiting, photophobia, impaired consciousness, and neck stiffness (Edlow 2000; Suarez 2015). Between 15% and 40% of people with aneurysmal subarachnoid haemorrhage have a thunderclap-like ‘warning headache’ that precedes the major haemorrhagic event by hours to days (Dupont 2010). The most common locations of aneurysmal rupture, in order of incidence, are the anterior communicating artery, the posterior communicating artery, the basilar artery, and the middle cerebral artery (Zacharia 2010). Initial diagnostic work-up consists of a computed tomography (CT) scan of the brain; further investigations may include lumbar puncture and angiography, in order to visualise and characterise possible vascular malformations and aneurysms (Suarez 2015). Risk factors for developing spontaneous subarachnoid haemorrhage are smoking, hypertension, and excessive alcohol consumption (Feigin 2005).

Aneurysmal subarachnoid haemorrhage is associated with high mortality and morbidity rates (Steiner 2013). The case fatality rate is approximately 30% to 45%, and 20% of people are left dependent in activities of daily living (Ingall 2000; Nieuwkamp 2009). Rebleeding and delayed cerebral ischaemia are major causes of death and dependency after the initial haemorrhage (Koenig 2012). Other important complications are hydrocephalus and hyponatraemia (Diringer 2011).

Non-aneurysmal perimesencephalic subarachnoid haemorrhage, in which there is a spontaneous bleeding in the perimesencephalic and preptontine cisterns without an angiographically confirmed source of bleeding, has an incidence of 0.5 per 100,000 person-years, and occurs at a mean age of 50 to 55 years (Flaherty 2005). Compared with aneurysmal subarachnoid haemorrhage, the prognosis is excellent, with almost no risk of rebleeding, and only a mild risk of delayed cerebral ischaemia (Steiner 2013).

Traumatic subarachnoid haemorrhage frequently accompanies traumatic brain injury (Armin 2006; Wu 2010). Severity ranges from mild cases with bleeding in one or more sulci of the cerebral convexities to rare, but fatal, non-aneurysmal basal artery ruptures (Bunai 2000; Takahara 1993). Delayed cerebral ischaemia may also occur in relation to traumatic subarachnoid haemorrhage, although it rarely occurs, has a milder course, and occurs earlier than spontaneous subarachnoid haemorrhage (Armin 2006; Kramer 2013).

Delayed cerebral ischaemia occurs in approximately 30% to 40% of people with subarachnoid haemorrhage, primarily in those with an aneurysmal aetiology (Budohoski 2014; Koenig 2012). Delayed cerebral ischaemia usually develops three to 14 days after the aneurysmal subarachnoid haemorrhage, despite preventive treatment with the calcium-channel antagonist nimodipine, and avoidance of hypovolaemia (Connolly 2012; Vergouwen 2010). Typical clinical features of delayed cerebral ischaemia are focal or global neurological deficits, or decreases in level of consciousness unrelated to the initial subarachnoid haemorrhage. Delayed cerebral ischaemia may either reverse or progress to cerebral infarction (Vergouwen 2010). Rebleeding affects 4% to 17% of people with an aneurysmal subarachnoid haemorrhage and up to 87% of rebleedings occur within the first six hours of the initial haemorrhage (Connolly 2012; Fuji 1996; Oheda 2015; Ohkuma 2003; Starke 2011; Tang 2014). Systolic blood pressure greater than 160 mmHg is associated with an increased risk of rebleeding (Ohkuma 2003; Tang 2014). Early surgical intervention with neurosurgical clipping or endovascular coiling, aimed at securing the source of bleeding, is the mainstay in the prevention of rebleeding (Starke 2011; Steiner 2013). The use of antifibrinolytic treatment (e.g. tranexamic acid) for aneurysmal subarachnoid haemorrhage appears to decrease the risk of rebleeding, but might increase the risk of delayed cerebral ischaemia. However, antifibrinolytic therapy does not appear to affect clinical outcomes (Bahraboglu 2013).

**Description of the intervention**

Management of arterial blood pressure in subarachnoid haemorrhage may be aimed at either deliberately lowering blood pressure below the patient’s initial blood pressure to induce hypertension (that is, deliberately increasing blood pressure above the patient’s initial blood pressure), depending on the situation.

Some clinicians suggest that interventions aimed at lowering blood pressure may reduce the risk of rebleeding in people with hypertension with aneurysmal subarachnoid haemorrhage, before clipping or coiling (Connolly 2012; Steiner 2013). Calcium-channel antagonists (e.g. nimodipine, nicardipine) and beta-adrenergic receptor antagonists (e.g. labetalol) are medications commonly used to induce hypotension (Connolly 2012; Steiner 2013).

For decades, interventions aimed at inducing hypertension have been used alone, or in combination with hypervolaemia and haemodilution to treat delayed cerebral ischaemia, following coiling or clipping (Diringer 2011; Kosnik 1976). Triple-H therapy is a combination of induced hypertension, hyervolaemia, and haemodilution, previously used in subarachnoid haemorrhage to reduce the risk of delayed cerebral ischaemia. More recently, there has been a shift in management towards induced hypertension and euvolaemia, but there is sparse evidence supporting either management strategy (Findlay 2016; Francoeur 2016; Sen 2003; Veldeman 2016). The most commonly used treatments for induced hypertension are sympathomimetic drugs, such as noradrenaline and phenylephrine (Koenig 2012; Raya 2014).
How the intervention might work

High systolic blood pressure is associated with an increased risk of rebleeding in unsecured aneurysmal subarachnoid haemorrhage (Alfotih 2014; Tang 2014). It has been suggested that antihypertensive treatment may decrease the risk of rebleeding, possibly by decreasing the pressure against the weakened wall of the aneurysm (Wijdicks 1990). People with other types of subarachnoid haemorrhage might also benefit from lowering blood pressure by an overall decrease in arterial pressure.

The pathophysiology of delayed cerebral ischaemia following subarachnoid haemorrhage is thought to be a combination of loss of autoregulation, formation of microthrombi, microcirculatory constriction, and the breakdown of extravasated blood, with the release of reactive oxygen species, leading to inflammation and vasospasm, which results in reduced cerebral blood flow, leading to ischaemia (Brathwaite 2014; de Rooij 2013; Macdonald 2014). Since autoregulation is frequently disturbed in subarachnoid haemorrhage, inducing hypertension with the aim of increasing cerebral blood flow may ensure sufficient cerebral perfusion, which in turn, might minimise cerebral parenchymal ischaemia and thereby lower the risk of progression to infarction (Koenig 2012).

Alteration of blood pressure in people with subarachnoid haemorrhage may be associated with adverse effects. Lowering blood pressure in order to prevent rebleeding could potentially increase the risk of delayed cerebral ischaemia (Wijdicks 1990), while induced hypertension for delayed cerebral ischaemia may carry an increased risk of cardiopulmonary complications (e.g. congestive heart failure and pulmonary oedema) and cerebral complications (e.g. haemorrhagic transformation of infarctions, hypertensive encephalopathy, and cerebral oedema) (Amin-Hanjani 1999; Diringer 2011; Otsubo 1990; Steiner 2013).

Why it is important to do this review

The current evidence on the effects of altering arterial blood pressure in people with subarachnoid haemorrhage is unclear. Our preliminary search identified few randomised clinical trials on this topic, despite the fact that medical alteration of blood pressure has been clinical practice for more than three decades (Connolly 2012; Diringer 2011; Kosnik 1976; Steiner 2013). International guidelines from the American Heart Association/American Stroke Association (AHA/ASA), the European Stroke Organization (ESO), and the Neurocritical Care Society (NSC) recommend inducing hypotension when systolic blood pressure exceeds 160 mmHg (Connolly 2012; Diringer 2011), or 180 mmHg (Steiner 2013), before occluding the aneurysm. These guidelines either recommend inducing hypertension in people with delayed cerebral ischaemia (Connolly 2012; Diringer 2011), or refrain from making such a recommendation due to lack of evidence (Steiner 2013). These guidelines are based on observational studies, case reports, and expert opinion.

One systematic review found no beneficial effect of induced hypertension in preventing or treating delayed cerebral ischaemia following aneurysmal subarachnoid haemorrhage (Veldeman 2016). However, the review did not search all relevant databases, and did not take the risks of systematic errors and random errors into account (Higgins 2021; Jakobsen 2014). One previous Cochrane Review found no evidence supporting the use of volume expansion (Rinkel 2004). In one systematic review, two of four uncontrolled studies found a significant increase in cerebral blood flow following induced hypertension (Dankbaar 2010). However, one small randomised clinical trial found no significant effect of induced hypertension on overall cerebral blood flow in people with subarachnoid haemorrhage when compared to controls with normal blood pressure (Gather 2018).

One trial has indicated that nimodipine in aneurysmal subarachnoid haemorrhage appears to decrease the risk of poor outcome, rebleeding, and delayed cerebral ischaemia, but not death (Mees 2008). Small pilot trials on preventing delayed cerebral ischaemia found significantly worse neuropsychological scores upon follow-up of participants allocated to blood pressure augmentation (Togashi 2015), and no difference between participants randomised to dobutamine or noradrenaline (Rondeau 2012).

Although a different type of intracranial haemorrhage, and, therefore, not directly comparable, inducing hypotension in people with acute spontaneous intracerebral haemorrhage was found to be safe in randomised and non-randomised trials (Anderson 2008; Anderson 2013; ATACH 2010; Koch 2009). One previous Cochrane Review concluded that there is a lack of evidence in favour of lowering blood pressure in people with acute ischaemic or haemorrhagic stroke (Bath 2014). The large randomised clinical trial, Anderson 2013, found no difference in the primary composite outcome of death or disability, between participants with intracerebral haemorrhage randomised to a systolic blood pressure target of less than 140 mmHg within one hour, or a conventional target of less than 180 mmHg. However, the secondary outcomes of disability and quality of life were significantly improved in participants who received intensive blood pressure-lowering therapy (Anderson 2013). In the ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) trial, there were no significant differences in rates of death or disability between participants randomised to a systolic blood pressure target of 110 mmHg to 139 mmHg within 4.5 hours using intravenous nicardipine versus a target of 140 mmHg to 179 mmHg (Qureshi 2016 (ATACH-2)).

Considering the variations in the use, results from trials and reviews, and the recommendations to deliberately alter blood pressure in the management of subarachnoid haemorrhage, it is of great importance that any potential beneficial and harmful effects are well established. Thus, we consider it relevant to conduct this Cochrane Review, taking into account both risks of random errors (‘play of chance’) and risk of systematic errors (‘bias’) (Higgins 2021; Jakobsen 2014).

OBJECTIVES

To assess the beneficial and harmful effects of altering arterial blood pressure (induced hypertension or lowered blood pressure) in people with acute subarachnoid haemorrhage.

METHODS

Criteria for considering studies for this review

Types of studies

We included all parallel-arm, cross-over, and cluster randomised clinical trials, regardless of publication status, type, setting, or language. We excluded quasi-randomised studies and
observational studies. However, during the literature search, if we identified observational studies reporting on long-term adverse events or rare adverse events, we planned to provide a narrative report of these results.

Types of participants
We included participants of any age and sex with subarachnoid haemorrhage (defined by trialists).

Types of interventions
We included any experimental intervention, aimed at inducing hypertension or lowering blood pressure, by either pharmacological or non-pharmacological means. For pharmaceutical interventions, we accepted any dose, frequency, and formulation, used as either monotherapy or in combination. For non-pharmacological interventions, we were not aware of any such interventions a priori, but we accepted any type and frequency of intervention. As control interventions, we accepted placebo or no intervention. We allowed co-interventions, if they were planned to be delivered equally to both the experimental and control group.

Types of outcome measures
We assessed two primary outcomes and five secondary outcomes. We primarily assessed the outcomes at three months after subarachnoid haemorrhage (we used the trials’ assessment time point closest to three months after subarachnoid haemorrhage) and at maximum follow-up.

Primary outcomes
• Death from all causes.
• Death (from all causes) or dependency (defined by trialists; measured on the modified Rankin Scale (mRS), or the extended Glasgow Outcome Scale (eGOS): we planned to perform a subgroup analysis of the various methods for measuring dependency as defined by trialists.

Secondary outcomes
• Proportion of participants with one or more serious adverse events. We defined serious adverse events as any untoward medical occurrence that resulted in death, was life-threatening, was persistent, required hospitalisation, led to significant disability, or jeopardised the patient (ICH-GCP 1997).
• Quality of life (any valid continuous scale used by trialists).
• Rebleeding (defined by trialists).
• Delayed cerebral ischaemia (defined by trialists).
• Hydrocephalus (defined by trialists).

Search methods for identification of studies
We searched for trials in all languages and, if necessary, arranged for the translation of relevant articles.

Electronic searches
We searched the following electronic databases and trial registry databases:

- Cochrane Stroke Group Register (from inception to 8 September 2020);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 9) in the Cochrane Library from inception to 8 September 2020 [Appendix 1];
- MEDLINE Ovid (from 1966 to 8 September 2020 [Appendix 2];
- Embase Ovid (from 1980 to 8 September 2020 [Appendix 3];
- Science Citation Index Expanded (ISI Web of Knowledge; from 1945 to 8 September 2020 [Appendix 4];
- Latin-American and Caribbean Health Sciences Literature (LILACS; from 1982 to 8 September 2020 [Appendix 5];
- Chinese Biomedical Literature Database (CBM; from 1979 to 27 January 2019 [Appendix 6];
- China National Knowledge Infrastructure (CNKI; from 1979 to 27 January 2019 [Appendix 7];
- Chinese Science Journal Database (VIP; from 1989 to 27 January 2019 [Appendix 8].

We agreed not to update the search of the Chinese databases because we did not identify any relevant literature during the first search.

The Cochrane Stroke Group Information Specialist developed the search strategies (except for LILACS).

We used Google Scholar to forward search included articles to identify other relevant literature.

In order to identify ongoing or unpublished trials, we searched the following electronic trial registry databases:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov); updated 8 September 2020 [Appendix 9];
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch; updated 8 September 2020 [Appendix 10];
- EU Clinical Trials Register (www.clinicaltrialregister.eu); updated 8 September 2020; included in the WHO ICTRP;
- ISRCTN Registry (www.isrctn.com); updated 8 September 2020; included in the WHO ICTRP;
- the Stroke Trials Registry (www.strokecenter.org/trials; updated 8 September 2018; no longer online).

Searching other resources
We handsearched reference lists of studies and reviews on the topic of therapeutic alteration of blood pressure in subarachnoid haemorrhage.

Data collection and analysis
We conducted data collection and analysis according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions Chapters 5, 6, 8, 9, 10, 14, and 15 (Higgins 2021), and as described by Jakobsen and colleagues (Jakobsen 2014).

Selection of studies
Two review authors (MM and WKK) independently screened the title and abstract of all records identified by the search and excluded records that were obviously irrelevant. We obtained full-text articles for all potentially eligible studies, and independently selected eligible studies according to the inclusion criteria.
and exclusion criteria. We reported the reasons for trial exclusion in the Characteristics of excluded studies table. We resolved all disagreements by discussion; if required, we consulted a third review author (JCJ). We collated multiple reports of the same study so that each study, not each reference, was the unit of interest in the review. We recorded the selection process and presented a PRISMA flow chart to visually display the selection of studies (Moher 2009).

Data extraction and management

Two review authors (MM and WKK) independently extracted data from included trials using a data collection form. For each included trial, we extracted: year of publication, first author, country, publication status, number of participants in each group, number of participants lost to follow-up in each treatment group, relevant baseline characteristics (e.g. age range and mean, sex ratio, comorbidities), any relevant scoring (e.g. Glasgow Coma Score (GCS) at admission, World Federation of Neurosurgical Societies (WFNS) score, or Hunt and Hess scale), method of diagnosing subarachnoid haemorrhage, type of subarachnoid haemorrhage (aneurysmal, non-aneurysmal, traumatic), type and timing of aneurysm treatment, active intervention (generic drug name, timing, route of administration, dose), comparator and co-interventions (e.g. haemostatic treatment), duration of intervention, follow-up duration, outcomes, time to rebleeding or delayed cerebral ischaemia, definition of delayed cerebral ischaemia, presence of intraventricular haematoma, presence of parenchymatous haemorrhage (intracerebral haemorrhage), type of non-pharmaceutical intervention, frequency of non-pharmaceutical intervention, length of treatment with non-pharmaceutical intervention, other medical complications, and source of funding. We cross-checked the completed data collection forms for each individual trial. We resolved all disagreements by discussion; if required, we consulted a third review author (JCJ). We entered data into Review Manager 5 (Review Manager 2014).

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies as described in the Cochrane Handbook for Systematic Reviews of Interventions using the Risk of Bias 1 tool (Higgins 2011a; Higgins 2011b). Two review authors (MM and WKK) independently assessed the included trials; they resolved all disagreements by discussion, or if required, by consulting a third review author (JCJ). We evaluated the risk of bias in random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias (for-profit bias for each trial) (see Appendix 11).

We classified each risk of bias item as low, unclear, or high. A trial was at overall low risk of bias if all risk of bias items were at low risk of bias. A trial was at overall high risk of bias if one or more risk of bias items were at either unclear or high. We based our primary conclusions on the results of our primary outcomes at low risk of bias. We presented the results of predefined outcomes in the summary of findings tables. We reported bias assessments for each trial in risk of bias tables. We assessed the items 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome result. Thus, we were able to assess the bias risk for each outcome result, in addition to each trial.

Measures of treatment effect

We presented dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) and corresponding P values. We reported the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH).

We presented continuous outcomes as the mean differences (MDs), with 95% CIs, and corresponding P values. If studies reported both end scores and change from baseline scores, we used end scores. If studies reported only change values, we analysed the results together with end scores (Higgins 2021). We also considered pooling similar continuous outcome scales, if we identified such results, using standard mean differences (SMDs), with 95% CIs, and corresponding P values.

Unit of analysis issues

For trials using a crossover design, we only planned to include data from the first period. For trials using multiple comparisons, we planned to split the control group between the comparisons to avoid double-counting of participants. We did not anticipate identifying any trials using a cluster-randomised design. However, we intended to include the data after correcting the actual sample size to the effective sample size using an intracluster correlation coefficient.

Dealing with missing data

We contacted trial investigators if data were missing or unclear. We did not use intention-to-treat data if the original report did not contain such data. We did not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis for dichotomous and continuous outcomes, we imputed data (see Sensitivity analysis). If standard deviations (SD) were not reported in a trial, we calculated the SDs using data from the trial, if possible.

Assessment of heterogeneity

We mainly used I² statistics to quantify heterogeneity. Interpretation of the I² statistics depends on the value (Higgins 2021):

- 0% to 40% might not be important;
- 30% to 60% may indicate moderate heterogeneity;
- 50% to 90% may indicate substantial heterogeneity;
- 75% to 100% indicates considerable heterogeneity.

In case of I² values that fall in the overlaps (e.g. 30% to 40%, 50% to 60%, or 75% to 90%), we classified the heterogeneity as, for example, 'might not be important to moderate heterogeneity', 'moderate to substantial heterogeneity', or 'substantial to considerable heterogeneity'.

Statistical tests (e.g. I² statistic) for heterogeneity have two problems: 1. there might not be enough power in the analysis to show even considerable heterogeneity, and 2. there might be 'too much data', so that small and clinically insignificant heterogeneity result in a large I² statistic estimate. This is especially true when analysing continuous outcomes. Therefore, in addition to calculating I² statistics, we planned to visually inspected forest plots to look for signs of study heterogeneity of the included trials if at least 10 trials had been included in an analysis (Jakobsen 2014).
Quote: “A forest plot is an essential tool to summarise information on individual studies, give a visual suggestion of the amount of study heterogeneity, and show the estimated common effect, all in one figure” (Fagerland 2015).

We also investigated possible heterogeneity through subgroup analyses (see Subgroup analysis and investigation of heterogeneity). Ultimately, we may have decided that a meta-analysis (e.g. pooling all types of subarachnoid haemorrhage in one analysis) should be avoided, for instance in the event of statistical heterogeneity due to the trials delivering the intervention in unexpected different ways (Higgins 2021; Jakobsen 2014).

Assessment of reporting biases

We assessed publication bias and other reporting biases by visual inspection of funnel plots for primary outcomes, if at least 10 trials were included for an outcome (Higgins 2021). We assessed the risk of bias using the asymmetry of the funnel plot.

For dichotomous outcomes, we tested asymmetry with the Harbord test, if Tau² was less than 0.1 (Harbord 2006), and with the Rücker test, if Tau² was more than 0.1 (Rücker 2008).

For continuous outcomes, we used the regression asymmetry test (Egger 1997).

Data synthesis

We separately analysed trials that assess interventions aimed at: lowering blood pressure; and increasing blood pressure.

For trials concerning delayed cerebral ischaemia, we separately analysed trials concerning: prevention of delayed cerebral ischaemia; and treatment of delayed cerebral ischaemia.

For statistical analysis, we used Review Manager 5 (Review Manager 2014), trial sequential analysis (TSA) software, provided by the Copenhagen Trial Unit (CTU; TSA 2011), and if necessary, STATA 14 (Stata).

Assessment of statistical and clinical significance

We analysed all primary and secondary outcomes using both a fixed-effect (DeLorme 1987), and random-effects model meta-analysis (DerSimonian 1986). It is often likely that a given intervention will have different effects across the included trials depending on different forms of the interventions, different definitions of the outcomes, different types of included participants, etc. The random-effects model assumption will, therefore, often be more realistic than the fixed-effect model assumption. If there is absence of statistical heterogeneity, the between-trial variance of the estimated intervention effects is close to zero, then the fixed-effect and the random-effects models will show identical results. If there is substantial statistical heterogeneity, the fixed-effect meta-analysis will, in some circumstances, show erroneous results because the between-trial variance is not appropriately accounted for. In such a case, the random-effects meta-analysis result should be regarded as the main result. We recommend reporting results from both fixed-effect and random-effects meta-analyses. If the fixed-effect and the random-effects meta-analyses show different results, then the most conservative result (the analysis with the highest P value) should be chosen as the main result. Choosing the most conservative result will take account of the mentioned pitfalls of the two analyses (Jakobsen 2014).

With each additional outcome assessed in a meta-analysis, the risk of falsely rejecting the null hypothesis increases. The Bonferroni adjustment accounts for the problems associated with multiplicity, but may often be too conservative, since the assumption of no correlation between outcomes may not be suitable (Jakobsen 2014; Jakobsen 2016). We calculated a multiplicity-adjusted significance threshold by taking a pragmatic midway between the Bonferroni adjustment and unadjusted P-value (commonly 0.05). We calculated the multiplicity-adjusted significance threshold as the prespecified P-value threshold divided by the value halfway between 1 (no adjustment) and the number of outcome comparisons (Bonferroni adjustment) (Jakobsen 2014; Jakobsen 2016). By these calculations, we considered a P value of 0.0333 or less as statistically significant for primary outcomes, and a P value of 0.0167 or less for secondary outcomes.

Trial sequential analysis

TSA is a method to minimise risk of random errors resulting from sparse data and repetitive testing for significance in cumulative meta-analyses (Brok 2008; Brok 2009; Jakobsen 2014; Thorlund 2009; Wetterleiv 2008). We used TSA in addition to the methodology currently recommended by Cochrane (Higgins 2021; Jakobsen 2014).

TSA estimates the a priori required number of participants for a meta-analysis to detect or reject a given intervention effect (the required information size); in addition, trial sequential monitoring boundaries are used to show if the information size adjusted boundaries for significance are crossed. The diversity-adjusted required information size depends on the anticipated intervention effect, variance of the anticipated difference in intervention effect (e.g. proportion of control participants with an event for dichotomous outcomes and a SD for continuous outcomes), variance of the intervention estimate between trials, and the predefined acceptable risk of statistical error (type I and II errors; Jakobsen 2014). Trial sequential monitoring boundaries can be constructed, depending on the required information size. If the trial sequential monitoring boundaries are crossed by the cumulative Z-curve before the required information size has been reached, this strongly indicates either a beneficial or harmful intervention effect, in which case, additional trials may be redundant. Conversely, if the monitoring boundaries are not crossed, this indicates that more trials are needed in order to confirm or reject an intervention effect. Monitoring boundaries for futility may be also be constructed which, if crossed by the cumulative Z-curve, will indicate the absence of the anticipated intervention effect (Thorlund 2011).

If one trial or more has been published, we analysed all primary and secondary outcomes by TSA. We added trial data to the analysis depending on year of publication. If more than one trial had been published in the same year, we added them alphabetically, by the surname of the first author (Wetterleiv 2008). We performed the TSA using both a fixed-effect and a random-effects model.
We estimated the diversity-adjusted required information size, based on the anticipated intervention effect (former studies, trials, and meta-analyses), the proportion of participants with an outcome in the control group for dichotomous outcomes or SD for continuous outcomes, and the variance of the intervention effect between trials, as suggested by the trials in the meta-analysis. For outcomes with no relevant studies, trials, or meta-analyses, the anticipated intervention effect would be the observed SD and an anticipated MD of SDs divided by two for continuous outcomes, and the proportion of outcomes in the control group and a relative risk reduction of 20% for dichotomous outcomes (Appendix 12). For primary outcomes, we set alpha to 3.33% and beta to 20%. For secondary outcomes, we set alpha to 1.67% and beta to 20% (Jakobsen 2014).

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses for the assessment of the primary outcomes.

- Type of subarachnoid haemorrhage:
  - aneurysmal;
  - non-aneurysmal aetiologies (e.g. traumatic, perimesencephalic, etc.).

- Type of intervention.

- Haemostatic treatment (e.g. tranexamic acid) as co-intervention.

- Haemostatic treatment (e.g. tranexamic acid) as co-intervention, with or without delayed cerebral ischaemia-preventive treatment.

- Dose of any pharmaceutical intervention.

For trials concerning aneurysmal subarachnoid haemorrhage, we also planned to perform the following subgroup analyses.

- Severity of subarachnoidal haemorrhage according to clinical scales (e.g. GCS at admission, WFNS score, and Hunt and Hess scale).

- Type of definitive treatment of the aneurysm:
  - surgical clipping;
  - endovascular treatment;
  - no treatment.

For trials concerning traumatic subarachnoid haemorrhage, we also planned to perform the following subgroup analyses.

- Severity of traumatic brain injury upon admission according to GCS.

- Severity of traumatic brain injury upon admission according to neuroradiological scales (e.g. Marshall classification of traumatic brain injury and Rotterdam CT score of traumatic brain injury).

For trials concerning delayed cerebral ischaemia, we also planned to perform the following subgroup analyses.

- Risk of developing delayed cerebral ischaemia according to neuroradiological scales (e.g. modified Fisher scale).

Sensitivity analysis

To assess the potential impact of bias, we planned to perform a sensitivity analysis where we excluded trials with an overall high risk of bias.

To assess the potential impact of missing data for dichotomous outcomes, we planned to perform the following two analyses on primary outcomes.

- Best-case, worst-case scenario: we assumed that all participants lost to follow-up in the intervention group survived, and had no serious adverse events, and all those with missing outcomes in the control group, did not survive and had a serious adverse event.

- Worst-case, best-case scenario: we assumed that all participants lost to follow-up in the intervention group did not survive, and had a serious adverse event, and all those with missing outcomes in the control group survived, and had no serious adverse events.

We reported results from both scenarios.

When analysing continuous outcomes regarding missing data, a 'beneficial outcome' were the group mean plus two SDs of the group mean, and a 'harmful outcome' were the group mean minus two SDs of the group mean (Jakobsen 2014).

Summary of findings and assessment of the certainty of the evidence

We constructed summary of findings tables presenting all primary (death from all causes, and death or dependency) and secondary (proportion of participants with one or more serious adverse events, quality of life, rebleeding, delayed cerebral ischaemia, and hydrocephalus) outcomes. To assess the certainty of the evidence, we used the GRADE approach, which involves assessing the within-study risk of bias, directness of evidence, heterogeneity of results, imprecision, and risk of publication bias (Guyatt 2008; Higgins 2021). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021). We based the summary of findings tables on all prestated outcomes, and conclusions in part on the results of 'overall low risk of bias' trials. We justified all decisions to downgrade the certainty of evidence in footnotes, and we made comments to aid the reader’s understanding of the review where necessary.

Results of the search

Our search yielded 28,060 records through searching Cochrane Stroke Register (231 records), CENTRAL (3205), MEDLINE (3019), Embase (16,938), Web of Science (2768), LILACS (73), CBM (703), CNKI (569), VIP (201), ClinicalTrials.gov (243), and WHO ICTRP (110). Of these, we excluded 2729 duplicates and 25,262 records based on title and abstract. We obtained 71 full-text records for...
possible inclusion. Of these, we included three trials and there were five reports of included trials (see Characteristics of included studies table). We excluded 62 studies and there was one report of an excluded study (see Characteristics of excluded studies table). We found no ongoing trials. See Figure 1 for PRISMA flow chart.
Figure 1. PRISMA flow diagram.

28,060 records identified through database searching

25,331 records after duplicates removed

25,331 records screened

25,262 records excluded

62 full-text articles excluded, with reasons (see 'Characteristics of excluded studies' table) and there was one report of an excluded study

71 full-text articles assessed for eligibility

3 studies included in qualitative synthesis and there were 5 reports of included trials

2 studies included in quantitative synthesis (meta-analysis)
Included studies
We included three trials (Gathier 2018; Neil-Dwyer 1985; Togashi 2015). Two trials randomised 61 participants with subarachnoid haemorrhage to induced hypertension versus no induced hypertension (Gathier 2018; Togashi 2015). One trial randomised 224 participants with subarachnoid haemorrhage to lowered blood pressure versus placebo (Neil-Dwyer 1985). The trials were published between 1985 and 2018. None of the trials appeared to be sponsored by the industry, but Neil-Dwyer 1985 did not mention conflicts of interest or describe how the trial was funded. All trials were at high risk of bias (Gathier 2018; Neil-Dwyer 1985; Togashi 2015). See Characteristics of included studies table for a more detailed description of the included studies.

Induced hypertension versus no induced hypertension
One trial randomising 41 participants used fluids in case of hypovolaemia as well as various vasopressors to induce hypertension in the experimental group (21 participants). The goal was a maximum mean arterial blood pressure of 130 mmHg or a maximum systolic blood pressure of 230 mmHg. In the control group (20 participants), hypotension (mean arterial blood pressure below 80 mmHg) was avoided using low-dose vasopressors. This trial was prematurely terminated due to lack of effect on overall cerebral perfusion and slow recruitment (Gathier 2018).

Another trial randomising 20 participants used a combination of normovolaemia, hypervolaemia, and vasopressors to induced hypertension in the experimental group (10 participants). The control group aimed for conventional blood pressure (10 participants) (Togashi 2015).

Lowered blood pressure versus no lowered blood pressure
One trial randomising 224 participants used beta-blockers to lower blood pressure in the experimental group (111 participants; phentolamine plus propranolol or propranolol alone) and placebo in the control group (93 participants) (Neil-Dwyer 1985).

Excluded studies
We excluded 62 studies; reasons are provided in the Characteristics of excluded studies table.

Studies awaiting classification
There are no studies awaiting classification.

Ongoing studies
We found no ongoing studies.

Risk of bias in included studies
The risk of bias evaluation for each of the risk of bias domains are presented in Figure 2 and Figure 3. All trials were at overall high risk of bias.
### Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias): all outcomes</th>
<th>Blinding of outcome assessment (detection bias): all outcomes</th>
<th>Incomplete outcome data (attrition bias): all outcomes</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathier 2018</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Neil-Dwyer 1985</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation
All included trials reported that they used random allocation. However, only two trials reported the method for randomising participants and utilised a randomisation-sequence generation that we deemed at low risk of bias (Gathier 2018; Togashi 2015).

Blinding
One trial was open-label and reported that participants and outcome assessors were blinded to treatment allocation, but that caregivers were aware of treatment allocation (Togashi 2015). One trial reported that the participants and outcome assessors were blinded to treatment allocation, but the treatment providers were unblinded (Gathier 2018). One trial used placebo and mentioned that the trial was ‘double-blind’, but provided no details on the method of blinding (Neil-Dwyer 1985). None of the trials described how they attempted to adequately blind the participants, personnel, and outcome assessors. Blinding of blood pressure alterations remain a practical issue in randomised clinical trials but should nonetheless be attempted. A method for blinding stakeholders in blood pressure target investigations has been proposed previously and future trials should attempt to incorporate adequate blinding of participants, personnel, and outcome assessors (Grand 2018).

In addition to assessing the risk of bias for each trial, we also assessed the risk of bias for each outcome in regard to blinding of the outcome assessors (see Table 1 and Table 2). Two trials reported blinded assessors carried out outcome assessment (Gathier 2018; Togashi 2015). In Gathier 2018, research nurses who were blinded to treatment allocation collected outcome measures. However, for serious adverse events and rebleeding, the principal investigator collected outcome measures, and it was not described if the principal investigator was blinded to treatment allocation (Gathier 2018). In Togashi 2015, the decision to test for delayed cerebral ischaemia with transcranial Doppler or CT was based on clinical assessments carried out by the treating physicians who were not blinded to treatment allocation. None of the trials described how they ensured adequate blinding of the outcome assessors. We judged the outcome at low risk of bias related to blinding of outcome assessment, if blinding of the outcome assessor was specifically mentioned for the outcome of interest. If blinding of the outcome assessor was not mentioned, it was judged at unclear risk of bias. In a trial, if an outcome measure was collected by personnel with no specific mention of blinding while other outcomes were collected by personnel with specific mention of blinding, then we judged the outcome measure collected by personnel with no specific mention of blinding to be at high risk of bias.

Incomplete outcome data
Incomplete outcome data did not impact the results related to induced hypertension versus control as none of the trials lost participants to follow-up (Gathier 2018; Togashi 2015). In the trial assessing the effects of lowered blood pressure as the experimental intervention, 20/224 participants dropped out during the intervention period, but there was an equal drop-out between groups (Neil-Dwyer 1985).

No participants were lost to follow-up in the two trials randomising participants to induced hypertension versus control. Therefore, we judged the risk of incomplete outcome data at low risk of bias for all outcomes (see Table 1) (Gathier 2018; Togashi 2015).

In the trial randomising participants to lowered blood pressure versus placebo, 11 participants in the lowered blood pressure group and nine participants in the placebo group were lost to follow-up. However, the dropout was similar, and we judged the outcomes at low risk of bias related to incomplete outcome data (see Table 2).

Selective reporting
For induced hypertension versus control, only Gathier 2018 registered the trial prior to randomisation. However, both trials randomising participants to induced hypertension versus control reported on death from all causes and death or dependency. Therefore, we judged the trials to be at low risk of bias related to selective outcome reporting (Gathier 2018; Togashi 2015). Both the trials also reported serious adverse events (Gathier 2018; Togashi 2015). One trial reported quality of life and rebleeding (Gathier 2018). One trial reported delayed cerebral ischaemia (Togashi 2015). None of the trials reported on the incidence of hydrocephalus (Gathier 2018; Togashi 2015). We also assessed the risk of selective outcome reporting to each outcome in addition to each trial (see Table 1 and Table 2). Togashi 2015 did not define serious adverse event, making us judge this outcome result to be at unclear risk of bias related to selective outcome reporting (see Table 1). Only Gathier 2018 reported quality of life and
rebleeding. We were unable to obtain protocols from Togashi 2015, making us judge selective outcome reporting related to quality of life and rebleeding as unclear (see Table 1).

For lowered blood pressure versus placebo, there was no protocol or trial registration available (Neil-Dwyer 1985). Therefore, we judged the trial to be at unclear risk of bias related to selective outcome reporting. The trial only reported on death from all causes. Therefore, the data related to death or dependency only consisted of death from all causes.

Other potential sources of bias

Too few trials were included to enable an assessment of publication bias. We also assessed for-profit bias, but none of the trials seemed to be sponsored by the industry or any other stakeholders with an interest in a given result.

Effects of interventions

See: Summary of findings 1 Induced hypertension versus placebo or no intervention for people with acute subarachnoid haemorrhage; Summary of findings 2 Lowered blood pressure versus placebo for people with subarachnoid haemorrhage

Induced hypertension

Death from all causes

Two trials randomising 61 participants reported death from all causes. Fixed-effect meta-analysis showed no evidence of a difference between induced hypertension and control at three months’ follow-up (RR 1.60, 95% CI 0.57 to 4.52; P = 0.38; Analysis 1.1). Visual inspection of the forest plot and I² statistic (I² = 0%) showed no signs of heterogeneity. TSA showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more (no TSA graph produced). No participants were lost to follow-up. Therefore, we did not assess the impact of incomplete outcome data for this result. This outcome result was at high risk of bias (see Table 1). The certainty of evidence was very low due to high risk of bias and imprecision.

The analysis of death or dependency at maximal follow-up showed a similar result (RR 1.29, 95% CI 0.78 to 2.13; P = 0.33; Analysis 2.2).

Serious adverse events

Two trials randomising 61 participants reported on serious adverse events. Fixed-effect meta-analysis showed no evidence of a difference between induced hypertension and control at three months’ follow-up on our adjusted threshold of statistical significance (RR 2.24, 95% CI 1.01 to 4.99; P = 0.05; Analysis 3.1). Visual inspection of the forest plot and I² statistics (I² = 0%) showed no signs of heterogeneity. TSA showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more (no TSA graph produced). No participants were lost to follow-up; therefore, we did not assess the impact of incomplete outcome data for this result. This outcome result was at high risk of bias (see Table 1). The certainty of evidence was very low due to high risk of bias and imprecision.

We post-hoc assessed all individual serious adverse events. We found no evidence of a difference between induced hypertension and control for any individual serious adverse event.

The analysis of serious adverse events at maximal follow-up showed a similar result (RR 2.24, 95% CI 1.01 to 4.99; P = 0.05; Analysis 3.2).

Quality of life

One trial reported quality of life (Gathier 2018). Therefore, meta-analysis could not be conducted. Quality of life was reported using the Stroke Specific Quality of Life Scale, where a higher score indicates a better quality of life. In the induced hypertension group, quality of life at follow-up was at a median of 47 points (interquartile range 35 to 55). In the control group, quality of life at follow-up was at a median of 49 points (interquartile range 35 to 55). TSA showed that we had insufficient information to confirm or reject our predefined MD of the SD divided by ‘2’ (Figure 4). This outcome was at high risk of bias (see Table 1). The certainty of evidence was very low due to high risk of bias and imprecision.
Figure 4. Trial Sequential Analysis graph of quality of life. The cumulative z-curve (the blue line) did not cross any of the monitoring boundaries (futility, benefit, or harm) and did not reach the diversity-adjusted required information size. Hence, there was not enough information to confirm or reject important intervention effects. MD: mean difference.

Rebleeding

One trial reported rebleeding (Gathier 2018). Therefore, meta-analysis could not be conducted. In the induced hypertension group, rebleeding occurred in 1/21 (5%) participants. In the control group, rebleeding occurred in 2/20 (10%) participants. Fisher's exact test showed no evidence of a difference between induced hypertension and control (P = 1.0). TSA showed that we had insufficient information to confirm or reject our predefined relative risk reduction of 20% or more. This outcome was at high risk of bias (see Table 1). The certainty of evidence was very low due to high risk of bias and imprecision.

The analysis of rebleeding at maximal follow-up showed a similar result (Fisher's exact test P = 1.0).

Delayed cerebral ischaemia

One trial randomising 20 participants reported on delayed cerebral ischaemia (Gathier 2018). Therefore, meta-analysis could not be conducted. In the induced hypertension group, delayed cerebral ischaemia occurred in 0/10 participants. In the control group, delayed cerebral ischaemia occurred in 1/10 (10%) participants. Fisher's exact test showed no evidence of a difference between induced hypertension and control (P = 1.0). TSA showed that we had insufficient information to confirm or reject a relative risk reduction of 20% or more (no TSA graph produced). This outcome was at high risk of bias (see Table 1). The certainty of evidence was very low due to high risk of bias and imprecision.

The analysis of delayed cerebral ischaemia at maximal follow-up showed a similar result (Fisher's exact test P = 1.0).

Hydrocephalus

Neither of the included trials reported on hydrocephalus.

Subgroup analyses

None of our predefined subgroup analyses could be conducted.

Lowered blood pressure

Only one trial randomising 224 participants assessed lowered blood pressure versus placebo (Neil-Dwyer 1985). Therefore, no meta-analyses could be conducted on lowered blood pressure in people with subarachnoid haemorrhage.

Death from all causes

One trial analysing 204 participants reported death from all causes. When assessing death from all causes closest to three months' follow-up (28 days), 13 participants in the lowered blood pressure
group died and 21 participants in the placebo group died. Fisher’s exact test showed no evidence of a difference between groups (P = 0.058). TSA showed that we had insufficient information to confirm or reject a relative risk reduction of 20% or more (no TSA graph produced). This outcome was at high risk of bias (see Table 2). The certainty of evidence was very low due to high risk of bias and imprecision.

The analysis of death from all causes at maximal follow-up using Fisher’s exact test also showed no evidence of a difference between lowered blood pressure and control (P = 0.084)

**Death or dependency**

No usable data was reported regarding dependency. Only data regarding death from all causes could be included in the analysis of death or dependency. Therefore, the analysis of death or dependency would show similar results as the death from all causes outcomes as assessed at both closest to three months’ follow-up and at maximal follow-up.

**Serious adverse events**

No serious adverse events were reported. Only data regarding death from all causes could be included in the analysis of serious adverse events. Therefore, the analysis of serious adverse events would show similar results as the death from all causes outcomes as assessed at both closest to three months’ follow-up and at maximal follow-up.

**Quality of life**

The study reported no data regarding quality of life.

**Rebleeding**

The study reported no data regarding rebleeding.

**Delayed cerebral ischaemia**

The study reported no data regarding rebleeding.

**Hydrocephalus**

The study reported no data regarding hydrocephalus.

**Subgroup analyses**

No subgroup analyses could be conducted due to the lack of trials regarding blood pressure lowering in people with subarachnoid haemorrhage.

**DISCUSSION**

**Summary of main results**

We included a total of two trials randomising 61 participants to induced hypertension versus no intervention (Gather 2018; Togashi 2015), and one trial randomising 224 participants to lowered blood pressure versus placebo (Nield-Dwyer 1985). All trials were at high risk of bias. The certainty of the evidence according to GRADE was very low for all outcomes.

**Induced hypertension versus control**

Meta-analyses showed no evidence of a difference between induced hypertension and control on death from all causes, death or dependency, and serious adverse events. Only one trial reported quality of life, therefore, we were unable to perform meta-analysis. Only one trial reported rebleeding and delayed cerebral ischaemia, therefore, we were unable to perform meta-analyses of these outcomes, but Fisher’s exact test showed no evidence of a difference between induced hypertension and no intervention on rebleeding and delayed cerebral ischaemia. Trial sequential analyses showed that we had insufficient information to confirm or reject our predefined minimal important intervention effects regarding death from all causes, death or dependency, quality of life, delayed cerebral ischaemia, and rebleeding.

None of the trials randomising participants to induced hypertension versus control reported on hydrocephalus. No subgroup analyses could be conducted for trials randomising participants to induced hypertension versus control.

**Lowered blood pressure versus placebo**

One trial randomised participants to lowered blood pressure versus placebo. Therefore, meta-analysis could not be performed for any outcomes. The trial only reported on death from all causes. We could not assess death or dependency, quality of life, rebleeding, delayed cerebral ischaemia, and hydrocephalus. Fisher’s exact test showed no evidence of a difference between lowered blood pressure and control on death from all causes. TSA showed that we had insufficient information to confirm or reject our predefined minimal important intervention effect regarding death from all causes. No subgroup analyses could be conducted for trials randomising participants to lowered blood pressure versus control.

**Overall completeness and applicability of evidence**

We only identified two trials assessing induced hypertension and only one trial assessing lowered blood pressure in people with subarachnoid haemorrhage. It is thought-provoking that we identified so few trials, considering that alteration of blood pressure in people with subarachnoid haemorrhage has been practice for more than three decades (Connolly 2012; Diringer 2011; Kosnik 1976; Steiner 2013). International guidelines recommend lowering the blood pressure when the systolic blood pressure exceeds 160 mmHg (Connolly 2012; Diringer 2011), or 180 mmHg (Steiner 2013), before occluding the aneurysm. No recommendations exist regarding postoperative blood pressure management in people with subarachnoid haemorrhage unless delayed cerebral ischaemia occurs. The guidelines either recommend inducing hypertension in people with delayed cerebral ischaemia (Connolly 2012; Diringer 2011), or refrain from making such a recommendation due to a lack of evidence (Steiner 2013). The findings presented in this systematic review might be highly influenced by random error (‘play of chance’) due to lack of information.

**Induced hypertension**

The trials assessing induced hypertension included few participants and were both at high risk of bias. All outcomes, except for quality of life, were also at high risk of bias. There was a lack of information to confirm or reject minimal important intervention effects for all outcomes. The reporting of serious adverse events was inadequate. Therefore, it is highly problematic to make any inferences about the use of induced hypertension in people with acute subarachnoid haemorrhage. One trial reported rebleeding and quality of life. No trials reported hydrocephalus.
Lowered blood pressure

The single trial assessing induced hypotension in people with subarachnoid haemorrhage included few participants, was at high risk of bias, and only reported usable data for death from all causes. Therefore, the effect estimates for death or dependency and serious adverse events were identical to that of death from all causes. There was a lack of information to confirm or reject minimal important intervention effects for all outcomes. No inferences can be made regarding the beneficial and harmful effects of our other predefined patient-important outcomes.

Quality of the evidence

None of the trials randomising participants to induced hypertension versus control blinded the participants or personnel. Two trials randomising participants to induced hypertension versus control described blinding of outcome assessors (Gathier 2018; Togashi 2015). The remaining trial did not report adequate blinding. The lack of adequate blinding, and the high risk of bias in general, increases the risk that our results overestimate the beneficial effects and underestimate the harmful effects (Hróbjartsson 2014; Savovic 2018). Masking blood pressure remains a practical issue in randomised clinical trials, but a method for blinding stakeholders in blood pressure trials has been described and future trials should attempt to incorporate blinding of the involved participants, personnel, and outcome assessors (Grand 2018).

The certainty of the evidence was very low for all outcome measures primarily due to imprecision and high risk of bias. We had between 0.23% and 11.8% of the information needed in the meta-analyses on induced hypertension to be conclusive about the results as estimated by trial sequential analyses. We only had 7.7% of the information needed to be conclusive on lowered blood pressure as estimated by TSA.

Potential biases in the review process

We attempted to avoid any biases in the review process by using a thorough search strategy to search all databases created by an information specialist. We also predefined our methodology in our protocol published prior to literature searching (Maagaard 2018). We included trials regardless of publication year, language, setting, and status without regard to participant age, sex, and comorbidities.

Agreements and disagreements with other studies or reviews

One previous systematic review found no beneficial effects on inducing hypertension in people with subarachnoid haemorrhage for the treatment or prevention of delayed cerebral ischaemia (Veldman 2016). We also found no beneficial effects of inducing hypertension in people with subarachnoid haemorrhage on death from all causes, death or dependency, serious adverse events, quality of life, rebleeding, or delayed cerebral ischaemia. Guidelines recommend lowering the blood pressure in people with hypertension in the presence of an unsecured aneurysm and induce hypertension in people with delayed cerebral ischaemia, but we found no evidence from randomised clinical trials validating these recommendations (Connolly 2012; Diringer 2011; Steiner 2013).

AUTHORS’ CONCLUSIONS

Implications for practice

Based on the current evidence, for both induced hypertension and lowered blood pressure, there is a lack of information needed to confirm or reject minimal important intervention effects on patient-important outcomes.

Implications for research

There is an urgent need for randomised clinical trials at low risk of bias assessing the beneficial and harmful effects of altering blood pressure in people with acute subarachnoid haemorrhage. Sparse evidence exists regarding interventions for altering blood pressure in people with subarachnoid haemorrhage. Currently, the international guidelines are primarily informed by observational studies, case reports, and expert opinion. None of trials randomising participants to induced hypertension versus control blinded the participants and personnel. The two trials randomising participants to induced hypertension versus control mentioned blinding of outcome assessors, but neither of them described how they ensured adequate blinding of the outcome assessors. Blinding stakeholders in blood pressure trials remains a practical issue, but should nonetheless be attempted. Future randomised trials should use the SPIRIT statement for their design and the CONSORT statement for their reporting. Moreover, the trials should use methods allowing for blinding of blood pressure and report on patient-centred outcomes such as mortality, serious adverse events, quality of life, rebleeding, hydrocephalus, and delayed cerebral ischaemia.

ACKNOWLEDGEMENTS

We acknowledge the Cochrane Stroke Group, in particular Hazel Fraser and Joshua Cheyne, for valuable assistance.

We acknowledge Dong-Jie Wu of the Hong Kong Baptist University, Hong Kong Chinese Medicine Authentication Centre, for assisting with searching the Chinese databases.

We acknowledge Xuehan Liu, Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine and Ruilin Chen, Clinical School of Traditional Chinese Medicine, Beijing University of Chinese Medicine for assisting with screening the search results of the Chinese databases.

We acknowledge Harrison Nelson for the excellent consumer peer review of this Cochrane Review.
References to studies included in this review

**Gathier 2018 (published data only)**


**Neil-Dwyer 1985 (published data only)**


**Togashi 2015 (published data only)**

**References to studies excluded from this review**

**An 2005 (published data only)**

**Bao 2004 (published data only)**

**Berge 2014 (published data only)**

**Bi 2017 (published data only)**

**Chang 2013a (published data only)**

**Chang 2013b (published data only)**

**Chen 2010 (published data only)**

**Chu 2013 (published data only)**

**Dong 2014 (published data only)**

**Dong 2015 (published data only)**

**Egge 2001 (published data only)**
Choudhari K. Prophylactic Hyperdynamic Postoperative Fluid Therapy after Aneurysmal Subarachnoid Hemorrhage: A Clinical, Prospective, Randomized, Controlled.
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Huang 2010 (published data only)

Huang 2017 (published data only)

Jia 2018 (published data only)

Li 2013 (published data only)

Li 2014 (published data only)

Li 2015 (published data only)

Liao 2017 (published data only)

Lin 1996 (published data only)

Lin 2010 (published data only)

Liu 2014 (published data only)

Li Y 2013 (published data only)
Ma 2014 (published data only)

MacDonald 2008 (published data only)

MacDonald 2011 (published data only)

MacDonald 2012 (published data only)

Nan 1991 (published data only)

Pei 2012 (published data only)

Polderman 2014 (published data only)
Polderman KH, Bajus D, Varon J. Use of clevidine (clevidipine) to control blood pressure (BP) in patients with intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). *Neurocritical Care* 2014;21(Suppl):223.

Potter 2009 (published data only)

Qi 2017 (published data only)

Reinert 2004 (published data only)

Shi 2006 (published data only)

Shi 2008 (published data only)

Song 2004 (published data only)

Song 2005 (published data only)

Tan 2001 (published data only)

Tan 2017 (published data only)

Tanaka 2015 (published data only)

Tao 2014 (published data only)

Unknown 2009 (published data only)

Wang 2004 (published data only)

Wang 2006a (published data only)
Additional references

Alfotih 2014

Amin-Hanjani 1999

Anderson 2008

Anderson 2013

Armin 2006

ATACH 2010

Baharoglu 2013

Bath 2014

Brathwaite 2014

Brok 2008
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

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Brok 2009

Budohoski 2014

Bunai 2000

Connolly 2012

Dankbaar 2010

DeMets 1987

de Rooij 2007

de Rooij 2013

DerSimonian 1986

Diringer 2011

Dupont 2010

Edlow 2000

Egger 1997

Fagerland 2015

Feigin 2005

Findlay 2016

Flaherty 2005

Francoeur 2016

Fujii 1996

Gathier 2018

Higgins 2021

Higgs 2021

Hróbjartsson 2014

ICH-GCP 1997

Ingall 2000

Jakobsen 2014

Grand 2018

Guyatt 2008

Harbord 2006

Higgins 2011a

Higgins 2011b

Hróbjartsson 2014

ICH-GCP 1997

Ingall 2000

Jakobsen 2014

Jakobsen 2016

Koch 2008

Koenig 2012

Kosnik 1976

Kramer 2013

Macdonald 2014

Marder 2014

Mees 2008

Moher 2009

Nieuwkamp 2009
Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurology 2009;8(7):635-42.

Oheda 2015
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

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Ohkuma 2001

Otsubo 1990

Qureshi 2016 (ATACH-2)

Raya 2014

Review Manager 2014 [Computer program]

Rinkel 2004

Rondeau 2012

Rücker 2008

Savovic 2018

Sen 2003

Starke 2011

Stata [Computer program]
Stata. College Station, TX, USA: StataCorp, 2014. Available at www.stata.com.

Steiner 2013

Suarez 2015

Takahara 1993

Tang 2014

Thorlund 2009

Thorlund 2011

Togashi 2015

TSA 2011 [Computer program]
Copenhagen Trial Unit Trial Sequential Analysis software. Version 0.9.5.10 Beta. Copenhagen, Denmark: Copenhagen Trial Unit, 2011. Available at www.ctu.dk/tsa/downloads.aspx.

van Gijn 2007

Veldeman 2016
Veldeman M, Höllig A, Clusmann H, Stevanovic A, Rossaint R, Coburn M. Delayed cerebral ischaemia prevention and treatment after aneurysmal subarachnoid haemorrhage:

**Vergouwen 2010**


**Wetterslev 2008**


**Wijdicks 1990**


**Zacharia 2010**


**Wu 2010**


**References to other published versions of this review**

**Maagaard 2018**


**CHARACTERISTICS OF STUDIES**

**Characteristics of included studies [ordered by study ID]**

**Gathier 2018**

**Study characteristics**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicentre, single-blind, randomised trial with masked outcome assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>SAH with an aneurysmatic bleeding pattern</td>
</tr>
<tr>
<td>Aged &gt; 18 years</td>
<td></td>
</tr>
<tr>
<td>Delayed cerebral ischaemia based on a decrease of ≥ 1 point on the Glasgow Coma Scale or the development of new focal neurological deficits according to NIHSS, diagnosed by a neurologist, neurosurgeon, or intensivist, unless the deterioration did not reflect delayed cerebral ischaemia as evaluated by the treating physician, or both decrease on GCS and development of new focal neurological deficits</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: co-existing severe head injury, perimesencephalic haemorrhage, history of ventricular cardiac rhythm disorders or heart failure, moribund, pregnancy, likely transfer to another hospital, and no informed consent</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Experimental group (n = 21): induced hypertension. Hypertension induced with fluids, if hypovolaemia was suspected as well as vasopressors. Positive inotropic agents could be added in case of low cardiac output. Vasopressors could be: noradrenaline, dopamine, phenylephrine, or terlipressin. Maximum mean arterial blood pressure aimed to be 130 mmHg or maximum systolic blood pressure aimed to be 230 mmHg. If participants showed no improvement in their neurological deficits within 24 hours, vasopressors were discontinued. Induced hypertension was continued for ≥ 48 hours in participants who showed improvement in their neurological deficits</td>
</tr>
<tr>
<td>Control group (n = 20): no hypertension. Therapy at the discretion of the treating physician. Hypotension (mean arterial blood pressure &lt; 80 mmHg) was prevented by low-dose vasopressors</td>
<td></td>
</tr>
<tr>
<td>Co-interventions: all participants received oral nimodipine and aimed for neutral fluid balance</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome</td>
</tr>
<tr>
<td>- Proportion of participants with poor outcome 3 months after randomisation (defined as modified Rankin Scale of 4, 5, or death)</td>
<td></td>
</tr>
</tbody>
</table>
Secondary outcomes

- Treatment failure (proportion of participants in the experimental group who did not achieve clinical improvement regarding symptoms of delayed cerebral ischaemia)
- Mortality 30 days after SAH
- Activities of daily living 3 months after randomisation
- Quality of life 3 months after randomisation (Stroke Specific Quality of Life Scale)
- Anxiety and depression 3 months after randomisation (Cognitive Failure Questionnaire)
- Functional outcome 12 months after randomisation (modified Rankin scale)
- Complications related to insertion of central venous catheter or intra-arterial catheter
- Intracranial complications related to induced hypertension including cardiac rhythm disorders, low cardiac output state, and cardiac ischaemia
- Direct medical costs of used healthcare resources compared between the 2 intervention groups 12 months after randomisation

Notes

Sources of support: none reported other than the support for the author CS Gathier

CS Gathier supported by the Dutch Heart Foundation (grant 2009B046) and the Brain Foundation Netherlands (grant 2009(1)-72). The other authors report no conflicts of interest

Follow-up closest to 3 months: 3 months

Maximal follow-up: 3 months

The trial was prematurely terminated due to lack of an effect on overall cerebral perfusion and slow recruitment

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Initially performed using sealed opaque envelopes, but was later changed to web-based randomisation with stratification for center with maximum random block size of eight.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “… web-based randomisation with stratification for center with maximum random block size of eight.”</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) all outcomes</td>
<td>High risk</td>
<td>Quote: “Clinical improvement within 24 hours was judged by the unblinded treating clinicians.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) all outcomes</td>
<td>Low risk</td>
<td>Quote: “Outcome measures were obtained by research nurses blinded for treatment allocation.”</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) all outcomes</td>
<td>Low risk</td>
<td>Quote: &quot;One patient randomised to the hypertension group did not receive treatment due to previously unknown cardiomyopathy.&quot;</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Protocol obtained, all outcomes reported.</td>
</tr>
</tbody>
</table>
### Gathier 2018 (Continued)

<table>
<thead>
<tr>
<th>Other bias</th>
<th>Low risk</th>
<th>No notable conflicts of interest.</th>
</tr>
</thead>
</table>

### Neil-Dwyer 1985

#### Study characteristics

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective, randomised, double-blind, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Aged 15–65 years, admitted within 48 hours of SAH confirmed by lumbar puncture</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: moribund, hypertension, ischaemic heart disease, congestive heart failure, or obstructive airways disease</td>
</tr>
<tr>
<td>Interventions</td>
<td>224 participants entered into trial</td>
</tr>
<tr>
<td></td>
<td>The first 118 participants received both phen tolamine 20 mg three-hourly and either propranolol 80 mg eight-hourly or placebo tablets</td>
</tr>
<tr>
<td></td>
<td>The last 106 participants received either propranolol long action 320 mg once daily or placebo</td>
</tr>
<tr>
<td></td>
<td>In the latter group, 50 participants were randomised so that 2 out of 3 participants received propranolol</td>
</tr>
<tr>
<td></td>
<td>Co-interventions: 6 participants received tranexamic acid, 18 received dexamethasone, anticonvulsants were administered to participants with seizure and as prophylactic treatment after surgery</td>
</tr>
<tr>
<td></td>
<td>Treatment was continued for 3 weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Neurological assessment on day 28 and at 1 year after SAH. Participants were graded as follows.</td>
</tr>
<tr>
<td></td>
<td>• Good outcome: no major neurological deficit, have returned to work or capable of working</td>
</tr>
<tr>
<td></td>
<td>• Poor outcome: major neurological deficit, incapable of returning to work</td>
</tr>
<tr>
<td>Notes</td>
<td>Sources of support: not reported</td>
</tr>
<tr>
<td></td>
<td>No mention of conflicts of interest</td>
</tr>
<tr>
<td></td>
<td>Follow-up closest to 3 months: 28 days</td>
</tr>
<tr>
<td></td>
<td>Maximal follow-up: 1 year</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No mention of randomisation method.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No mention of allocation concealment.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) all outcomes</td>
<td>Low risk</td>
<td>Quote: “Treatment was double-blind, only the anaesthetists has access to the code.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Judgement: probably done.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned.</td>
</tr>
</tbody>
</table>
### Neil-Dwyer 1985 (Continued)

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias) all outcomes</th>
<th>Low risk</th>
<th>11 participants from intervention group and 9 from control group withdrew.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol could be obtained. Only death from all causes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No mention of conflicts of interest.</td>
</tr>
</tbody>
</table>

### Study characteristics

|Methods| Open-label, randomised, controlled pilot trial using a 2-way factorial design |
|Participants| Men and women aged ≥ 18 years with aneurysmal SAH of any clinical grade documented on CT scan treated with clipping or coiling within 72 hours of bleeding. Exclusion criteria: history of traumatic SAH; non-aneurysmal SAH; presence of an unsecured intracranial aneurysm at risk of rupture; delayed referral with clipping or coiling after 72 hours of initial bleeding; undetermined time of symptom onset; intracranial hypertension (intracranial pressure > 25 mmHg); history within the past 6 months or physical findings on admission of decompensated congestive heart failure; acute or recent myocardial infarction; second- or third-degree atrioventricular block; chronic renal failure requiring dialysis; suspected or confirmed pregnancy; non-English speaking; prior Alzheimer’s, stroke, degenerative condition, cerebral tumour, or mental retardation; severe terminal disease with < 6 months’ life expectancy; refusal of informed consent. |
|Interventions| Experimental group (n = 10): normovolemic or hypervolemic and augmented blood pressure (systolic blood pressure goal 140–220 mmHg) using noradrenaline or phenylephrine. Control group (n = 10): normovolemic or hypervolemic and conventional blood pressure (systolic blood pressure goal 120–160 mmHg) using noradrenaline or phenylephrine to increase blood pressure and labetalol or hydralazine to decrease blood pressure. |
|Outcomes| Primary outcome | Modified Rankin Scale at 6 months as assessed by the extended Glasgow Outcome Scale and neurobehavioural performance using various neuropsychological tests. Secondary outcomes | Changed in transcranial doppler velocities | Occurrence of delayed cerebral ischaemia | New stroke on CT scan | Serious adverse events | Adverse events |
|Notes| Sources of support: the Anesthesiology and Critical Care Outcome Research Network (ACCORN) and departmental seed funds. The authors reported no personal, financial, or institutional conflicts of interest. Follow-up closest to 3 months: 10 days | Maximal follow-up: 6 months |
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Quote: &quot;Computer-generated random number list.&quot;</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td>Judgement: probably done.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Quote: &quot;Allocation was concealed in sequential sealed envelopes.&quot;</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td>Judgement: probably done.</td>
</tr>
<tr>
<td>Blinding of participants and</td>
<td>High risk</td>
<td>Quote: &quot;Single-blinded, as participants were not aware of the treatment allocation;</td>
</tr>
<tr>
<td>personnel (performance bias)</td>
<td></td>
<td>however, caregivers were aware of the study algorithms.&quot;</td>
</tr>
<tr>
<td>all outcomes</td>
<td></td>
<td>Judgement: probably done.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>Quote: &quot;The outcome evaluation was objective in nature and the assessments were</td>
</tr>
<tr>
<td>(detection bias)</td>
<td></td>
<td>collected by investigators blinded to the treatment allocation.&quot;</td>
</tr>
<tr>
<td>all outcomes</td>
<td></td>
<td>Judgement: probably done.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>Quote: &quot;No patients who dropped out post-randomisation or were lost to follow-up at</td>
</tr>
<tr>
<td>(attrition bias)</td>
<td></td>
<td>six months.&quot;</td>
</tr>
<tr>
<td>all outcomes</td>
<td></td>
<td>Judgement: probably done.</td>
</tr>
<tr>
<td>Selective reporting (reporting</td>
<td>Low risk</td>
<td>No protocol available, but death from all causes and death or dependency.</td>
</tr>
<tr>
<td>bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No conflicts of interest.</td>
</tr>
</tbody>
</table>

CT: computed tomography; n: number of participants; NIHSS: National Institutes of Health Stroke Scale; SAH: subarachnoid haemorrhage.

**Characteristics of excluded studies** [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>An 2005</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Bao 2004</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Berge 2014</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>BI 2017</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Chang 2013a</td>
<td>Intervention not aimed at altering arterial blood pressure.</td>
</tr>
<tr>
<td>Chang 2013b</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Chen 2010</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Chu 2013</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Dong 2014</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dong 2015</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Egge 2001</td>
<td>Triple-H therapy (haemodilution, hypervolaemia, hypertension) vs no intervention; therefore, not strictly induced hypertension vs no intervention.</td>
</tr>
<tr>
<td>Fan 2003</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Fang 2003</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Frontera 2010</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Gan 2012</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Gomis 2010</td>
<td>Methylprednisolone as experimental intervention; this has a different mode of action and is not aimed at controlling blood pressure.</td>
</tr>
<tr>
<td>Graf 1974</td>
<td>Not true randomisation. Physician preference could place participants in either of the intervention groups.</td>
</tr>
<tr>
<td>Graf 1981</td>
<td>Not true randomisation. Physician preference could place participants in either of the intervention groups.</td>
</tr>
<tr>
<td>Hu 1998</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Hu 2017</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Huang 2010</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Huang 2017</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Jia 2018</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Li 2013</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Li 2014</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Li 2015</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Liao 2017</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Lin 1996</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Lin 2010</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Liu 2014</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Li Y 2013</td>
<td>Wrong intervention.</td>
</tr>
<tr>
<td>Ma 2014</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>MacDonald 2008</td>
<td>Clazosentan as experimental intervention; this has a different mode of action and is not aimed at controlling blood pressure.</td>
</tr>
<tr>
<td>MacDonald 2011</td>
<td>Clazosentan as experimental intervention; this has a different mode of action and is not aimed at controlling blood pressure.</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MacDonald 2012</td>
<td>Clazosentan as experimental intervention; this has a different mode of action and is not aimed at controlling blood pressure.</td>
</tr>
<tr>
<td>Nan 1991</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Pei 2012</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Polderman 2014</td>
<td>No data regarding SAH participants.</td>
</tr>
<tr>
<td>Potter 2009</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Qi 2017</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Reinert 2004</td>
<td>Both experimental and control groups received antihypertensive drugs.</td>
</tr>
<tr>
<td>Shi 2006</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Shi 2008</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Song 2004</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Song 2005</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Tan 2001</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Tan 2017</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Tanaka 2015</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Tao 2014</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Unknown 2009</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Wang 2004</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Wang 2006a</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Wang 2006b</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Wang 2016</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Wang 2020</td>
<td>Non-haemorrhagic intracranial aneurysm.</td>
</tr>
<tr>
<td>Wijdicks 1990</td>
<td>Retrospective observational study.</td>
</tr>
<tr>
<td>Wu 2006a</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Wu 2006b</td>
<td>Participants did not have SAH.</td>
</tr>
<tr>
<td>Yano 1993</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Zall 1990</td>
<td>Both experimental and control groups received antihypertensive drugs (adenosine vs nitroglycerin).</td>
</tr>
<tr>
<td>Zhang 1962</td>
<td>Not randomised.</td>
</tr>
</tbody>
</table>
**SAH: subarachnoid haemorrhage.**

**DATA AND ANALYSES**

### Comparison 1. Death from all causes

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Death from all causes closest to 3 months</td>
<td>2</td>
<td>61</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.60 [0.57, 4.52]</td>
</tr>
<tr>
<td>1.2 Death from all causes at maximal follow-up</td>
<td>2</td>
<td>61</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.60 [0.57, 4.52]</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1: Death from all causes, Outcome 1: Death from all causes closest to 3 months**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Induced hypertension</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Gathier 2018</td>
<td>6</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7</td>
<td>31</td>
<td>4</td>
</tr>
</tbody>
</table>

Total events: 31

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%

Test for overall effect: Z = 0.89 (P = 0.38)

Test for subgroup differences: Not applicable

**Analysis 1.2. Comparison 1: Death from all causes, Outcome 2: Death from all causes at maximal follow-up**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Induced hypertension</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Gathier 2018</td>
<td>6</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7</td>
<td>31</td>
<td>4</td>
</tr>
</tbody>
</table>

Total events: 31

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%

Test for overall effect: Z = 0.89 (P = 0.38)

Test for subgroup differences: Not applicable
## Comparison 2. Death or dependency

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Death or dependency closest to 3 months</td>
<td>2</td>
<td>61</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.29 [0.78, 2.13]</td>
</tr>
<tr>
<td>2.2 Death or dependency at maximal follow-up</td>
<td>2</td>
<td>61</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.29 [0.78, 2.13]</td>
</tr>
</tbody>
</table>

### Analysis 2.1. Comparison 2: Death or dependency, Outcome 1: Death or dependency closest to 3 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Induced hypertension</th>
<th>Control</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Gathier 2018</td>
<td>14</td>
<td>21</td>
<td>95.8%</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>1</td>
<td>10</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>31</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

- Total events: 15
- Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
- Test for overall effect: Z = 0.98 (P = 0.33)
- Test for subgroup differences: Not applicable

### Analysis 2.2. Comparison 2: Death or dependency, Outcome 2: Death or dependency at maximal follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Induced hypertension</th>
<th>Control</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Gathier 2018</td>
<td>14</td>
<td>21</td>
<td>95.8%</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>1</td>
<td>10</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>31</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

- Total events: 15
- Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
- Test for overall effect: Z = 0.98 (P = 0.33)
- Test for subgroup differences: Not applicable

## Comparison 3. Serious adverse events

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Serious adverse events closest to 3 months</td>
<td>2</td>
<td>61</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.24 [1.01, 4.99]</td>
</tr>
<tr>
<td>3.2 Serious adverse events at maximal follow-up</td>
<td>2</td>
<td>61</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.24 [1.01, 4.99]</td>
</tr>
</tbody>
</table>
### Analysis 3.1. Comparison 3: Serious adverse events, Outcome 1: Serious adverse events closest to 3 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Induced hypotension</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathier 2018</td>
<td>11</td>
<td>5</td>
<td>83.7%</td>
<td>2.10 [0.89, 4.96]</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>3</td>
<td>1</td>
<td>16.3%</td>
<td>3.00 [0.37, 24.17]</td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td><strong>31</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
<td>2.24 [1.01, 4.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable

<table>
<thead>
<tr>
<th>Induced hypertension</th>
<th>Events</th>
<th>Total</th>
<th>Control</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathier 2018</td>
<td>11</td>
<td>21</td>
<td>5</td>
<td>20</td>
<td>10</td>
<td>83.7%</td>
<td>2.10 [0.89, 4.96]</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>3</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>16.3%</td>
<td>3.00 [0.37, 24.17]</td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td><strong>31</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td>2.24 [1.01, 4.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable

### Analysis 3.2. Comparison 3: Serious adverse events, Outcome 2: Serious adverse events at maximal follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Induced hypotension</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathier 2018</td>
<td>11</td>
<td>5</td>
<td>83.7%</td>
<td>2.10 [0.89, 4.96]</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>3</td>
<td>1</td>
<td>16.3%</td>
<td>3.00 [0.37, 24.17]</td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td><strong>31</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
<td>2.24 [1.01, 4.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable

<table>
<thead>
<tr>
<th>Induced hypertension</th>
<th>Events</th>
<th>Total</th>
<th>Control</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gathier 2018</td>
<td>11</td>
<td>21</td>
<td>5</td>
<td>20</td>
<td>10</td>
<td>83.7%</td>
<td>2.10 [0.89, 4.96]</td>
</tr>
<tr>
<td>Togashi 2015</td>
<td>3</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>16.3%</td>
<td>3.00 [0.37, 24.17]</td>
</tr>
<tr>
<td><strong>Total</strong> (95% CI)</td>
<td><strong>31</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td></td>
<td>2.24 [1.01, 4.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable

Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

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### ADDITIONAL TABLES

#### Table 1. Definition and follow-up of outcomes in trials comparing induced hypertension with placebo or no intervention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials (year)</th>
<th>Outcome reported in published articles</th>
<th>Definition/scale used</th>
<th>Primary, secondary, or explorative outcome in trial</th>
<th>Follow-up period or day of assessment (after inclusion in trial)</th>
<th>Risk of bias: blinding of outcome assessor</th>
<th>Risk of bias: selective outcome reporting</th>
<th>Risk of bias: incomplete outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all causes</td>
<td>Togashi 2015</td>
<td>Yes</td>
<td>Not applicable</td>
<td>Secondary</td>
<td>6 months</td>
<td>Low risk of bias. Outcome assessors were blinded to treatment allocation.</td>
<td>Low risk of bias. Outcome reported.</td>
<td>Low risk of bias.</td>
</tr>
<tr>
<td></td>
<td>Gathier 2018</td>
<td>Yes</td>
<td>Not applicable</td>
<td>Secondary</td>
<td>3 months</td>
<td>Low risk of bias. Outcome assessors were blinded to treatment allocation.</td>
<td>Low risk of bias. Outcome reported.</td>
<td>Low risk of bias.</td>
</tr>
<tr>
<td>Death or dependency</td>
<td>Togashi 2015</td>
<td>Yes</td>
<td>Modified Rankin scale</td>
<td>Primary outcome</td>
<td>6 months</td>
<td>Low risk of bias for both outcome measures as the outcome assessors were blinded to treatment allocation.</td>
<td>Low risk of bias. Outcome reported.</td>
<td>Low risk of bias.</td>
</tr>
<tr>
<td></td>
<td>Gathier 2018</td>
<td>Yes</td>
<td>Modified Rankin scale</td>
<td>Primary outcome</td>
<td>3 months</td>
<td>Low risk of bias. Outcome assessors were blinded to treatment allocation.</td>
<td>Low risk of bias. Outcome reported.</td>
<td>Low risk of bias.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Togashi 2015</td>
<td>Yes</td>
<td>Not specified</td>
<td>Secondary</td>
<td>Not specified</td>
<td>Low risk of bias. Outcome assessors were blinded to treatment allocation.</td>
<td>Unclear risk of bias. Protocol not available and trial not registered. Definition of outcome was not specified in article other than (quote) &quot;we also monitored and recorded occurrences of serious adverse events and</td>
<td>Low risk of bias.</td>
</tr>
</tbody>
</table>

Cochrane Library
Cochrane Database of Systematic Reviews
Table 1. Definition and follow-up of outcomes in trials comparing induced hypertension with placebo or no intervention (Continued)

<table>
<thead>
<tr>
<th>Quality of life</th>
<th>Togashi 2015</th>
<th>Yes</th>
<th>Stroke Specific Quality of Life</th>
<th>Secondary</th>
<th>D-90</th>
<th>Low risk of bias.</th>
<th>Low risk of bias, as trial protocol or prospective trial registration was available.</th>
<th>Low risk of bias.</th>
<th>No loss to follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>Togashi 2015</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Unclear risk of bias.</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Quote: “An SAE is any untoward medical occurrence in a patient or trial subject, which does not have a causal relationship with the treatment, and: (1) results in death; (2) is life threatening (at the time of the event); (3) requires prolongation of inpatients’ hospitalization; (4) results in persistent or significant disability or incapacity; (5) is a new event of the trial likely to affect the safety of the subjects”
| Delayed cerebral ischaemia | Togashi 2015 | No  | —     | —     | —     | Unclear risk of bias.  
Outcome reported, but it was not specified with the diagnosis was clinical or radiological.  
No protocol available and outcome not reported. |  
| Gathier 2018 | Yes  | Included as a serious adverse event. Not specified if the diagnosis was clinical or radiological  
Quote: “During hospital admission.”  
High risk of bias.  
The treating physicians and nurses were not blinded to treatment allocation. Therefore, the clinical assessment leading to testing for delayed cerebral ischaemia was performed by personnel not blinded to treatment allocation. | Secondary  
Not specified | High risk of bias.  
The treating physicians and nurses were not blinded to treatment allocation. Therefore, the clinical assessment leading to testing for delayed cerebral ischaemia was performed by personnel not blinded to treatment allocation.  
Low risk of bias.  
Outcome reported and systematically assessed.  
Low risk of bias.  
No loss to follow-up. |  
| Hydrocephalus | Not reported in any trials | —     | —     | —     | —     | —     | —     | —     |
### Table 2. Definition and follow-up of outcomes in trials comparing lowered blood pressure with placebo or no intervention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials (year)</th>
<th>Outcome reported in published articles</th>
<th>Definition/scale used</th>
<th>Primary, secondary, or explorative outcome in trial</th>
<th>Follow-up period or day of assessment (after inclusion in trial)</th>
<th>Risk of bias: blinding of outcome assessor</th>
<th>Risk of bias: selective outcome reporting</th>
<th>Risk of bias: incomplete outcome data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from all causes</td>
<td>Neil-Dwyer 1985</td>
<td>Yes</td>
<td>Not applicable</td>
<td>Not specified</td>
<td>12 months</td>
<td>Unclear risk of bias. Blinding of outcome assessor not mentioned.</td>
<td>Low risk of bias. Outcome reported.</td>
<td>Low risk of bias. 11 participants in intervention group and 9 participants lost to follow-up in control group lost to follow-up.</td>
</tr>
<tr>
<td>Death or dependency</td>
<td>Neil-Dwyer 1985</td>
<td>No</td>
<td>Only death from all causes reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Not reported in any trials</td>
<td>No</td>
<td>Only death from all causes reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Not reported in any trials</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>Not reported in any trials</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Delayed cerebral ischaemia</td>
<td>Not reported in any trials</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Not reported in any trials</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees 613
#2 MeSH descriptor: [Intracranial Hemorrhages] this term only 260
#3 MeSH descriptor: [Intracranial Aneurysm] this term only 519
#4 MeSH descriptor: [Rupture, Spontaneous] this term only 125
#5 #3 and #4 30
#6 MeSH descriptor: [Aneurysm, Ruptured] this term only 154
#7 MeSH descriptor: [Brain] explode all trees 11154
#8 MeSH descriptor: [Meninges] explode all trees 300
#9 #7 or #8 11432
#10 #6 and #9 11
#11 ((subarachnoid or arachnoid) near/6 (haemorrhage* or hemorrhage* or bleed* or blood*)):ti,ab,kw (Word variations have been searched) 1686
#12 MeSH descriptor: [Vasospasm, Intracranial] this term only 161
#13 ((cerebral or intracranial or cerebrovascular) near/6 (vasospasm or spasm)):ti,ab,kw (Word variations have been searched) 433
#14 SAH:ti,ab,kw (Word variations have been searched) 577
#15 #1 or #2 or #5 or #10 or #11 or #12 or #13 or #14 2134
#16 MeSH descriptor: [Antihypertensive Agents] explode all trees 8024
#17 (antihypertens* or anti-hypertens*):ti,ab,kw (Word variations have been searched) 17144
#18 ((blood pressure or hypertension*) near/5 (lower* or reduc* or decreas* or control*)):ti,ab,kw (Word variations have been searched) 29224
#19 ((high or elevat* or rais*) near/2 blood pressure):ti,ab,kw (Word variations have been searched) 3828
#20 MeSH descriptor: [Vasodilator Agents] explode all trees 3803
#21 vasodilat*:ti,ab,kw (Word variations have been searched) 10381
#22 (acetylcholine or adenosine or adrenomedullin or alprostadil or amiodarone or amiodipine or amrinone or amyl nitrite or bencyclane or bepridil or beta-histidine or bradykinin or calcium or celioprol or chromonor or collforsin or cromakalim or cyclandelate or diazoxide or dihydroyeorgcristine or dihydroergocryptine or dilazep or diltiazem or diprydamole or diphylline or enoxime or ergoloid mesylates or erythritol or erythriptyl tetranitrare or felodipine or fenoldopam or flunarizine or hexobendine or hydralazine or iloprost or isorbidin nitrate or isosuprin or isradipine or kallidin or khellin or lidoflazine or mibebradil or milrinone or molsidomine or moxonil or nafronyl or nebivolol or nicardipine or nicergoline or nicorandil or nicotinol or nifedipine or nisoldipine or nisordipine or nitrendipine or nitric oxide or nitroglycerin or nitroprusside or nonachlazine or nyldrin or opxenrotil or oxyfedrine or papavere or pentaerythritol tetranitrare or pentoyxilwine or perhexilme or phenoxypamazine or pinacidil or pindolol or polynamylene or pranoprotil or proranolol or sildenafil citrate or sodium azide or nusloidil or tadalafil or theobromine or theophylline or thioclor or tolazoline or triapidil or trimetazidine or verapamil or vincaine or xanthinol):ti,ab,kw (Word variations have been searched) 48309
#23 [or #16–#22] 82811
#24 MeSH descriptor: [Calcium Channel Blockers] explode all trees 2929
#25 (calcium near/3 (inhibit* or antagonist? or block*)):ti,ab,kw (Word variations have been searched) 6520
#26 (amiodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxinis or diltiazem or felodipine or fendline or flunarizine or gallopamil or isradipine or lidoxyline or mibebradil or nicardipine or nifedipine or nitrosedipine or nitrendipine or perhexilme or preylamine or tiapamil hydrochlorivelverapamil or omega-agatoxin iva or omega-conotoxyn gia or omega-conotoxynsb):ti,ab,kw (Word variations have been searched) 13524
#27 [or #24–#26] 16438
#28 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees 4113
#29 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees 2141
#30 ((angiotensin or dipetidyl) near/3 (convert* or enzyme or inhibit* or receptor* or block* or antagonist*)):ti,ab,kw (Word variations have been searched) 13028
#31 (((ace or renin) near/3 inhibit*) or ACEI):ti,ab,kw (Word variations have been searched) 4830
#32 (aceplapril or altipirapril or benazepril or captopril or ceronapril or clazapril or delapril or enalapril or fosinopril or iradipil or imidapril or lisinopril or moexipril or movetipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril or aliskiren or renikmin):ti,ab,kw (Word variations have been searched) 9677
#33 (KT3-671 or candesarat or eprosartan or irbesartan or losartan or olmesartan or tasosartan or telsimartan or valsartan):ti,ab,kw (Word variations have been searched) 6366
#34 (abetensartan or azilsartan or candesarat or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milvasartan or olmesartan or sapiroatan or tasosartan or telsimartan or valsartan or zolasartan):ti,ab,kw (Word variations have been searched) 6426
#35 [or #28–#34] 21182
#36 MeSH descriptor: [Adrenergic Antagonists] explode all trees 5810
#37 (andrenergic near/3 (alpha or antagonist*)):ti,ab,kw (Word variations have been searched) 1
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

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Appendix 2. MEDLINE Ovid search strategy

1. Subarachnoid Hemorrhage/
2. intracranial hemorrhages/or cerebral hemorrhage/
3. Intracranial Aneurysm/
4. Rupture, Spontaneous/
5. 3 and 4
6. Aneurysm, Ruptured/
7. exp brain/ or exp meninges/
8. 6 and 7
9. ((subarachnoid or arachnoid) adj6 (haemorrhage$ or hemorrhage$ or bleed$ or blood$)).tw.
10. Vasospasm, Intracranial/
11. ((cerebral or intracranial or cerebrovascular) adj6 (vasospasm or spasm)).tw.
12. subarachnoid haemorrhage.tw.
13. 1 or 2 or 5 or 8 or 9 or 10 or 11 or 12
14. exp Antihypertensive Agents/
15. (anti-hyptertens$ or anti-hypertension$).tw.
16. (blood pressure or hypertens$) adj5 (lower$ or reduc$ or decreases or control$)).tw.
17. (high or elevat$ or rais$) adj2 blood pressure).tw.
18. exp Vasodilator Agents/
19. vasodilat$ .tw.
20. (acetylcholine or adenosine or adrenomedullin or alprostadil or amiodarone or amlodipine or amrinone or amyl nitrite or bencyclane or bepridil or betahtistine or bradykinin or calcitonin or celiprolol or chromonar or colforsin or cromakalim or diazoxide or dihydroergocristine or dihydroergocryptine or dilazep or diltiazem or dipyridamole or dphylline or enoximone or ergoloid mesylates or erythritol or erythrityl tetranitrate or felodipine or fenoldopam or flunarizine or hexobendine or hydralazine or iloprost or isosorbide dinitrate or isosuprine or isradipine or kallidin or kheilin or lidoflazine or mibefradil or milrinone or minoxidil or molsidomine or moxisylyte or nafronril or nebivolol or niciaridine or nicergoline or nicorandil or nicotinyl or nifedipine or nimodipine or nisoldipine or nitrendipine or nitric oxide or nitroglycerin or nitroprusside or nonachlazine or nylidrin or oxyprenol or oxyedrine or papaverine or pentaerythor tetranitrate or pentoxifylline or perhexiline or phenoxybenzamine or pinacidil or pindolol or polymethyl or prenylamine or propranolol or sildenafil citrate or sodium azide o rsuloctid il or tadalafl or theobromine or theophylline or thiouaracil or tolaelozole or trapidil or trimetazidine or verapamil or vincamine or xanthinol).tw.
21. or/14-20
22. exp Calcium Channel Blockers/
23. (calcium adj3 (inhibit$ or antagonist? or block$)).tw.
24. (amlodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazem or felodipine or fendiline or flunarizine or gallopam or isradipine or lidoflazine or magnesium sulfate or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or tiapamil hydrochlorideverapamil or omega-agatoxin iiva or omega-conotoxin gvia or omega-conotoxins).tw.
25.or/22-24
26. exp Angiotensin-Converting Enzyme Inhibitors/ or exp Angiotensin Receptor Antagonists/
27. ((angiotensin or dipeptidy$) adj3 (convert$ or enzyme or inhibit$ or recept$ or block$)).tw.
28. (((ace or renin) adj3 inhibit$) or ACEI).tw.
29. expenalapril/
30. (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril or aliskiren or remikiren).tw.
31. exp losartan/
32. (KT3-671 or candesartan or eprosartan or irbesartan or losartan or olmesartan or tasosartan or valsartan).tw.
33.or/26-32
34. adrenergic antagonists/ or exp adrenergic alpha-antagonists/ or exp adrenergic beta-antagonists/
35. (andrenergic adj3 (alpha or antagonist$)).tw.
36. (andrenergic or alpha or receptor$) adj3 block$.tw.
37. (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw.
38. (beta adj3 (antagonist$ or receptor$ or adrenergic? block$)).tw.
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)
Appendix 3. Embase search strategy

1. subarachnoid hemorrhage/
2. subarachnoid space/
3. exp brain hemorrhage/ or brain artery aneurysm rupture/
4. exp intracranial aneurysm/ or carotid artery aneurysm/
5. rupture/ or blood vessel rupture/
6. 4 and 5
7. aneurysm/ or aneurysm rupture/
8. exp brain/ or exp meninx/
9. 7 and 8
10. ((subarachnoid or arachnoid) adj6 (haemorrhage$ or hemorrhage$ or bleed$ or blood$)).tw.
11. ((cerebral or brain or intracranial or cerebrovascular) adj5 (vasospasm or spasm)).tw.
12. sah.tw.
13. 1 or 2 or 3 or 6 or 9 or 10 or 11 or 12
14. exp antihypertensive agent/ or antihypertensive therapy/
15. (antihypertens$ or anti-hypertens$).tw.
16. ((blood pressure or hypertens$) adj5 (lower$ or reduc$ or decreas$ or control$)).tw.
17. ((high or elevat$ or rais$) adj2 blood pressure).tw.
18. exp vasodilator agent/
19. vasodilat$.
20. (acetycholine or adenosine or adrenomedullin or alprostadil or amiodarone or amloidipine or amrinone or amyl nitrite or bencyclane or bepridil or betahistine or bradykinin or calcitonin or celioprol or chromonar or colforsin or cromakalim or cyclandelate or diazoxide or dihydroergocristine or dihydroergocryptine or dilapez or diltiazem or dipyridamole or dyp hyline or enoximone or ergoloid mesylates or erythritol or erythryl tetranitrate or felodipine or fenoldopam or flunarizine or hexobendine or hydralazine or iloprost or isosorbide dinitrate or isoxsuprine or kallidin or khellin or lidoflazine or mibefradil or milrinone or molsidomine or mosixylute or nafonryl or nebivolol or nicardipine or nercergolin or nicoandil or nicotinyl or nifedipine or nimodipine or nitroprusside or nitroprusside or nitroglycerin or nitroprusside or nonachlazine or ny lidrin or oxprenol or oxfedrine or papaverine or pentaerythritol tetranitrate or pentoxifylline or perhexiline or phenoxbenzamine or pinacidil or pindolol or polymethyl or prenylimane or propronolol or sildenafil citrate or sodium azide or sru loctidil or tadalafl or theobromine or theophylline or thiourea or tolazoline or troplidil or trimetazidine or verapamil or vincamine or xanthinol).tw.
21. or/14-19
22. exp calcium channel blocking agent/
23. (calcium adj3 (inhibit$ or antagonist? or block$)).tw.
24. (amloidipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazem or felodipine or fenduline or flunarizine or gallopamil or isradipine or lidoflazine or magnesium sulfate or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or nitroglycerin or nitroprusside or nonachlazine or ny liden or oxprenol or oxyprene or papaverine or pentaerythritol tetranitrate or pentoxifylline or perhexiline or phenoxbenzamine or pinacidil or pindolol or polymethyl or prenylimane or propronolol or sildenafil citrate or sodium azide or su loctidil or tadalafl or th eobromine or theophylline or thiourea or tolazoline or troplidil or trimetazidine or verapamil or vincamine or xanthinol).tw.
25. or/22-24
26. exp angiotensin antagonist/
27. angiotensin converting enzyme inhibit$.tw.
28. (angiotensin adj3 (receptor antagonist$ or receptor block$)).tw.
29. (ace or renin) adj3 inhibit$.tw or ACEI).tw.
30. (alacepril or alltopril or anconenin or benazepril or captopril or ceranapril or cienapril or clazapril or deacteylacepril or delapril or derapril or enalapril or enalanapril or epicaptopril or fasilodril or fosinopril or foroxymithine or gempatrilat or idapril or imidapril or indapapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or ramiplir$ or rentiapril or saralasin or s or nitrosocaptopril or spirapril$ or temocapril$ or teprotide or trandolapril$ or utiapril$ or zabicipril$ or zofenopril$).tw.
31. (abtesaran or azilsartan or candesartan or dasatan or elisartan or embusarten or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesaran or saprisarten or tasosarten or telmisarten or valsarten or zolasarten).tw.
32. (KT3-671 or candesartan or eprosartan or irbesartan or losartan or olmesaran or tasosarten or telmisarten or valsarten).tw.
33. or/26-32
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)

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Appendix 4. Web of Science search strategy

#73 #72 AND #59 AND #3
#72 #71 OR #70 OR #69 OR #68 OR #67 OR #66 OR #65 OR #64 OR #63 OR #62 OR #61 OR #60
#71 TS=controls
#70 TS=(assign* or allocat*)
#69 Ti=trial
#68 TS=(placebo* or sham)
#67 TS=(cross-over or cross over or crossover)
#66 TS=(singl* or doubl* or tripl* or trebl*) NEAR/5 (blind* or mask*)
#65 TS=((control or experiment* or intervention) NEAR/5 (treatment or therapy or procedure or manage*))
#64 TS=(quasi-random* or quasi random* or pseudo-random* or pseudo random*)
#63 TS=((control or treatment or experiment* or intervention) NEAR/5 (group* or subject* or patient*))
#62 TS=(clinical* NEAR/5 trial*)
#61 TS=((controlled NEAR/5 (trial* or stud*))
#60 TS=(random* or RCT or RCTs)
#59 #58 OR #34
#58 #57 OR #53 OR #44
#57 #56 OR #55 OR #54
Interventions for altering blood pressure in people with acute subarachnoid haemorrhage (Review)
or cyanoidopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalpenrolol or dilevalol or epanolol or esmolol or exaprolol or flatinol or fieslitol or fluoxoxolol or hydroxybenzylpindolol or hydroxycarteolol or hydroxymetropolol or indenolol or iodocyanopindolol or iodopindolol or iopirocol or isoxaprolol or laboutal or landirol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprokol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nifedarol or nifediprol or oxeprenalol or pafenalol or pamatalol or penbutolol or pindolol or pratolol or pridmilodol or prizdilol or proncalol or pronenalol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tetaanolol or tiisoxolol or tilisolol or timolol or tolamolol or tolpoprolol or tribendiol or xibenolol)
# 22 TS=(beta near/3 (antagonist* or receptor* or "adrenergic? block"))
# 21 TS=(alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin)
# 20 TS=(|endeenergetic or alpha or receptor*) near/3 block*)
# 19 TS=(|endeenergetic near/3 (alpha or antagonist*))
# 18 #17 OR #16 OR #15 OR #14 OR #13
# 17 TS=(abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or spirisartan or telmisartan or valsartan)
# 16 TS=(|TK3-671 or candesartan or eprosartan or losartan or olmesartan or telmisartan or valsartan)
# 15 TS=(|alsepril or alitopril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spiropril or temocapril or trandolapril or zofenopril or aliskiren or remikiren)
# 14 TS=((|ace or renin) near/3 inhibit* or ACEI)
# 13 TS=(|angiotensin or dipeptidyl) near/3 (convert* or enzyme or inhibit* or receptor* or block* or ant agon*))
# 12 #11 OR #10
# 11 TS=(|amlodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazem or felodipine or feldiniline or flumarizine or gallopamil or isradipine or lidofazline or magnesium sulfate or mibebradil or nicardipine or nifedipine or nimodipine or nitrendipine or or perhexiline or prenylamine or tiapamil hydrochlorideverapamil or omega-agatoxin iva or omega-conotoxin gvi or omega-conotoxins)
# 10 TS=(|calcium near/3 (inhibit* or antagonist? or block*))
# 9 #8 OR #7 OR #6 OR #5 OR #4 OR #3
# 8 TS=(|acetycholine or adenosine or adrenomedullin or alprostadil or amiodarone or amiodipine or amrinone or amyl nitrite or bencyclane or bepridil or betaadine or bradykinin or calcitonin or celiprolol or chromonar or cromakalim or cyclandelate or dixonide or dihydroergocristine or dihydroergocryptine or dilazep or diltiazem or diprydamole or diphyllyne or enoximone or ergolid mesylates or erythritol or erythryll tetranitrate or felodipine or fenoldopam or flumarizine or hexobendine or hydralazine or iloprost or isosorbide dinitrate or isoxsuprine or isradipine or kallidin or khelein or lidofazline or mibebradil or mliarinone or minoxidil or molsidomine or molsidone or msynoxyl or mnefobil or naciazin or nicardipine or nigerine or nicardipindil or nifedipine or nimodipine or nisoldipine or nitrendipine or nitric oxide or nitroglycerin or nitrophrine or nonnachazine or nylinid in or oxprenolol or oxyfendine or papaverine or penetaerythritol tetranitrate or pentoxifylline or perhexiline or phenoxybenzamine or pinacilid or pindolol or polymethyl or prenylamine or propranolol or sildenafil citrate or sodium azide or sulocilidt or tadafalid or theobromine or theophylline or theouracil or tozoloinol or trapidil or trimetazidine or verapamil or vincamine or xanthinol)
# 7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 6 TS=((|high or elevat* or rais*) near/2 blood pressure)
# 5 TS=((|blood pressure* or hypertens*) near/5 (lower* or reduc* or decreas* or control*))
# 4 TS=(|antihypertens* or anti-hypertens*)
# 3 #2 OR #1
# 2 TS=((|cerebral or intracranial or cerebrovascular) near/6 (vasospasm or spasmsg))
# 1 TS=(|subarachnoid or arachnoid) near/6 (haemorrhage* or hemorrhage* or bleed* or blood*))

Appendix 5. LILACS search strategy

Latin American and Caribbean Health Sciences Literature

1. hemorragia subaracnoidea

Appendix 6. CBM search strategy

1. 全部字段= 蛛网膜下腔出血 or 颅内出血 or 脑出血 or 动脉瘤破裂 or 血管痉挛
2. 全部字段= 抗高血压药 OR 抗高血压 OR 血压升高 OR 血管扩张剂 OR 钙阻滞剂 OR 钙拮抗剂 OR 血管紧张素转化酶抑制剂 OR 血管紧张素受体拮抗剂 OR 肾上腺素能拮抗剂 OR 糖皮质激素
3. 1 and 2

Appendix 7. CNKI search strategy

1. SU=('蛛网膜下腔出血'+'颅内出血'+'脑出血'+'动脉瘤破裂'+'血管痉挛')
Appendix 8. VIP search strategy

1. U=蛛网膜下腔出血 OR 所内出血OR 脑出血OR 动脉瘤破裂OR 血管痉挛
2. U=(抗高血压药 OR 抗高血压 OR 血压升高 OR 血管扩张剂 OR 钙阻滞剂 OR 钙拮抗剂 OR 血管紧张素转化酶抑制剂 OR 血管紧张素受体拮抗剂 OR 肾上腺素能拮抗剂 OR 糖皮质激素)
HIGH BLOOD PRESSURE DISORDER, HIGH BLOOD PRESSURES, HIGH BP, HIGH; ARTERIAL TENSION, HIGH; BLOOD PRESSURE, HTN, HYPERPIESIA, HYPERPIESIS, HYPERTENSIVE CARDIOVASCULAR DISEASE OR SYNDROME, HYPERTENSIVE DISEASE, HYPERTENSIVE DISEASE, NOS, HYPERTENSIVE DISEASES, HYPERTENSIVE DISEASES (10-115), HYPERTENSIVE DISORDER, HYPERTENSIVE DISORDER, SYSTEMIC ARTERIAL (DISORDER), HYPERTENSIVE VASCULAR DISEASE, Hypertension - VOLUME BLOOD, VOLUME, BLOOD, VOLUMES, BLOOD, blood volume - 815-816 VASODILATING AGENTS, VASODILATING AGENT, VASODILATING AGENT (PRODUCT), VASODILATING AGENT, NOS, VASODILATING AGENTS, VASORELAXANTS, vasodilator - angiotensin - adrenergic - 722 THIAZIDE DIURETICS, BENZOTHIAZIDINE DIURETICS, DIURETICS, BENZOTHIAZIDINE, DIURETICS, THIAZIDE, THIAZIDE, THIAZIDE DIURETIC, THIAZIDE DIURETIC (PRODUCT), THIAZIDE DIURETIC (SUBSTANCE), THIAZIDE DIURETIC, NOS, THIAZIDE DIURETICS, THIAZIDE DIURETICS (MEDICATION), THIAZIDE-RELATED DIURETIC, thiazides

Appendix 11. Assessment of risk of bias in included studies

Random sequence generation
- Low risk of bias: if sequence generation was achieved using computer random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were considered adequate if performed by an independent adjudicator.
- Unclear risk of bias: if the method of randomisation was unclear.
- High risk of bias: if the allocation sequence was not randomised.

Allocation sequence concealment
- Low risk of bias: if the allocation of participants was performed by a central independent unit, on-site locked computer, identically looking numbered sealed opaque envelopes, drug bottles, or containers prepared by an independent investigator. There must have been no risk of the investigator knowing the sequence.
- Unclear risk of bias: if the trial was classified as randomised but the allocation concealment process was unclear.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants.

Blinding of participants and personnel
- Low risk of bias: if the participants and the personnel were blinded to treatment allocation, and this was described.
- Unclear risk of bias: if the procedure of blinding was unclear.
- High risk of bias: if blinding of participants and personnel was not performed.

Blinding of outcome assessment
- Low risk of bias: if the trial investigators performing the outcome assessments were blinded to the intervention.
- Unclear risk of bias: if the procedure of blinding was unclear.
- High risk of bias: if blinding of outcome assessment was not performed.

Incomplete outcome data
- Low risk of bias: 1. the numbers and reasons for dropouts or withdrawals in all groups were clearly reported, and may have been described as similar in both groups, and the trial handled missing data appropriately in intention-to-treat analyses using proper methodology, e.g. multiple imputations, or 2. there were no or few dropouts or withdrawals. Generally, we considered the trial at low risk of bias due to incomplete outcome data if the number of dropouts was 5% or less; however, this level was regarded as guiding, not definitive.
- Unclear risk of bias: the numbers and reasons for withdrawals and dropouts were not clearly stated.
- High risk of bias: the pattern of dropouts could be described as being different in the two intervention groups, or the trial used improper methodology in dealing with the missing data, e.g. last observation carried forward.

Selective outcome reporting
- Low risk of bias: a protocol was published before or at the time the trial was begun, and the outcomes defined in the protocol were reported on. If there was no protocol or the protocol was published after the trial had begun, reporting of the primary outcomes classified this domain at low risk of bias.
- Unclear risk of bias: if there was no protocol or the primary outcomes were not reported on.
- High risk of bias: if the outcomes in the protocol were not reported on.

Other (for-profit bias)
- Low risk of bias: if the trial was not financed by a company that might have had an interest in a given result.
- Unclear risk of bias: if there was no description of how the trial was financed.
- High risk of bias: if the trial was financed or had other involvement by a company that might have had an interest in a given result.
Overall risk of bias

We assessed the overall risk of bias of each trial as:

- low risk of bias: the trial was classified as overall 'low risk of bias' only if all of the bias domains described in the paragraphs above were classified as low risk of bias.
- high risk of bias: the trial was classified as overall 'high risk of bias' if any of the bias risk domains described in the paragraphs above were classified as 'unclear' or 'high risk of bias'.

Appendix 12. Trial sequential analysis input

Induced hypertension

Death from all causes at 3 months' follow-up

Alpha-spending boundary input: incidence in the control arm 13.33%, relative risk reduction 20%, alpha 3.33%, beta 20%, diversity 0%

Effect measure: risk ratio

Model: fixed-effect

The alpha-spending boundary was ignored due to too little information in the analysis. Therefore, a trial sequential analysis-adjusted confidence interval could not be calculated. Hence, there was not enough information to confirm or reject important intervention effects.

Death or dependency at 3 months' follow-up

Alpha-spending boundary input: incidence in the control arm 36.66%, relative risk reduction 20%, alpha 3.33%, beta 20%, diversity 0%

Effect measure: risk ratio

Model: fixed-effect

The alpha-spending boundary was ignored due to too little information in the analysis. Therefore, a trial sequential analysis-adjusted confidence interval could not be calculated. Hence, there was not enough information to confirm or reject important intervention effects.

Serious adverse events at 3 months' follow-up

Alpha-spending boundary input: incidence in the control arm 20.00%, relative risk reduction 20%, alpha 1.67%, beta 20%, diversity 0%

Effect measure: risk ratio

Model: fixed-effect

The alpha-spending boundary was ignored due to too little information in the analysis. Therefore, a trial sequential analysis-adjusted confidence interval could not be calculated. Hence, there was not enough information to confirm or reject important intervention effects.

Quality of life at 3 months' follow-up

Alpha-spending boundary input: mean difference 7.4 (the standard deviation of 14.8 in the trial divided by '2'), variance 221.25, alpha 1.67%, beta 20%, diversity 0%

Effect measure: mean difference

Model: fixed-effect

The alpha-spending boundary did not cross any of the monitoring boundaries and did not reach the required information size. Hence, there was not enough information to confirm or reject important intervention effects.

Rebleeding at 3 months' follow-up

Alpha-spending boundary input: incidence in the control arm 10.00%, relative risk reduction 20%, alpha 1.67%, beta 20%, diversity 0%

Effect measure: risk ratio

Model: fixed-effect

The alpha-spending boundary was ignored due to too little information in the analysis. Therefore, a trial sequential analysis-adjusted confidence interval could not be calculated. Hence, there was not enough information to confirm or reject important intervention effects.
**Delayed cerebral ischaemia at 3 months' follow-up**

Alpha-spending boundary input: incidence in the control arm 10.00%, relative risk reduction 20%, alpha 1.67%, beta 20%, diversity 0%

Effect measure: risk ratio

Model: fixed-effect

The alpha-spending boundary was ignored due to too little information in the analysis. Therefore, a trial sequential analysis-adjusted confidence interval could not be calculated. Hence, there was not enough information to confirm or reject important intervention effects.

**HISTORY**

Protocol first published: Issue 8, 2018

**CONTRIBUTIONS OF AUTHORS**

MM: screened literature, extracted data, performed statistical analyses, assessed risk of bias and GRADE, and wrote the first draft of the Cochrane Review.

WKK: screened literature, extracted data, performed risk of bias assessments, and amended the Cochrane Review.

CO: contributed with invaluable comments, aided in risk of bias assessments, and amended the Cochrane review

CG: contributed with invaluable comments and methodological insights, and amended the Cochrane Review.

J CJ: assisted with interpretation of statistical analyses and writing of the final version of the Cochrane Review.

All authors agreed on the final version of the Cochrane Review.

**DECLARATIONS OF INTEREST**

MM: none.

WKK: *work as a health professional*: Neurology Residency, University Hospital Rigshospitalet, Copenhagen, Capital Region, Denmark (MD; during specialisation in neurology).

CO: *support for attending meetings or travel, including sabbaticals and study tours*: conference invitation, Merck Sharp & Dohme (funds paid to author). *Ownership of stock shares or stock options*: shareholder, Novo Nordisk (funds paid to author). *Work as a health professional*: medical doctor, private practice in Copenhagen (May 2020 to January 2021); medical doctor, Department of Internal Medicine, Herlev Hospital, Denmark

CG: none.

J CJ: none.

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**External sources**

- No external sources of support., Denmark

  No external sources of support.

**DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

There were no differences between the protocol and the review.
INDEX TERMS

Medical Subject Headings (MeSH)
Activities of Daily Living; Blood Pressure; *Brain Ischemia; Quality of Life; *Subarachnoid Hemorrhage

MeSH check words
Humans