National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[D] Evidence review for medical management strategies

NICE guideline NG228

Methods, evidence and recommendations

November 2022

Final

National Institute for Health and Care Excellence

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Evidence review underpinning recommendations 1.1.8 to 1.1.9 and 1.2.1 to 1.2.3 and research recommendations in the NICE guideline.

1.1 Review question: What is the clinical and cost effectiveness of medical management strategies for adults with confirmed subarachnoid haemorrhage?

1.2 Introduction

People with a confirmed diagnosis of aneurysmal subarachnoid haemorrhage are at risk of rebleeding, disability and death. In current practice patients are considered for neurointervention or neurosurgery to secure the culprit aneurysm, minimise the risk of rebleeding, and improve clinical outcome.

Several medical management strategies have also been proposed to prevent rebleeding and to minimise the risk of complications for people with confirmed aSAH. These medical treatments aim to optimise fluid balance and prevent electrolyte disturbance, control blood pressure and temperature, modulate fibrinolysis, prevent seizures, and reduce the risk of complications of SAH such as delayed cerebral ischaemia. Current practice has largely evolved from historical practice, modified over time by consensus.

The management of ‘vasospasm’ has included “HHH” therapy; (hypertension, hypervolaemia and haemodilution), which aims to improve cerebral blood flow and prevent ischaemic neurological deficits. Potential hazards of this approach have recently been considered, and the approach challenged.

This review assesses the clinical and cost-effectiveness of medical management strategies for patients with a confirmed diagnosis of aSAH.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm.

Interventions	• Fluid management
	  ○ colloid
	  ○ crystalloid
	• Temperature control
	• Control of hypertension
	  ○ Beta blockers
	  ○ Nitrates
	  ○ Calcium channel blockers
	• Seizure management/Seizure prophylaxis
	• Nimodipine
	• Antifibrinolytic
	  ○ Tranexamic acid
	  ○ Aminocaproic acid
	• Analgesia/sedation

	• Electrolyte (management of sodium disorders) ○ Hypertonic saline ○ Steroid management
Comparisons	• Within class comparison • No treatment
Outcomes	CRITICAL: • Mortality • Health and social-related quality of life • (any validated measure) • Degree of disability or dependence in daily activities, (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Change in grade of aSAH • Rebleed of index aneurysm IMPORTANT • Return to usual daily activity i.e. work • Rate of major complications: DCI, hydrocephalus, intracranial hypertension • Length of hospital stay
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, observational studies will be considered.

1.4 Clinical evidence

1.4.1 Included studies

Thirty-nine papers from 29 studies were included in the review;[4, 8, 21, 30, 47-51, 58, 65, 77, 82, 87, 100, 104, 107, 109, 136, 137, 143-146, 155-157, 162, 163, 165, 169-171, 174, 188, 210, 211, 223, 225] these are summarised in Table 2 below. Twenty-five of the included studies were randomized controlled trials, and three were retrospective cohort trials. Evidence from observational trials was only considered for inclusion where no evidence for the critical outcomes of the evidence review was available from RCTs. Observational data was also only considered if outcome adjustment or population matching was performed for the key confounder of patient age. Evidence from the included studies is summarised in the clinical evidence summary below (Table 3 - Table 10). No evidence was identified for this review on analgesia or sedation.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix G:.

1.4.2 Excluded studies

See the excluded studies list in Appendix J:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Fluid management				
Bercker 2018[21]	**Colloid:** Received HES 10% continuously via infusion system to prevent hypovolaemia. N=183 **Crystalloid:** Patients received exclusively crystalloid. Application of crystalloids aimed at avoiding hypovolaemia and at maintaining a well-adjusted fluid balance. N=93 Follow-up: post-operatively	Patients with SAH as primary diagnosis in the hospital information system. Germany	• Complication: Vasospasm	Retrospective cohort No significant difference between cohorts for participant age.
Ibrahim 2013[100]	Pre/post intervention **Colloid:** Received colloid (plasma, dextran, starch, and/or albumin) administration for fluid balance management during DIND risk period. N=41	Patients admitted with CT confirmed SAH. USA	• Degree of disability • Complication: DCI • Complication: cerebral infarcts	Retrospective cohort Propensity score matching was performed based on age, gender, pre-existing heart conditions, hypertension, nicotine use, WFNS scores, aneurysm location, clazosentan treatment, subarachnoid clot burden, and

Study	Intervention and comparison	Population	Outcomes	Comments
	Control: Matched patients who did not receive colloids during DIND risk period. Unclear if other fluids were received. N=82 Follow-up: post-intervention			severity of angiographic vasospasm.
Temperature control				
Anderson 2006[8]/ Todd 2005[211] (IHAST)	Peri-procedural **Hypothermia:** Intraoperative hypothermia (33°C) N=499 **Normothermia:** Intraoperative normothermia (37°C) N=501 Patients were covered with a forced-air blanket connected to heating/cooling unit. The use of a circulating water mattress and/or intravenous cold saline as cooling aids was optional. Follow-up: 3 months	Patients undergoing surgical aneurysm clipping within 14 days after an acute aneurysmal SAH. USA	• Mortality • Degree of disability • Complication: DCI • Complication: Infarction • Length of hospital stay	RCT Other medications (e.g., nondepolarizing relaxants, mannitol, and vasoactive agents) were used as needed.
Control of hypertension				

Study	Intervention and comparison	Population	Outcomes	Comments
Haley 1993[77]	Pre/post intervention **Nicardipine:** High dose nicardipine; received 0.15 mg/kg/hr of nicardipine by continuous infusion for up to 14 days following haemorrhage. N=449 **Placebo:** Patients received placebo by continuous infusion for up to 14 days following haemorrhage. N=457 Follow-up: 3 months	Patients with a recent aneurysmal SAH. USA	• Mortality • Degree of disability	RCT
Neil-Dwyer 1983[156]/ Neil-Dwyer 1985[157]	Pre- intervention **Beta-blocker:** Received standard management with the addition of medication with the adrenergic blocking agents propranolol and phentolamine (or propranolol alone) for 3 weeks. N=111 **Placebo:** Received standard management only with matched placebo intervention. N=93	Patients presenting within 48 hours of an SAH confirmed by LP. UK	• Mortality • Return to usual daily activity (able to work)	RCT Unclear if any surgical intervention was received.

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 1 year			
Seizure management/Seizure prophylaxis				
Panczykowski 2016[165]	Pre/post intervention **Antiepileptic drugs:** Prophylactic antiepileptic drug (AED) administration upon presentation for patients suffering spontaneous SAH. The dose and duration of treatment were left to the discretion of the attending neurosurgeon (range 7 to 30 days). N=152 **Control:** Patients who did not receive AED were analysed as controls. N=201 Follow-up: 1 year	All patients presenting to for spontaneous SAH retrospectively reviewed. USA	• Mortality • Degree of disability • Complication: DCI	Cohort Propensity score matching to account for clinical covariates associated with prophylactic AED administration. The covariates used to generate this propensity score were clinical characteristics (admission Hunt-Hess score, cisternal SAH thickness, intraventricular haemorrhage, and intraparenchymal haemorrhage), procedural characteristics (aneurysm occlusion modality, craniotomy for haemorrhage evacuation), and monitoring characteristics (use of EEG monitoring). Significant difference in mean age (56±13 vs 52±11, p 0.01).
Nimodipine				
Allen 1983[4]	Pre/post intervention **Nimodipine:**	Neurologically normal patients with intracranial aneurysmal subarachnoid haemorrhage.	• Mortality • Rebleed	RCT Medical and surgical management determined by patient physician. Surgery could

Study	Intervention and comparison	Population	Outcomes	Comments
	Initial dose of 0.7mg/kg^{-1} nimodipine within 96 hours of SAH, before 0.35 mg/kg^{-1} given every four hours for 21 full days. N=58 **Placebo:** Matched placebo given for 21 days. N=63 Follow-up: 21 days	USA		not be performed before 24 hours administration of study drug.
Juvela 1990[104]	Pre/post intervention **Nimodipine:** Initial dose of nimodipine 0.25 ug/kg^{-1}/min^{-1} by continuous infusion administered via an infusion pump. After 2 hours, the dose was increased to 0.5 ug/ kg^{-1}/min^{-1}, which was maintained until 7-10 days after the onset of SAH and for at least 3 days after surgery if the patient was operated on >8 days from SAH. After intravenous administration, nimodipine or placebo was administered orally for up to 21 days after the SAH. The oral dose was 60-mg tablets every 4 hours. N=21	Patients admitted <96 hours after the onset of SAH.	• Mortality • Degree of disability • Rebleed • Major complication: DCI	RCT Pre and post-intervention medical management. Thirty-eight patients were operated on.

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo: Equivalent regime with placebo control. N=20 Follow-up: 6 months			
Messeter 1987[143]	Intra/postoperative **Nimodipine:** Intraoperative nimodipine $2.5x10^{-1}$ m solution to the exposed arterial segments followed by intravenous administration at 2mg/hour for at least 9 days. N=13 **Control:** No nimodipine received in control group, every other aspect of care was the same. N=7 Follow-up: 3 months	Patients admitted with rupture of saccular aneurysm resulting in a major SAH. Sweden	• Mortality • Major complication: DCI	RCT
Neil-Dwyer 1987[155]/ Mee 1988[137]	Pre/post intervention **Nimodipine:** Two 30mg Nimodipine tablets given orally every 4 hours for 21 days. N=38	Patients admitted with subarachnoid haemorrhages UK	• Mortality • Rebleed • Major complication: DCI	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo: Two placebo tablets given orally every 4 hours for 21 days. N=37 Follow-up: 3 months			
Ohman 1988[162]/ Ohman 1991[163]	Pre/post intervention **Nimodipine:** IV nimodipine for 7 to 10 days after ictus, and orally for a total of 21 days. N=104 **Placebo:** Received placebo in similar manner to nimodipine group. N=109 Follow-up: 1 year	Patients with verified aneurysmal subarachnoid haemorrhage of Grades I to III (Hunt and Hess). Finland	• Mortality • Degree of disability • Re-bleed • Complication: DCI	RCT
Petruk 1988[169]	Pre/post intervention **Nimodipine:** 90 mg nimodipine every 4 hours, started preoperatively and within 96 hours of ictus for 21 days. N=91 **Placebo:**	Patients who had suffered from aneurysmal SAH within the last 96 hours. Canada	• Mortality • Degree of disability • Re-bleed • Complication: DCI	RCT Direct surgery on ruptured aneurysm in ~60% of patients

Study	Intervention and comparison	Population	Outcomes	Comments
	Received placebo at the same regime as nimodipine group. N=97 Follow-up: 3 months			
Philippon 1986[170]	Pre/post intervention **Nimodipine:** 60 mg nimodipine every 4 hours, started preoperatively and within 72 hours of ictus for 21 days. N=31 **Placebo:** Received placebo at the same regime as nimodipine group. N=39 Follow-up: 21 days	Patients suffering from subarachnoid haemorrhage, due to aneurysm rupture. France	• Mortality • Re-bleed • Complication: DCI • Complication: Hydrocephalus	RCT
British aneurysm trial: Pickard 1989[171]/ Teasdale 1989[210]	**Nimodipine:** Nimodipine was given as fast release tablets containing 30 mg active compound (two tablets given orally every four hours). Treatment was started within 96 hours after ictus and routinely continued for 21 days in survivors, unless there were clinical indications for stopping. N=278	Pre/post intervention Patients admired within 96 hours after the onset of symptoms and signs of subarachnoid haemorrhage. UK	• Mortality • Degree of disability • Re-bleed • Complication: cerebral infarct • Complication: DCI	RCT Nimodipine or placebo was given both before and after operation and in patients considered to be too ill for angiography or surgery. ~50% underwent surgery. Unclear what intervention (if any) other than study drug was given for aSAH.

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo: Matching placebo given over the same regime. N=276 Follow-up: 6 months			
Antifibrinolytic				
Chandra 1978[30]	Pre/post intervention **Tranexamic acid:** Patients received IV tranexamic acid, 6 gm daily for 14 to 21 days. N=20 **Placebo:** Patients received conventional therapy of bedrest and dexamethasone when cerebral edema developed, plus isotonic saline. N=19 Follow-up: 30 days	Patients with fresh subarachnoid haemorrhage from a ruptured aneurysm. Indonesia	• Morality • Re-bleed	RCT
Fodstad 1978[51] Fodstad 1980[49] Fodstad 1981[50] Fodstad 1982[47] Fodstad 1982[48]	Pre/post intervention **Tranexamic acid:** Conservative management (bedrest and sedation) and TXA given as hourly infusion, 1g in 100ml saline every 4	Patients admitted to hospital within 3 days after a SAH due to ruptured aneurysm. Sweden	• Morality • Re-bleed • Complication: DCI	RCT Operated on during 6 week study period: TXA group (33), control group (32)

Study	Intervention and comparison	Population	Outcomes	Comments
	hours during week 1 and either 1 g 6- hourly during the second to fifth weeks inclusive, and 1 g 8-hourly during the sixth week (trial 1) or every 6 hours during week 2, with 1.5g given orally every 6 hours 3rd to 6th week (trial 2). N=53 **Control:** Conservative management (bedrest and sedation) only. N=52 Follow-up: 6 weeks			
Gelmers 1980[58]	Pre/post intervention **Tranexamic acid:** Tranexamic acid within 3 days of ictus, 4g/day over 4 doses, mostly by IV but on occasion orally. N=31 **Placebo:** Patients allocated to control group received no antifibrinolytic therapy. N=26 Mean duration of intervention: 17 days.	Patients diagnosed by LP with SAH and severe headache of acute onset. The Netherlands	• Morality • Re-bleed	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 3 months			
Hillman 2002[87]	Pre-intervention **Tranexamic acid:** 1-g dose of tranexamic acid was given intravenously as soon as diagnosis of SAH had been verified in the local hospitals (before the patients were transported), followed by doses of 1 g every 6 hours until the aneurysm was occluded; this treatment did not exceed 72 hours. N=254 **Usual care:** Control group received no tranexamic acid. N=251 Follow-up: 6 months	Patients suffering SAH verified on CT scans within 48 hours prior to the first hospital admission. Sweden	• Morality • Degree of disability • Complication: DCI • Re-bleed	RCT
Kaste 1979[107]	Pre-intervention **Tranexamic acid:** 1g IV tranexamic acid every 4 hours up until surgery or for 21 days if surgery was not feasible. N=32 **Placebo:**	Patients aged under 61 years with a diagnosis of subarachnoid haemorrhage.	• Mortality • Change in clinical grade • Re-bleed	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	50ml saline given as placebo. N=32 Follow-up: 30 days			
Maurice-Williams 1978[136]	Pre-intervention **Tranexamic acid:** The treated patients also received tranexamic acid 6 g/day for 42 days or until operation, by intravenous infusion for the first seven days and thereafter orally 15 g every six hours. N=25 **Placebo:** Controls received bed rest and sedation. N=25 Follow-up: 6 weeks	All patients admitted with a proved spontaneous subarachnoid haemorrhage within 96 hours of the first haemorrhage. UK	• Mortality • Degree of disability • Rebleed • Complication: Hydrocephalus	RCT Nine of the treated group and six of the controls underwent operation a mean of 24 and 16 days respectively after bleeding.
Post 2020[174]	Pre-intervention **Tranexamic acid:** Tranexamic acid – Bolus of 1g TXA was given intravenously immediately following randomisation, directly followed by 1 g continuous IV infusion every 8 hours. Treatment was continued until the start of endovascular or surgical	Adults admitted with signs and symptoms for less than 24 hours indicating subarachnoid haemorrhage and had a non-contrast CT confirming SAH. The Netherlands	• Mortality • Rebleed • Degree of disability • DCI • Hydrocephalus	

Study	Intervention and comparison	Population	Outcomes	Comments
	treatment of aneurysm or until a maximum of 24 hours after start of the medication. N=480 **Usual care:** Controls received care as usual. N=475 Follow-up: 6 months			
Roos 2000[188]	Pre-intervention **Tranexamic acid:** Patients received IV tranexamic acid, 6g daily (1g every 4 hours) for the first week and 6g daily PO (1.5g every 6 hours) for the second and third week. N=229 **Placebo:** Control group followed the same regime receiving placebo. N=233 Follow-up: 21 days	Patients admitted within 96 hours after onset of SAH, in whom treatment of the aneurysm was delayed beyond 48 hours after SAH. The Netherlands	• Degree of disability • Complication: DCI • Complication: Hydrocephalus • Re-bleed	RCT All patients received standard medical treatment with nimodipine for 3 weeks.
van Rossum 1977[223]	Pre-intervention **Tranexamic acid:**	Patients diagnosed with SAH. The Netherlands	• Mortality • Rebleed	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	Received IV tranexamic acid, 4 gm per day for ten consecutive days. N=26 **Placebo:** Control group received saline for ten consecutive days. N=25 Follow-up: 3 months			
Vermeulen 1984[225]	Pre-intervention **Tranexamic acid:** Treatment started within 72 hours of ictus with maximum duration of four weeks (IV bolus for four weeks or IV bolus for two weeks and oral for two weeks). 6g TXA per day over 6 doses for first week and 4g per day thereafter. Treatment stopped if surgery for aneurysms was undertaken. N=241 **Placebo:** An equivalent placebo received for the control group. N=238 Follow-up: 3 months	Patients with signs and symptoms of SAH and with confirmatory information on initial CT scan.	• Mortality • Degree of disability • Complications: Infarction • Complications: hydrocephalus • Rebleed	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
Girvin 1973[65]	**Aminocaproic acid:** Preoperative treatment with aminocaproic acid. N=39 **Standard care:** The control group received no aminocaproic acid. N=27 Follow-up: 30 days	Patients with ruptured intracranial aneurysm who bled within 7 days of study admission.	• Mortality • Rebleed	RCT Intracranial aneurysm. No information on location of bleed.
Electrolyte (management of sodium disorders)				
Hasan 1989[82]	**Steroid management:** Treatment with fludrocortisone acetate was always started <72 hours after the haemorrhage. The drug was administered intravenously or orally, 400 ug/day in two doses, for a maximum duration of 12 days. N=46 **Standard care:** Received standard care with no fludrocortisone acetate. N=45	Patients with signs and symptoms of subarachnoid haemorrhage and with confirmatory evidence on the initial computed tomogram or in the cerebrospinal fluid. The Netherlands/ UK	• Complication: DCI	RCT Surgery was planned between Days 7 and 10 in London and on Day 12 in Rotterdam and Utrecht.
Moro 2003[146]	**Steroid management:** Treated with hydrocortisone at 1200 mg/d (300 mg/6 h) from the day after direct surgery until day 10. After day 10, the dose was gradually reduced, and the	SAH patients who underwent direct surgery within 48 hours after onset. Japan	• Complication: symptomatic vasospasm	RCT Hypervolemia was induced immediately after surgery, and administration of plasma

Study	Intervention and comparison	Population	Outcomes	Comments
	administration was ended on day 14. N=14 **Standard care:** Received standard care with no hydrocortisone. N=14 Follow-up: 10 days			expander at 1 L/d was begun 3 days after onset until day 14.
Katayama 2007[109]	**Steroid management:** Treated with hydrocortisone at 1200 mg/d (300 mg/6 h) from the day after direct surgery until day 10. After day 10, the dose was gradually reduced, and the administration was ended on day 14. N=35 **Standard care:** The placebo was administrated intravenously at 1200 mg/d (300 mg every 6 hours) from day 0 to 10, 600 mg/d (300 mg every 12 hours) on days 11 and 12, and 300 mg/d on days 13 and 14. N=36 Follow-up: 10 days	SAH patients admitted to hospitals within 48 hours and undergoing surgery and available to receive the test drug within 72 hours. Japan	• Complication: symptomatic vasospasm	RCT The management protocol was set to maintain serum sodium at <140 mmol/L, central venous pressure (CVP) within 8 to 12 cmH_2O and a positive water balance.
Mori 1999[145] Mori 1999[144]	**Steroid management:** Treated with 0.3 mg/day of	Patients admitted with ruptured intracranial	• Complication: symptomatic vasospasm	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
	fludrocortisone for 14 days. Sodium and fluid balance were in excess of maintenance levels to maintain positive water balance. N=15 **Standard care:** Received standard care only, with no fludrocortisone. N=15 Follow-up: 14 days	aneurysms who were hospitalised within 1 day and underwent craniotomy and aneurysm clipping within 2 days of ictus. Japan		

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Fluid management (pre/post intervention)

Table 3: Clinical evidence summary: Pre/post intervention colloid versus control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Pre/post intervention: Colloid (95% CI)
Complication: DCI	123 (1 study)	⨁⊖⊖⊖ VERY LOW1,2 due to imprecision, risk of bias	RR 0.78 (0.35 to 1.71)	Moderate	
				220 per 1000	48 fewer per 1000 (from 143 fewer to 156 more)
Complications: Cerebral infarction				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Pre/post intervention: Colloid (95% CI)
	123 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to imprecision, risk of bias	RR 1.08 (0.74 to 1.57)	476 per 1000	38 more per 1000 (from 124 fewer to 271 more)
Degree of disability (mRS): Good (<4) scale 0-6; high score represents poor outcome	123 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to imprecision, risk of bias	RR 1.1 (0.91 to 1.32)	Moderate	
				756 per 1000	76 more per 1000 (from 68 fewer to 242 more)
Degree of disability (mRS): Poor (≥4) scale 0-6; high score represents poor outcome	123 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to imprecision, risk of bias	RR 0.7 (0.32 to 1.52)	Moderate	
				244 per 1000	73 fewer per 1000 (from 166 fewer to 127 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias					

Table 4: Clinical evidence summary: Post intervention colloid versus crystalloid

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Crystalloid	Risk difference with Colloid (95% CI)
Complication: Vasospasm	276 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.97 (1.21 to 3.21)	Moderate	
				172 per 1000	167 more per 1000 (from 36 to 380 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Crystalloid	Risk difference with Colloid (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Temperature control

Table 5: Clinical evidence summary: Peri-intervention hypothermia versus normothermia

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with normothermia	Risk difference with peri-interventional hypothermia (95% CI)
Mortality	1000 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.91 (0.56 to 1.48)	Moderate	
				64 per 1000	6 fewer per 1000 (from 28 fewer to 31 more)
Degree of disability: Unimpaired	873 (1 study) 3 months	⨁⨁⨁⨁ HIGH	RR 1.07 (1.01 to 1.14)	Moderate	
				795 per 1000	56 more per 1000 (from 8 more to 111 more)
Degree of disability: Impaired	873 (1 study) 3 months	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 0.71 (0.53 to 0.95)	Moderate	
				205 per 1000	59 fewer per 1000 (from 10 fewer to 96 fewer)
Complications: Cerebral infarction	1001 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.87 (0.52 to 1.45)	Moderate	
				60 per 1000	8 fewer per 1000 (from 29 fewer to 27 more)
Complications: DCI				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with normothermia	Risk difference with peri-interventional hypothermia (95% CI)
	1001 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1.05 (0.59 to 1.86)	44 per 1000	2 more per 1000 (from 18 fewer to 38 more)
Length of hospital stay	1000 (1 study)	⨁⨁⨁⨁ HIGH		The mean length of hospital stay in the control groups was 16 days	The mean length of hospital stay in the intervention groups was 0 higher (1.25 lower to 1.25 higher)

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

Control of hypertension

Table 6: Clinical evidence summary: Pre-intervention B-blocker versus control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with pre-intervention B-blocker (95% CI)
Mortality	204 (1 study) 1 month	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.52 (0.28 to 0.98)	Moderate	
				258 per 1000	124 fewer per 1000 (from 5 fewer to 186 fewer)
Mortality	195 (1 study) 1 year	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 0.56 (0.32 to 0.97)	Moderate	
				193 per 1000	85 fewer per 1000 (from 6 fewer to 131 fewer)
Return to daily activity (able to work)	204 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.4 (1.13 to 1.72)	Moderate	
				548 per 1000	219 more per 1000 (from 71 more to 395 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with pre-intervention B-blocker (95% CI)
1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 7: Clinical evidence summary: Pre/post-intervention calcium channel blocker (nicardipine) versus control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with pre/post intervention Calcium channel blocker (95% CI)
Mortality	906 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.94 (0.71 to 1.25)	Moderate	
				179 per 1000	11 fewer per 1000 (from 52 fewer to 45 more)
Degree of disability (GOS): Good	906 (1 study) 3 months	⨁⨁⨁⨁ HIGH	RR 0.98 (0.87 to 1.1)	Moderate	
				560 per 1000	11 fewer per 1000 (from 73 fewer to 56 more)
Degree of disability (GOS): Moderate	906 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1 (0.7 to 1.42)	Moderate	
				120 per 1000	0 fewer per 1000 (from 36 fewer to 50 more)
Degree of disability (GOS): Severe	906 (1 study) 3 months	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 1.27 (0.81 to 1.99)	Moderate	
				70 per 1000	19 more per 1000 (from 13 fewer to 69 more)
Degree of disability (GOS): Vegetative	906 (1 study) 3 months	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 0.29 (0.1 to 0.88)	Moderate	
				31 per 1000	22 fewer per 1000 (from 4 fewer to 28 fewer)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Seizure management/Seizure prophylaxis

Table 8: Clinical evidence summary: Seizure prophylaxis versus control for subarachnoid haemorrhage

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Seizure prophylaxis versus control (95% CI)
Degree of disability: mRS ≥3 (Poor) scale 0-6; high score represents poor outcome	353 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to indirectness, imprecision, risk of bias	RR 0.87 (0.59 to 1.28)	Moderate	
				249 per 1000	32 fewer per 1000 (from 102 fewer to 70 more)
Complication: DCI	356 (1 study)	⨁⨁⊖⊖ LOW1,3,4 due to indirectness, risk of bias, large effect	RR 2.85 (1.84 to 4.42)	Moderate	
				118 per 1000	218 more per 1000 (from 99 more to 404 more)
1 Matching to account for clinical covariates associated with prophylactic AED administration, not for confounding factors for SAH. 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 4 Upgraded by 1 increment if the magnitude of effect is large (RR = 2-5 or RR = 0.5-0.2)					

Nimodipine

Table 9: Clinical evidence summary: Pre/post intervention: Nimodipine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pre/post intervention nimodipine (95% CI)
Mortality	340 (3 studies) 21 days	⨁⊖⊖⊖ VERY LOW1 due to risk of bias, imprecision	RR 1.11 (0.75 to 1.64)	Moderate	
				117 per 1000	13 more per 1000 (from 29 fewer to 75 more)
Mortality	1016 (5 studies) 3 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.77 (0.51 to 1.16)	Moderate	
				270 per 1000	62 fewer per 1000 (from 132 fewer to 43 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pre/post intervention nimodipine (95% CI)
Mortality	595 (2 studies) 6 months	⨁⨁⨁⨀ MODERATE3 due to imprecision	RR 0.69 (0.49 to 0.98)	Moderate	
				184 per 1000	57 fewer per 1000 (from 4 fewer to 94 fewer)
Mortality	213 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 0.8 (0.41 to 1.57)	Moderate	
				156 per 1000	31 fewer per 1000 (from 92 fewer to 89 more)
Rebleed	186 (2 studies) 21 days	⨁⨁⨀⨀ LOW3 due to imprecision	RR 0.66 (0.28 to 1.56)	Moderate	
				114 per 1000	39 fewer per 1000 (from 82 fewer to 64 more)
Rebleed	996 (4 studies) 3 months	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.88 (0.47 to 1.66)	Moderate	
				150 per 1000	18 fewer per 1000 (from 80 fewer to 99 more)
Rebleed	595 (2 studies) 6 months	⨁⨁⨁⨀ MODERATE3 due to imprecision	RR 0.61 (0.39 to 0.97)	Moderate	
				169 per 1000	66 fewer per 1000 (from 5 fewer to 103 fewer)
Rebleed	183 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 1.52 (0.56 to 4.09)	Moderate	
				65 per 1000	34 more per 1000 (from 29 fewer to 201 more)
Degree of disability (GOS): Good recovery	154 (1 study) 21 days	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 4.18 (1.21 to 14.38)	Moderate	
				37 per 1000	118 more per 1000 (from 8 more to 495 more)
Degree of disability (GOS): Moderate disability	154 (1 study) 21 days	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 0.76 (0.33 to 1.75)	Moderate	
				146 per 1000	35 fewer per 1000 (from 98 fewer to 109 more)
Degree of disability (GOS): Severe disability	154 (1 study) 21 days	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision	RR 0.65 (0.34 to 1.23)	Moderate	
				256 per 1000	90 fewer per 1000 (from 169 fewer to 59 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pre/post intervention nimodipine (95% CI)
Degree of disability (GOS): Vegetative	154 (1 study) 21 days	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.60 (0.31 to 1.15)	Moderate	
				256 per 1000	102 fewer per 1000 (from 177 fewer to 38 more)
Degree of disability (GOS): Good recovery	708 (2 studies) 3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 1.74 (0.68 to 4.48)	Moderate	
				355 per 1000	263 more per 1000 (from 114 fewer to 1000 more)
Degree of disability (GOS): Moderate disability	708 (2 studies) 3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.79 (0.22 to 2.88)	Moderate	
				151 per 1000	32 fewer per 1000 (from 118 fewer to 284 more)
Degree of disability (GOS): Severe disability	708 (2 studies) 3 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.45 (0.26 to 0.76)	Moderate	
				132 per 1000	73 fewer per 1000 (from 32 fewer to 98 fewer)
Degree of disability (GOS): Vegetative	708 (2 studies) 3 months	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 0.40 (0.13 to 1.23)	Moderate	
				59 per 1000	35 fewer per 1000 (from 51 fewer to 14 more)
Degree of disability (GOS): Independent	213 (1 study) 3 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 1.06 (0.93 to 1.21)	Moderate	
				789 per 1000	47 more per 1000 (from 55 fewer to 166 more)
Degree of disability (GOS): Dependent	213 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW3 due to risk of bias, imprecision	RR 0.92 (0.34 to 2.44)	Moderate	
				73 per 1000	6 fewer per 1000 (from 48 fewer to 105 more)
Degree of disability (GOS): Good recovery	554 (1 study) 6 months	⊕⊕⊕⊖ MODERATE3 due to imprecision	RR 1.17 (1.04 to 1.32)	Moderate	
				612 per 1000	104 more per 1000 (from 24 more to 196 more)
Degree of disability (GOS): Moderate disability	554 (1 study) 6 months	⊕⊕⊕⊖ MODERATE3 due to imprecision	RR 1.49 (0.81 to 2.74)	Moderate	
				58 per 1000	28 more per 1000 (from 11 fewer to 101 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pre/post intervention nimodipine (95% CI)
Degree of disability (GOS): Severe disability	554 (1 study) 6 months	⊕⊕⊕⊕ HIGH	RR 0.38 (0.19 to 0.74)	Moderate	
				105 per 1000	65 fewer per 1000 (from 27 fewer to 85 fewer)
Degree of disability (GOS): Vegetative	554 (1 study) 6 months	⊕⊕⊖⊖ LOW3 due to imprecision	OR 0.51 (0.05 to 4.91)	Moderate	
				7 per 1000	3 fewer per 1000 (from 7 fewer to 26 more)
Degree of disability (GOS): independent	41 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.09 (0.75 to 1.58)	Moderate	
				700 per 1000	63 more per 1000 (from 175 fewer to 406 more)
Degree of disability (GOS): dependent	41 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.26 (0.32 to 4.98)	Moderate	
				150 per 1000	39 more per 1000 (from 102 fewer to 597 more)
Degree of disability (GOS): Good recovery	213 (1 study) 1 year	⊕⊕⊕⊖ LOW1 due to risk of bias	RR 0.99 (0.83 to 1.18)	Moderate	
				706 per 1000	7 fewer per 1000 (from 120 fewer to 127 more)
Degree of disability (GOS): Moderate disability	213 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 1.51 (0.68 to 3.39)	Moderate	
				83 per 1000	42 more per 1000 (from 27 fewer to 198 more)
Degree of disability (GOS): Severe disability	213 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	RR 0.87 (0.27 to 2.77)	Moderate	
				55 per 1000	7 fewer per 1000 (from 40 fewer to 97 more)
DCI	70 (1 study) 21 days	⊕⊕⊖⊖ LOW3 due to imprecision	RR 0.46 (0.16 to 1.3)	Moderate	
				282 per 1000	152 fewer per 1000 (from 237 fewer to 85 more)
DCI	1016 (5 studies) 3 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias	RR 0.58 (0.44 to 0.75)	Moderate	
				135 per 1000	57 fewer per 1000 (from 34 fewer to 76 fewer)
DCI				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Pre/post intervention nimodipine (95% CI)
	41 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	RR 0.76 (0.24 to 2.44)	250 per 1000	60 fewer per 1000 (from 190 fewer to 360 more)
DCI	183 (1 study) 1 year	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision	RR 0.63 (0.33 to 1.17)	Moderate	
				228 per 1000	84 fewer per 1000 (from 153 fewer to 39 more)
Cerebral infarct	554 (1 study) 6 months	⨁⨁⨁⨀ MODERATE3 due to imprecision	RR 0.66 (0.5 to 0.87)	Moderate	
				333 per 1000	113 fewer per 1000 (from 43 fewer to 167 fewer)
Complication: Hydrocephalus	70 (1 study) 21 days	⨁⨁⨀⨀ LOW3 due to imprecision	RR 1.26 (0.08 to 19.32)	Moderate	
				26 per 1000	7 more per 1000 (from 24 fewer to 476 more)
Complication: Hydrocephalus	75 (1 study) 3 months	⨁⨁⨀⨀ LOW3 due to imprecision	RR 0.49 (0.05 to 5.14)	Moderate	
				54 per 1000	28 fewer per 1000 (from 51 fewer to 224 more)

Outcome data were pooled for common time-points i.e. 21 days, 3 months, 6 months, 1 year.

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

2 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, unexplained by subgroup analysis

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

Antifibrinolytic

Table 10: Clinical evidence summary: Pre/post intervention tranexamic acid compared to standard care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Pre/post intervention tranexamic acid (95% CI)
Mortality	1048 (3 studies) <30 days	⨁⨁⨁⨀ MODERATE2 due to imprecision	RR 0.94 (0.75 to 1.19)	Moderate	
				213 per 1000	13 fewer per 1000 (from 53 fewer to 40 more)
Mortality	105 (2 studies) 6 weeks	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.22 (0.64 to 2.36)	Moderate	
				229 per 1000	50 more per 1000 (from 82 fewer to 311 more)
Mortality	587 (3 studies) 3 months	⨁⨀⨀⨀ VERY LOW2,3 due to imprecision, inconsistency	RR 0.78 (0.45 to 1.35)	Moderate	
				374 per 1000	82 fewer per 1000 (from 206 fewer to 131 more)
Mortality	1450 (2 studies) 6 months	⨁⨁⨁⨁ HIGH	RR 1.03 (0.85 to 1.25)	Moderate	
				213 per 1000	6 more per 1000 (from 32 fewer to 53 more)
Rebleed	2025 (5 studies) <30 days	⨁⨁⨀⨀ LOW2,3 due to imprecision, inconsistency	RR 0.57 (0.38 to 0.87)	Moderate	
				178 per 1000	77 fewer per 1000 (from 64 fewer to 121 fewer)
Rebleed	105 (2 studies) 6 weeks	⨁⨁⨀⨀ LOW2,3 due to imprecision, inconsistency	RR 0.36 (0.05 to 2.82)	Moderate	
				316 per 1000	202 fewer per 1000 (from 300 fewer to 575 more)
Rebleed	587 (3 studies) 3 months	⨁⨁⨁⨁ HIGH	RR 0.43 (0.29 to 0.64)	Moderate	
				235 per 1000	134 fewer per 1000 (from 85 fewer to 167 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Pre/post intervention tranexamic acid (95% CI)
Degree of disability (mRS): good outcome (0-2) scale 0-6; high score represents poor outcome	945 (1 study) 6 months	⨁⨁⨁⨀ MODERATE2 due to imprecision	RR 0.86 (0.76 to 0.98)	557 per 1000	78 fewer per 1000 (from 11 fewer to 134 fewer)
Degree of disability (GOS): independent	479 (1 study) 3 months	⨁⨁⨁⨁ HIGH	RR 1 (0.84 to 1.18)	Moderate	
				529 per 1000	0 fewer per 1000 (from 85 fewer to 95 more)
Degree of disability (GOS): dependent	479 (1 study) 3 months	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.29 (0.77 to 2.15)	Moderate	
				97 per 1000	28 more per 1000 (from 22 fewer to 112 more)
Degree of disability (GOS): poor outcome (death, vegetative or severe disability)	462 (1 study) 3 months	⨁⨁⨁⨀ MODERATE2 due to imprecision	OR 1.21 (0.84 to 1.74)	Moderate	
				451 per 1000	47 more per 1000 (from 43 fewer to 137 more)
Degree of disability (GOS): 5	505 (1 study) 6 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 1 (0.85 to 1.18)	Moderate	
				538 per 1000	0 fewer per 1000 (from 81 fewer to 97 more)
Degree of disability (GOS): 4	505 (1 study) 6 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.25 (0.87 to 1.8)	Moderate	
				167 per 1000	42 more per 1000 (from 22 fewer to 134 more)
Degree of disability (GOS): 3	505 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 0.83 (0.51 to 1.35)	Moderate	
				124 per 1000	21 fewer per 1000 (from 61 fewer to 43 more)
Degree of disability (GOS): 2	508 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 2.38 (0.54 to 10.57)	Moderate	
				8 per 1000	11 more per 1000 (from 4 fewer to 77 more)
Grade of aSAH: Boterell's classification 1				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Pre/post intervention tranexamic acid (95% CI)
	56 (1 study)	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 1.12 (0.97 to 1.29)	893 per 1000	107 more per 1000 (from 27 fewer to 259 more)
Grade of aSAH: Boterell's classification 2	56 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision	peto OR 0.13 (0.01 to 2.14)	Moderate	
				71 per 1000	61 fewer per 1000 (from 70 fewer to 70 more)
Grade of aSAH: Boterell's classification 3	56 (1 study)	⊕⊕⊖⊖ LOW2 due to imprecision	peto OR 0.14 (0 to 6.82)	Moderate	
				36 per 1000	31 fewer per 1000 (from 36 fewer to 167 more)
Complication: DCI	1922 (3 studies) Postoperative period	⊕⊕⊕⊕ HIGH	RR 0.99 (0.83 to 1.18)	Moderate	
				189 per 1000	6 fewer per 1000 (from 47 fewer to 47 more)
Complication: death from DCI	105 (2 studies) 6 weeks	⊕⊕⊖⊖ LOW2 due to imprecision	RR 2.93 (0.74 to 11.55)	Moderate	
				35 per 1000	68 more per 1000 (from 9 fewer to 369 more)
Complication: cerebral infarction	479 (1 study) 3 months	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 1.62 (1.11 to 2.35)	Moderate	
				151 per 1000	94 more per 1000 (from 17 more to 204 more)
Complication: hydrocephalus	1936 (4 studies) Post-op to 6 months	⊕⊕⊕⊖ MODERATE2 due to imprecision	RR 1.11 (1 to 1.23)	Moderate	
				373 per 1000	41 more per 1000 (from 0 fewer to 86 more)

Outcome data were pooled for common time-points i.e. <30 days, 6 weeks, 3 months, 6 months.

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

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

3 Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, unexplained by subgroup analysis

Table 11: Clinical evidence summary: Pre/post intervention aminocaproic acid compared to standard care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with pre-intervention aminocaproic acid (95% CI)
Mortality	66 (1 study) Preoperative period	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.21 (0.39 to 3.74)	Moderate	
				148 per 1000	31 more per 1000 (from 90 fewer to 406 more)
Rebleed	66 (1 study) Preoperative period	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 2.42 (0.89 to 6.57)	Moderate	
				148 per 1000	210 more per 1000 (from 16 fewer to 824 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence summary: Post intervention steroids compared to standard care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care	Risk difference with Pre intervention: Steroid management (95% CI)
Complication DCI	91 (1 study) 28 days	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.7 (0.35 to 1.4)	Moderate	
				311 per 1000	93 fewer per 1000 (from 202 fewer to 124 more)
Complication symptomatic vasospasm	129 (3 studies) 10-14 days	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 0.49 (0.21 to 1.16)	Moderate	
				200 per 1000	102 fewer per 1000 (from 158 fewer to 32 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix H:.

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Fluid management

The cost of different colloids is shown in Table 13 below, as identified in the clinical review. Unit costs for Dextran were not available.

Table 13: UK costs of drugs to manage fluid management

Solution	Preparation	Dose	Cost per unit
Albumin	Infusion	50mg per 1ml	£13.50 - £67.50
Fresh frozen plasma	Infusion	200ml	£75.00
Tetrastarch	Infusion	6% 500ml	£10.63 - £15.30

Source: British National Formulary, August 2020[102];

Temperature control

The 2019 NHS supply chain catalogue indicates that the cost a cooling blanket is £379, and the connecting cooling unit is £11,394.[158]

Control of hypertension

The unit costs of beta-blockers and calcium channel blockers identified in the clinical review are shown in Table 14 below.

Table 14: UK costs of drugs to manage hypertension

Drug	Preparation	Dose	Cost per unit
Beta blockers			
Propranolol	Tablet	80mg	£0.05
		160mg	£0.11
Calcium channel blockers			
Nicardipine	Injection	10mg/10ml	£10.00
	Capsule	20mg	£0.14
	Capsule	30mg	£0.17

Source: British National Formulary, August 2020 [102]

Seizure management/Seizure prophylaxis

The unit costs of phenytoin and levetiracetan are provided below. These were the two most common anti-epileptic drugs prescribed in the clinical study included in the review.

Table 15: UK costs of drugs to manage fluid management

Solution	Preparation	Dose	Cost per unit
Phenytoin	Tablet	100mg	£0.39
	Capsule	100mg	£0.13
		300mg	£0.33
Levetiracetam	Granule sachet	1000mg	£1.27
	Tablet	1000mg	£0.22
	Infusion	500mg/5ml	£12.73

Source: British National Formulary, August 2020[102]

Nimodipine

The unit costs of both oral and intravenous nimodipine are shown in Table 16 below.

Table 16: UK costs of nimodipine

Drug	Preparation	Dose	Cost per unit	Cost per day
Nimodipine	Tablet	30mg	£0.40	£3.60[(a)]
	Infusion	10mg	£13.60	£489.60[(b)]

Source: British National Formulary, August 2020[102]
(a) Cost per day calculated assuming people will receive a dose of 60mg every 4 hours for 18 hours per day.
(b) Cost per day calculated assuming people will receive a dose of 60mg every for 24 hours per day.

The British National Formulary states that when using nimodipine for the prevention of ischaemic neurologic deficits 60mg should be administered every 4 hours for a maximum of 21 days. Using these doses, the total cost of a course of oral nimodipine for prevention of ischaemic neurological deficits is £76 per person. If parenteral infusion is required for a full 21-day course, then the total cost is higher at £10,282 per person. However, the committee noted that intravenous nimodipine is rarely required for a full 21-day course; whereby once absorption of intravenous nimodipine is established, patients will receive enteral nimodipine for the remainder of the 21-day course.

Anti-fibrinolytics

The unit costs of both oral and intravenous tranexamic acid are shown in Table 17 below.

Table 17: UK costs of antifibrinolytics

Drug	Preparation	Dose	Cost per unit
Tranexamic acid	Tablet	500mg	£0.10
	Infusion	500mg	£1.50

Source: British National Formulary, August 2020[102]

Analgesics /sedatives

No clinical evidence was identified for these comparators and therefore unit costs were not sought.

Electrolytes

No clinical evidence was identified for these comparators and therefore unit costs were not sought.

1.6 Evidence statements

1.6.1 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee highlighted that the primary goal of medical intervention is to prevent adverse sequelae of the aneurysmal subarachnoid haemorrhage. Change in grade of aSAH (such as WFNS score) was considered to be a critical outcome, along with mortality, health and social-related quality of life, degree of disability (modified Rankin scale, Glasgow outcome scale) and rebleeding from the index aneurysm. Return to daily activity, length of hospital stay, and rate of major complications were considered to be important outcomes.

1.7.1.2 The quality of the evidence

Most of the evidence was graded at low quality. Where outcome data was downgraded, this was mostly due to inclusion of studies with a non-randomised study design, imprecision of outcome data, and risk of bias. Evidence from observational studies is often assessed to be a lower quality due to inherent risk of selection bias from a lack of randomisation and the potential influence of confounding factors. The non-randomised studies that were included performed propensity matching or demonstrated that groups were matched for the key confounder of age, but no subsequent adjustment of outcome data was made for confounding factors. The committee agreed that this was a possible risk of confounding bias and limited the quality of the evidence reviewed. There was a high risk of uncertainty around a number of outcomes due to significant statistical imprecision around the summary effect estimates. This was indicated by wide-ranging confidence intervals crossing the thresholds which demonstrate clinical significance, with which the committee would typically judge if an intervention shows benefit or harm. The committee noted that the small size of studies and the low event rate of outcomes likely contributed towards this imprecision and reduced the overall quality of outcome data.

The committee noted that several of the studies included in the evidence review were conducted in the 1980s, when a 3-week delay between admission and surgery was common practice and before the introduction of endovascular coiling. The committee highlighted that it would be challenging to generalise findings from these trials to clinical practice in the present day. The evidence was included because of lack of other more recent evidence.

The committee was surprised at the lack of more compelling contemporary evidence for the use of enteral nimodipine in the management of aSAH. This lack of recent evidence influenced their decision to make a weak recommendation to consider the use of nimodipine rather than offer it. The committee noted that the use of nimodipine is entrenched in clinical practice for patients with aneurysmal subarachnoid haemorrhage, but considered that further

research should be undertaken in this area to determine the effectiveness of nimodipine in contemporary practice. The committee therefore made a research recommendation to investigate the use of nimodipine in the contemporary management of aSAH (see Appendix K:).

The committee commented that the data on tranexamic acid (TXA) derived mainly from small studies dating from the 1970s and 1980s. The majority of the evidence around TXA included in this evidence review came from older trials with a three-week course of TXA or placebo before neurosurgical clipping or conservative management. The committee noted two RCTs, one a larger trial published in 2020, assessing the efficacy of a short course of early tranexamic acid within 24 hours of subarachnoid haemorrhage. The committee considered the evidence, which evaluated early initiation of TXA for a short duration along with early interventional treatment to secure the aneurysm was more reflective of current practice and focussed their discussion for recommendations around this body of evidence.

The committee agreed that the evidence around fluid management, temperature control, control of hypertension, seizure prophylaxis and management, and use of electrolytes in people with aSAH was of insufficient quality and quantity to justify any recommendations. The committee agreed that these areas would unlikely be considered priority areas for further research in the care of people with SAH. The committee did not consider it appropriate to make consensus recommendations for these general areas of medical management in the context of lack of specific evidence indicating people with SAH require management that differs from current standard management in these areas.

1.7.1.3 Benefits and harms

Fluid management

Fluid administration in people with subarachnoid haemorrhage aims to prevent the poor outcomes associated with hypovolaemia, but aggressive fluid administration has increasingly been considered as potentially harmful. The committee noted that the evidence on fluid management demonstrated a trend to benefit using intravenous colloid for the degree of disability at follow up, although this was not considered to be clinically significant. One non-randomised study compared fluid therapy with crystalloid or colloid and showed an increased rate of vasospasm in patients treated with colloid. However, the committee considered that the quality and quantity of evidence from both studies was too low to draw any conclusions on benefits and harms in this population. The committee agreed that they could not make a specific recommendation about fluid administration in people with SAH. The committee were aware of the NICE Guideline on intravenous fluid therapy in over 16s which they considered has general applicability to people with SAH.

Temperature control

The committee were aware of the use of therapeutic hypothermia as a treatment after cardiac arrest and recent support for its use as neuroprotective treatment in stroke. Evidence from 1 RCT comparing surgical clipping of aneurysms under conditions of hypothermia versus treatment under normothermia in people with aSAH showed a slight reduction in degree of disability at follow-up, although the committee agreed that this difference was clinically significant. This single study also demonstrated no difference between temperature control strategies for the rates of mortality or complications. The committee agreed that they could not, with any degree of certainty, comment on the benefits and harms of temperature control in people with SAH.

Control of hypertension

Medical therapies to reduce the risks of re-bleeding after subarachnoid haemorrhage include reduction of blood pressure to a level at which re-bleeding is unlikely. Historically treatment of aSAH included strict blood pressure control with fluid restriction and antihypertensive

therapy. The potential harms from this approach are subsequent morbidity and mortality from the complications of hypovolemia and hypotension.

The committee reviewed evidence from 1 RCT assessing the use of pre-operative beta-blockers with or without phentolamine in people with aSAH scheduled for surgical clipping. The trial reported a clinically significant reduction in mortality and higher rates of return to work with the use of beta-blockers meeting a clinically significant increase. However, the committee noted that the trial was conducted before endovascular coiling was routinely available, and that the 3-week interval between admission and surgical intervention in the trial would seldom occur in current practice. The committee considered that the findings could not be applied to current practice in the management of aSAH.

The committee also agreed that the trial comparing nicardipine, a calcium channel blocker, to standard care showed no clinically important benefit between intervention strategies for mortality or degree of disability and noted nicardipine is rarely used as a hypotensive agent in current clinical practice.

The committee were unable to make any specific recommendations on the control of hypertension in SAH in the acute phase but agreed that chronically, blood pressure should be managed in line with the NICE guideline on hypertension in adults.

The committee were concerned that systemic blood pressure targets for people with SAH and hypertension may differ from blood pressure targets in the general population with hypertension. The committee therefore agreed a research recommendation to assess the clinical and cost-effectiveness of a lower blood pressure treatment target relative to the standard blood pressure treatment target for people with subarachnoid haemorrhage.

Seizure management/Seizure prophylaxis

The committee highlighted that SAH may result in seizures both acutely and in the long-term, and considered the possible benefits of both preventing and managing seizures in the acute setting with people who have had an aSAH. One non-randomised study reported the effect of prophylactic anti-epileptic drugs on the degree of disability and rate of DCI in patients with aSAH. The study showed no difference between those receiving anti-epileptic drugs (AEDs) and those not receiving AEDs in the number of patients with a high disability score but showed a clinically significant increase in the number of people experiencing DCI with AEDs. The committee suggested that AEDs are not used routinely for seizure prophylaxis in people with aSAH but may be appropriate for the management of repeated seizures. The committee agreed that the evidence on routine use of AEDs was insufficient to support a recommendation.

No evidence was identified for management of seizures in people with aneurysmal subarachnoid haemorrhage. The committee considered that seizures should be managed in line with the NICE guidelines on epilepsies.

Nimodipine

The committee discussed the findings from 11 papers (from 8 RCTs) reporting the use of nimodipine in people with aSAH. Nimodipine is considered to prevent neurological deficits due to delayed cerebral ischaemia (DCI). The evidence showed that compared to placebo, there was a clinically significant benefit from use of nimodipine showing a reduction in mortality from 3 months onwards. There were also clinically important differences with nimodipine with fewer episodes of re-bleeding up to 6 months, improved degree of disability up to 6 months, and fewer episodes of DCI with nimodipine up to 1 year, although the data showed a degree of imprecision.

The committee noted that the entirety of this RCT level evidence came from trials conducted before the introduction of endovascular coiling into routine practice and involved mostly patients undergoing neurosurgical clipping after a period of medical stabilisation. In most

trials nimodipine was commenced up to 96 hours after ictus and continued for up to 3 weeks before surgical management. Hence, the results of the trials were not considered to be directly applicable to contemporary practice, in which patients with aSAH are frequently treated by endovascular coiling within 48 hours of ictus. The committee could not be sure that the benefits from nimodipine are maintained with current treatments to secure the ruptured aneurysm, but they considered without evidence of harms a recommendation to consider nimodipine was appropriate.

Several of the trials included in the evidence review used intravenous nimodipine for a few days before switching to oral nimodipine for completion of the 21-day course of treatment. The committee noted that intravenous nimodipine use is rare and only used within ICU settings. Formulations of nimodipine suitable for intravenous use are expensive and the committee were concerned that intravenous treatment in patients with patients with SAH may not be cost-effective. The committee also acknowledged that in current practice nimodipine tablets are often crushed for enteral administration (via a nasogastric tube) to people with SAH who are ventilated, have reduced consciousness, or are unable to swallow tablets for some other reason. The committee noted that intravenous nimodipine may be useful for patients in whom poor absorption of the drug is suspected, and that intra-arterial nimodipine may be used to treat cerebral arterial spasm during percutaneous interventions. Based on these observations and on their experience the committee agreed recommendations to consider enteral nimodipine for patients with confirmed SAH, with use of intravenous treatment reserved for patients in whom enteral administration is not suitable.

The committee acknowledged that clinical equipoise currently favours the use of nimodipine in people with aSAH, but anticipated that this review of the evidence and the recommendation to consider (rather than offer) nimodipine in future practice will lead to a change in equipoise over time, so that a future randomised trial should be feasible. The committee also made a research recommendation for the use of nimodipine in contemporary practice.

Antifibrinolytic

The committee discussed the possible benefits and harms of antifibrinolytic therapy in people with aSAH in the acute setting. Rebleeding is an important cause of death and disability in aSAH and can be caused by dissolution of the clot by activation of the fibrinolytic system. Antifibrinolytic therapy may have the capacity to limit this risk.

The effects of tranexamic acid in people with aSAH were reported by 14 RCTs. The full body of evidence suggested that the potential benefits of antifibrinolytics are countered by the apparent increased risks of delayed cerebral ischaemia with prolonged treatment. The committee agreed that the evidence showed clinically important differences with a reduced risk of mortality, although of lower quality due to imprecision, and a reduced rate of re-bleeding with tranexamic acid compared to placebo. The committee also noted the findings from one trial showing an increased risk of cerebral infarction with tranexamic acid and considered that this may have been due to the long (3-week) course of treatment.

As long courses of tranexamic acid may be associated with risk, short courses of tranexamic acid have been proposed and are occasionally used in current practice if timely intervention to secure the ruptured intracranial arterial aneurysm is not available. Two studies reported that early administration of short courses of tranexamic acid (less than 72 hours) relative to placebo, resulted in a reduction in the risk of rebleeding, but no significant difference in death or disability at 6 months. The committee noted that data from these trials suggests that time from admission to intervention to secure the aneurysm is key to improving outcomes for patients, because rebleeding commonly occurs within a few hours of aneurysm rupture. The committee were therefore concerned that short course tranexamic acid should not be used to delay intervention to secure the ruptured intracranial arterial aneurysm.

The committee agreed the evidence did not support a recommendation for a short course of intravenous tranexamic acid in people with aneurysmal subarachnoid haemorrhage.

The committee reviewed the evidence from 1 RCT with 66 participants showing a clinically significant increase in risk of mortality and re-bleeding with aminocaproic acid but considered that the quality of the evidence was too low to hold any confidence in these findings.

Electrolytes

The committee noted that electrolyte disturbances are frequently observed during the acute and subacute period after aSAH and may potentially worsen outcomes.

Four RCTs reported the use of glucocorticoids or mineralo-corticoids compared to standard care in patients with aSAH. The evidence from these studies showed a clinically important benefit with fewer episodes of DCI and symptomatic vasospasm with steroids, but the committee highlighted the low quality of the evidence. The committee also noted that corticosteroids are not currently used routinely in clinical practice for the management of aSAH and questioned the high doses of hydrocortisone used in one of the included trials. No evidence was found for the use of hypertonic saline to manage the sodium disorders associated with aSAH. The committee noted that this is a challenging area and the aetiology of sodium disorders is often heterogeneous. The committee were not able to make specific recommendations on electrolyte disturbances for people with SAH.

Analgesia/sedation

No evidence was found for the use of specific analgesics or sedatives in people with aSAH. The committee agreed that it was important to manage pain associated with aSAH appropriately and decided to make a consensus recommendation to reflect current practice and ensure that people with a suspected or confirmed subarachnoid haemorrhage are given effective pain relief, including opioid analgesia if needed. The committee discussed that analgesics with a sedative effect can impact neurological assessment but agreed that this should not preclude effective treatment of pain. Therefore, the committee made a recommendation to take account of the sedating and pupillary effects of opioid analgesia when conducting a neurological assessment. The committee agreed that research into the use of currently available sedatives and analgesics is not likely to have major impact on clinical practice and is not of high priority. The committee therefore decided not to make a research recommendation.

1.7.2 Cost effectiveness and resource use

No published economic evaluations were identified for this review. Unit costs were therefore presented to the committee for consideration of cost effectiveness.

The committee discussed that the clinical evidence was insufficient to make any recommendations for fluid management, temperature control, control of hypertension, and seizure management or prophylaxis, and therefore the cost effectiveness of these treatments could not be assessed. However, the committee discussed that there was a potential clinical benefit associated with the use of nimodipine for mortality, re-bleed, degree of disability and episodes of delayed cerebral ischaemia, although this is very uncertain.

The committee discussed that for most people with aneurysmal subarachnoid haemorrhage, nimodipine would be administered enterally (orally or via naso-gastric tube). The calculated cost per patient for a full course of nimodipine when administered in this way is relatively low at £76.

The committee discussed that the costs associated with disability caused by aSAH are often high due to necessary long-term costs of care. Although uncertain, the clinical evidence suggests a trend in reduced disability in patients who receive nimodipine, and therefore the committee considered that long term costs of care could be lower in this group. Furthermore,

the cost of detecting and managing delayed cerebral ischaemia is often high. The clinical evidence suggests a possible trend towards reduced incidence of delayed cerebral ischaemia for those on nimodipine. Therefore, the committee considered that overall costs would likely be lower for those on nimodipine, although this is uncertain.

The committee considered that there is a potential gain in QALYs with the use of nimodipine due to the reduced mortality, as well as the avoidance of re-bleed, disability and delayed cerebral ischaemia, which may have a significant detriment on quality of life.

Overall, the committee considered that the administration of enteral nimodipine could be a cost-effective use of resources as it incurs a relatively low short-term cost with potential long-term benefits.

The committee discussed that in a small subset of patients, nimodipine may have to be administered intravenously because the enteral route is not available (for example, when a nasogastric tube cannot be tolerated) or nimodipine is not absorbed after enteral administration. Failure to absorb nimodipine is suspected in sedated and ventilated patients when the volume of feed aspirated from a nasogastric tube is high. Recovery of absorption is determined when the volume of feed aspirated from the nasogastric tube declines, implying that the feed is leaving the stomach and progressing through the alimentary tract. A full 21-day course of intravenous nimodipine costs around £10,000 (at a cost of £489.60 per day), but the committee agreed that a full course is rarely given – more commonly patients will receive intravenous nimodipine until nasogastric access is restored or absorption is established, at which point patients will receive enteral nimodipine for the remainder of the 21-day course (at a cost of £3.60 per day). The committee noted that intravenous nimodipine should not be used if nimodipine can be given enterally.

The committee also discussed the use of short-course tranexamic acid, noting that tranexamic acid resulted in a clinically significant reduction in the risk of rebleeding but showed no significant difference for death or disability. The committee also noted the cost of tranexamic acid is relatively cheap (£1.50 per 500mg infusion), and short-course tranexamic acid would only be prescribed for 24 – 72 hours (given at an initial loading dose of 1g over ten minutes, followed by an intravenous infusion of 1g to be given over 8 hours). The overall cost of short-course tranexamic acid is £12.00 - £30.00. Subsequently the committee agreed their was insuffient clinical evidence to support a recommendation for tranexamic acid.

1.7.3 Other factors the committee took into account

The committee were aware of ongoing trials investigating the potential for benefit from the cardioprotective effects of beta blockers in the management of neurosurgical conditions. The committee noted that there is a consideration that beta blockers may have use for their cardio-protective properties beyond their antihypertensive properties, although they agreed that there is currently insufficient evidence to confirm this. The committee were unable to make any recommendation on the use of beta blockers but agreed that this ongoing research into their potential cardio-protective role may inform future practice.

No evidence was found to recommend intravenous fluid regimes in people with aneurysmal subarachnoid haemorrhage. The committee were aware of the recommendations within the NICE IV fluids in adults guideline and considered these applicable for patients who require intravenous fluid support.

The committee also highlighted that it is good practice to offer interventions to reduce the risk of venous thromboembolism to people with an aneurysmal subarachnoid haemorrhage and made a recommendation cross referring to the NICE guideline on venous thromboembolism in over 16s. The committee highlighted that the recommendations under the ‘Cranial Surgery’ and ‘Open vascular surgery or endovascular aneurysm repair’ headings would be particularly relevant to people who have had an aSAH. The committee also noted that the NICE VTE prophylaxis guideline includes assessment of bleeding risk and alternatives to

pharmacological VTE prophylaxis, and therefore applies to people admitted to hospital with aneurysmal subarachnoid haemorrhage, both before and after their aneurysm is secured.

The committee agreed that if opioid analgesia has been administered it should be documented in the person's healthcare record for future reference should subsequent neurological assessment be carried out, and the sedating and pupillary effects noted.

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Appendices

Appendix A: Review protocols

Table 18: Review protocol for medical management

ID	Field	Content
0.	PROSPERO registration number	CRD42019132515
1.	Review title	What is the clinical and cost effectiveness of medical management strategies for adults with confirmed subarachnoid haemorrhage?
2.	Review question	What is the clinical and cost effectiveness of medical management strategies for adults with confirmed subarachnoid haemorrhage?
3.	Objective	To determine which medical management strategy for subarachnoid haemorrhage is the most clinically and cost-effective.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language only The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Aneurysmal subarachnoid haemorrhage
6.	Population	Inclusion: Adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm. Exclusion: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
7.	Intervention/Exposure/Test	• Fluid management ○ colloid ○ crystalloid • Temperature control • Control of hypertension

		○ Beta blockers ○ Nitrates ○ Calcium channel blockers • Seizure management/Seizure prophylaxis • Nimodipine • Antifibrinolytic ○ Tranexamic acid ○ Aminocaproic acid • Analgesia/sedation • Electrolyte (management of sodium disorders) ○ Hypertonic saline ○ Steroid management
8.	Comparator/Reference standard/Confounding factors	Comparators: • Within class comparison • No treatment
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, search for non-randomised studies will be considered if they adjust for key confounders (age), starting with prospective cohort studies.
10.	Other exclusion criteria	Exclusions: • Adults with subarachnoid haemorrhage caused by head injury, ischaemic stroke or an arteriovenous malformation. • Children and young people aged 15 years and younger.
11.	Context	
12.	Primary outcomes (critical outcomes)	• Mortality • Health and social-related quality of life (any validated measure) • Degree of disability or dependence in daily activities (any validated measure e.g. Modified Rankin Scale and patient-reported outcome measures) • Change in grade of aSAH • Rebleed of index aneurysm
13.	Secondary outcomes (important outcomes)	• Return to usual daily activity i.e. work • Rate of major complications: DCI, hydrocephalus, intracranial hypertension • Length of hospital stay Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
14.	Data extraction (selection and coding)	• EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be

		screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. • EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • Subgroups will be investigated separately if meta-analysed results show heterogeneity.

17.	Analysis of sub-groups	Strata:
		• Pre-surgical/endovascular intervention
		• Post-surgical/endovascular intervention
		
		Subgroups (if heterogeneity):
		• Grade of haemorrhage at presentation
		  ○ Good
		  ○ Poor
		• Location of treatment (as reported by studies)		

18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date	3 February 2021		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail SAH@nice.org.uk		

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: • Ms Gill Ritchie • Mr Ben Mayer • Mr Audrius Stonkus • Mr Vimal Bedia • Ms Emma Cowles • Ms Jill Cobb • Ms Amelia Unsworth
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the

		NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Subarachnoid haemorrhage; medical management; complications	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Table 19: Health economic review protocol

Review question	All questions where health economic evidence applicable
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[154] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will decide based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

This literature search strategy was used for the following review;

- What is the clinical and cost effectiveness of medical management strategies for adults with confirmed subarachnoid haemorrhage?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[154]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

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

Table 20: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 –24 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies

Database	Dates searched	Search filter used
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Fluid Therapy/
28.	Rehydration Solutions/
29.	Hemodilution/
30.	exp Colloids/
31.	(volume adj3 (expand* or expans* or replace* or therap*)).ti,ab.
32.	(hydration or rehydration or re-hydration).ti,ab.
33.	(fluid* adj3 (therap* or manage* or managing or control*)).ti,ab.
34.	(hypervolaem* or hypervolem* or hemodilution or haemodilution).ti,ab.
35.	(crystalloid* or colloid* or dextran* or hetastarch or hydroxyethyl starch or pentastarch or HES or HAES).ti,ab.
36.	((hemodynamic or haemodynamic) adj3 (manage* or managing or therap* or control* or treatment*)).ti,ab.

37.	((temperature or fever or hyperpyrexia) adj3 (manage* or control* or reduc* or limit* or lower*)).ti,ab.
38.	(antipyretic* or anti-pyretic*).ti,ab.
39.	Antipyretics/
40.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol).ti,ab.
41.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
42.	exp Adrenergic beta-Antagonists/
43.	Nitrates/
44.	(nitrate* or glyceryl trinitrate or isosorbide or Nitroglycerin* or trinitroglycerin or TNG or GTN or trinitroxypropane or nitroprusside).ti,ab.
45.	Nitroglycerin/
46.	Nitroprusside/
47.	exp Calcium Channel Blockers/
48.	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
49.	(amlodipine or clevidipine or diltiazem or felodipine or lacidipine or lercanidipine or nicardipine or nifedipine or verapamil).ti,ab.
50.	((hypertens* or blood pressure or BP) adj3 (manage* or managing or control* or reduc* or limit* or lower*)).ti,ab.
51.	((anti-hypertens* or antihypertens*) adj3 (drug* or agent*)).ti,ab.
52.	Antihypertensive Agents/
53.	(anticonvulsant* or anti-convulsant* or anti epileptic* or antiepileptic* or phenytoin or Levetiracetam or AED*).ti,ab.
54.	Phenytoin/
55.	Anticonvulsants/
56.	(seizure* adj3 (prevent* or prophyla* or management* or treatment* or control*)).ti,ab.
57.	Levetiracetam/
58.	Nimodipine/
59.	Nimodipine.ti,ab.
60.	Antifibrinolytic Agents/
61.	(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin* or fibrinolysis) adj3 inhibitor*)).ti,ab.
62.	Tranexamic Acid/
63.	(tranexamic or txa or cyklokapron).ti,ab.
64.	Aminocaproic Acid/
65.	(Aminocaproic or aminohexanoic or Ahx).ti,ab.
66.	exp analgesia/
67.	exp Analgesics/
68.	analges*.ti,ab.
69.	Acetaminophen/
70.	(acetaminophen or paracetamol).ti,ab.
71.	((pain* or headache*) adj3 (manage* or managing or control* or treat* or relief*)).ti,ab.
72.	exp Anesthesia/
73.	Conscious Sedation/
74.	Deep Sedation/
75.	(sedat* or an?esthe*).ti,ab.
76.	electrolyte*.ti,ab.

77.	(hypona?tremi* or hyperna?tremi* or Hyperkal?emi* or hypokal?emi* or Hypochlor?emi* or hyperchlor?emi* or hyperosmol* or hypo-osmol*).ti,ab.
78.	exp Water-Electrolyte Imbalance/
79.	Water-Electrolyte Balance/
80.	exp Electrolytes/
81.	(hypotoni* or hypo-toni*).ti,ab.
82.	((saline or sodium) adj3 (fluid* or solution* or manage* or managing or control* or therap*)).ti,ab.
83.	Saline Solution, Hypertonic/
84.	(steroid* or corticosteroid* or Glucocorticoid* or Glucocorticosteroid* or Mineralocorticoid*).ti,ab.
85.	Steroids/
86.	(hydrocortisone or fludrocortisone or methylprednisolone or dexamethasone or prednisolone or cortisol).ti,ab.
87.	exp Hydrocortisone/
88.	Methylprednisolone/
89.	Dexamethasone/
90.	((salt or sodium) adj3 (wasting or imbalance* or replac* or disorder*)).ti,ab.
91.	or/27-90
92.	26 and 91
93.	Meta-Analysis/
94.	exp Meta-Analysis as Topic/
95.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
96.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
97.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
98.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
99.	(search* adj4 literature).ab.
100.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
101.	cochrane.jw.
102.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
103.	or/93-101
104.	randomized controlled trial.pt.
105.	controlled clinical trial.pt.
106.	randomi#ed.ti,ab.
107.	placebo.ab.
108.	randomly.ti,ab.
109.	Clinical Trials as topic.sh.
110.	trial.ti.
111.	or/104-110
112.	Epidemiologic studies/
113.	Observational study/
114.	exp Cohort studies/
115.	(cohort adj (study or studies or analys* or data)).ti,ab.

116.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
117.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
118.	Controlled Before-After Studies/
119.	Historically Controlled Study/
120.	Interrupted Time Series Analysis/
121.	(before adj2 after adj2 (study or studies or data)).ti,ab.
122.	exp case control study/
123.	case control*.ti,ab.
124.	Cross-sectional studies/
125.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
126.	or/112-125
127.	92 and (103 or 111 or 126)

Embase (Ovid) search terms

1.	*subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	fluid therapy/
26.	oral rehydration solution/
27.	hemodilution/
28.	colloid/

29.	(volume adj3 (expand* or expans* or replace* or therap*)).ti,ab.
30.	(hydration or rehydration or re-hydration).ti,ab.
31.	(fluid* adj3 (therap* or manage* or managing or control*)).ti,ab.
32.	(hypervolaem* or hypervolem* or hemodilution or haemodilution).ti,ab.
33.	(crystalloid* or colloid* or dextran* or hetastarch or hydroxyethyl starch or pentastarch or HES or HAES).ti,ab.
34.	((hemodynamic or haemodynamic) adj3 (manage* or managing or therap* or control* or treatment*)).ti,ab.
35.	((temperature or fever or hyperpyrexia) adj3 (manage* or control* or reduc* or limit* or lower*)).ti,ab.
36.	(antipyretic* or anti-pyretic*).ti,ab.
37.	antipyretic agent/
38.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol).ti,ab.
39.	((beta or b) adj3 (block* or antagonist*)).ti,ab.
40.	exp beta adrenergic receptor blocking agent/
41.	nitrate/
42.	(nitrate* or glyceryl trinitrate or isosorbide or Nitroglycerin* or trinitroglycerin or TNG or GTN or trinitroxypropane or nitroprusside).ti,ab.
43.	glyceryl trinitrate/
44.	nitroprusside sodium/
45.	exp calcium channel blocking agent/
46.	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
47.	(amlodipine or clevidipine or diltiazem or felodipine or lacidipine or lercanidipine or nicardipine or nifedipine or verapamil).ti,ab.
48.	((hypertens* or blood pressure or BP) adj3 (manage* or managing or control* or reduc* or limit* or lower*)).ti,ab.
49.	((anti-hypertens* or antihypertens*) adj3 (drug* or agent*)).ti,ab.
50.	exp antihypertensive agent/
51.	(anticonvulsant* or anti-convulsant* or anti epileptic* or antiepileptic* or phenytoin or Levetiracetam or AED*).ti,ab.
52.	Phenytoin/
53.	exp anticonvulsive agent/
54.	(seizure* adj3 (prevent* or prophyla* or management* or treatment* or control*)).ti,ab.
55.	levetiracetam/
56.	nimodipine/
57.	Nimodipine.ti,ab.
58.	exp antifibrinolytic agent/
59.	(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin* or fibrinolysis) adj3 inhibitor*)).ti,ab.
60.	tranexamic acid/
61.	(tranexamic or txa or cyklokapron).ti,ab.
62.	aminocaproic acid/
63.	(Aminocaproic or aminohexanoic or Ahx).ti,ab.
64.	exp analgesia/
65.	exp analgesic agent/
66.	analges*.ti,ab.
67.	paracetamol/

68.	(acetaminophen or paracetamol).ti,ab.
69.	((pain* or headache*) adj3 (manage* or managing or control* or treat* or relief*)).ti,ab.
70.	exp anesthesia/
71.	exp sedation/
72.	(sedat* or an?esthe*).ti,ab.
73.	electrolyte*.ti,ab.
74.	(hypona?tremi* or hyperna?tremi* or Hyperkal?emi* or hypokal?emi* or Hypochlor?emi* or hyperchlor?emi* or hyperosmol* or hypo-osmol*).ti,ab.
75.	exp electrolyte balance/
76.	exp electrolyte disturbance/
77.	exp Electrolytes/
78.	(hypotoni* or hypo-toni*).ti,ab.
79.	((saline or sodium) adj3 (fluid* or solution* or manage* or managing or control* or therap*)).ti,ab.
80.	hypertonic solution/
81.	(steroid* or corticosteroid* or Glucocorticoid* or Glucocorticosteroid* or Mineralocorticoid*).ti,ab.
82.	steroid/
83.	(hydrocortisone or fludrocortisone or methylprednisolone or dexamethasone or prednisolone or cortisol).ti,ab.
84.	hydrocortisone/
85.	fludrocortisone/
86.	methylprednisolone/
87.	dexamethasone/
88.	prednisolone/
89.	((salt or sodium) adj3 (wasting or imbalance* or replac* or disorder*)).ti,ab.
90.	or/25-89
91.	24 and 90
92.	random*.ti,ab.
93.	factorial*.ti,ab.
94.	(crossover* or cross over*).ti,ab.
95.	((doubl* or singl*) adj blind*).ti,ab.
96.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
97.	crossover procedure/
98.	single blind procedure/
99.	randomized controlled trial/
100.	double blind procedure/
101.	or/92-100
102.	systematic review/
103.	meta-analysis/
104.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
105.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
106.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
107.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
108.	(search* adj4 literature).ab.

109.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
110.	cochrane.jw.
111.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
112.	or/102-111
113.	Clinical study/
114.	Observational study/
115.	family study/
116.	longitudinal study/
117.	retrospective study/
118.	prospective study/
119.	cohort analysis/
120.	follow-up/
121.	cohort*.ti,ab.
122.	120 and 121
123.	(cohort adj (study or studies or analys* or data)).ti,ab.
124.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
125.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
126.	(before adj2 after adj2 (study or studies or data)).ti,ab.
127.	exp case control study/
128.	case control*.ti,ab.
129.	cross-sectional study/
130.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
131.	or/113-119,122-130
132.	91 and (101 or 112 or 131)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Subarachnoid Hemorrhage] explode all trees
#2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) near/3 (hemorrhag* or haemorrhag* or bleed* or blood*)):ti,ab
#3.	(SAH or aSAH):ti,ab
#4.	MeSH descriptor: [Intracranial Aneurysm] explode all trees
#5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) near/3 (aneurysm* or aneurism* or hematoma* or haematoma*)):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Fluid Therapy] this term only
#8.	MeSH descriptor: [Rehydration Solutions] this term only
#9.	MeSH descriptor: [Hemodilution] explode all trees
#10.	MeSH descriptor: [Colloids] explode all trees
#11.	(volume near/3 (expand* or expans* or replace* or therap*)):ti,ab
#12.	(hydration or rehydration or re-hydration):ti,ab
#13.	(fluid* near/3 (therap* or manage* or managing or control*)):ti,ab
#14.	(hypervolaem* or hypervolem* or hemodilution or haemodilution):ti,ab
#15.	(crystalloid* or colloid* or dextran* or hetastarch or hydroxyethyl starch or pentastarch or HES or HAES):ti,ab

#16.	((hemodynamic or haemodynamic) near/3 (manage* or managing or therap* or control* or treatment*)):ti,ab
#17.	((temperature or fever or hyperpyrexia) near/3 (manage* or control* or reduc* or limit* or lower*)):ti,ab
#18.	(antipyretic* or anti-pyretic*):ti,ab
#19.	MeSH descriptor: [Antipyretics] explode all trees
#20.	(Acebutolol or Atenolol or Bisoprolol or carvedilol or Celiprolol or Esmolol or labetalol or Metoprolol or Nebivolol or Oxprenolol or nadolol or propranolol or Timolol):ti,ab
#21.	((beta or b) near/3 (block* or antagonist*)):ti,ab
#22.	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#23.	MeSH descriptor: [Nitrates] this term only
#24.	(nitrate* or glyceryl trinitrate or isosorbide or Nitroglycerin* or trinitroglycerin or TNG or GTN or trinitroxypropane or nitroprusside):ti,ab
#25.	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#26.	(calcium near/3 (block* or inhibit* or antagonist*)):ti,ab
#27.	(amlodipine or clevidipine or diltiazem or felodipine or lacidipine or lercanidipine or nicardipine or nifedipine or verapamil):ti,ab
#28.	((hypertens* or blood pressure or BP) near/3 (management or control* or reduc* or limit* or lower*)):ti,ab
#29.	((anti-hypertens* or antihypertens*) near/3 (drug* or agent*)):ti,ab
#30.	MeSH descriptor: [Antihypertensive Agents] this term only
#31.	(anticonvulsant* or anti-convulsant* or anti epileptic* or antiepileptic* or phenytoin or Levetiracetam or AED*):ti,ab
#32.	MeSH descriptor: [Phenytoin] this term only
#33.	MeSH descriptor: [Anticonvulsants] this term only
#34.	(seizure* near/3 (prevent* or prophyla* or management* or treatment* or control*)):ti,ab
#35.	MeSH descriptor: [Nimodipine] this term only
#36.	Nimodipine:ti,ab
#37.	MeSH descriptor: [Antifibrinolytic Agents] this term only
#38.	(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin* or fibrinolysis) near/3 inhibitor*)):ti,ab
#39.	MeSH descriptor: [Tranexamic Acid] explode all trees
#40.	(tranexamic or txa or cyklokapron):ti,ab
#41.	MeSH descriptor: [Aminocaproic Acid] this term only
#42.	(Aminocaproic or aminohexanoic or Ahx):ti,ab
#43.	MeSH descriptor: [Analgesia] explode all trees
#44.	MeSH descriptor: [Analgesics] explode all trees
#45.	analges*:ti,ab
#46.	MeSH descriptor: [Acetaminophen] this term only
#47.	(acetaminophen or paracetamol):ti,ab
#48.	((pain* or headache*) near/3 (manage* or managing or control* or treat* or relief*)):ti,ab
#49.	MeSH descriptor: [Anesthesia] explode all trees
#50.	MeSH descriptor: [Conscious Sedation] this term only
#51.	(sedat* or anesthe* or anaesthe*):ti,ab
#52.	electrolyte*:ti,ab
#53.	(hypona?tremi* or hyponatremi* or hyperna?tremi* or hypernatremi* or Hyperkalemi* or Hyperkalaemi* or hypokalemi* or hypokalaemi* or Hypochlor?emi* or Hypochloremi* or hyperchloremi* or hyperchlor?emi* or hyperosmol* or hypo-osmol*):ti,ab

#54.	MeSH descriptor: [Deep Sedation] this term only
#55.	MeSH descriptor: [Water-Electrolyte Imbalance] explode all trees
#56.	MeSH descriptor: [Water-Electrolyte Balance] this term only
#57.	MeSH descriptor: [Electrolytes] explode all trees
#58.	(hypotoni* or hypo-toni*):ti,ab
#59.	((saline or sodium) near/3 (fluid* or solution* or manage* or managing or control* or therap*)):ti,ab
#60.	MeSH descriptor: [Saline Solution, Hypertonic] this term only
#61.	(steroid* or corticosteroid* or Glucocorticoid* or Glucocorticosteroid* or Mineralocorticoid*):ti,ab
#62.	MeSH descriptor: [Steroids] this term only
#63.	(hydrocortisone or fludrocortisone or methylprednisolone or dexamethasone or prednisolone or cortisol):ti,ab
#64.	MeSH descriptor: [Hydrocortisone] explode all trees
#65.	MeSH descriptor: [Methylprednisolone Acetate] this term only
#66.	MeSH descriptor: [Dexamethasone] this term only
#67.	((salt or sodium) near/3 (wasting or imbalance* or replac* or disorder*)):ti,ab
#68.	(OR #7-#67)
#69.	#6 and #68

B.2 Health Economics literature search strategy

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

Table 21: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2003 – 23 June 2020	Exclusions Health economics studies
Embase	2003 – 23 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 23 June 2020 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Subarachnoid Hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp Intracranial Aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23

25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

Embase (Ovid) search terms

1.	subarachnoid hemorrhage/
2.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)).ti,ab.
3.	(SAH or aSAH).ti,ab.
4.	exp intracranial aneurysm/
5.	((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial or brain or saccular or berry or wide-neck*) adj3 (aneurysm* or aneurism* or hematoma* or haematoma*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/

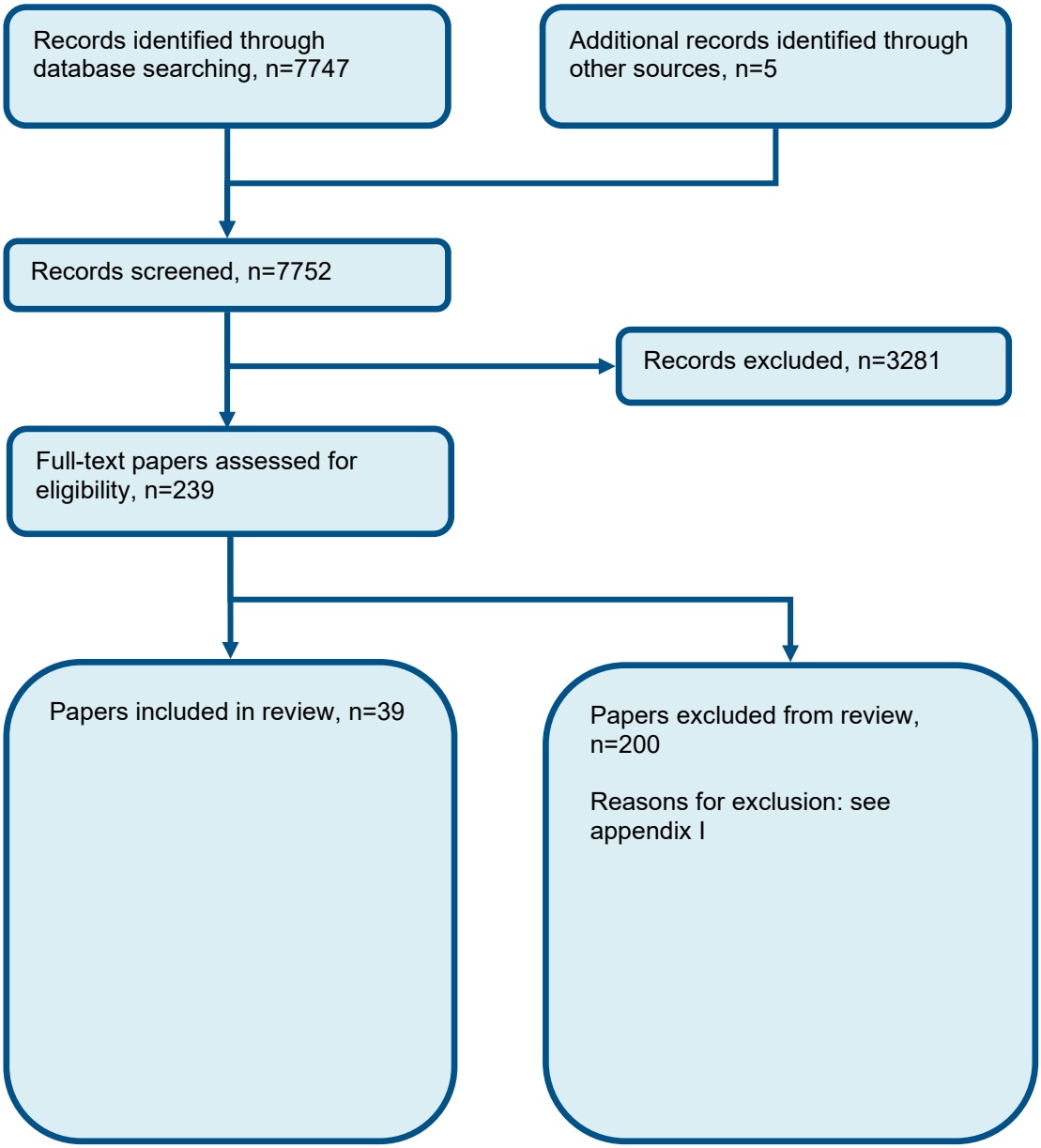
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Subarachnoid Hemorrhage EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#3.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (hemorrhag* or haemorrhag* or bleed* or blood*)))
#4.	((SAH or aSAH))
#5.	#1 OR #2 OR #3 OR #4
#6.	MeSH DESCRIPTOR Aneurysm EXPLODE ALL TREES
#7.	((aneurysm* or hematoma* or haematoma*))
#8.	#6 OR #7
#9.	MeSH DESCRIPTOR Intracranial Aneurysm EXPLODE ALL TREES
#10.	(((subarachnoid* or arachnoid* or cerebral or intracranial or intra-cranial) adj3 (aneurysm* or hematoma* or haematoma*)))
#11.	#9 OR #10
#12.	MeSH DESCRIPTOR Aneurysm, ruptured
#13.	(((ruptur* or weak* or brain or trauma*) adj3 (aneurysm* or hematoma* or haematoma*)))
#14.	#12 OR #13
#15.	(#5 or #8 or #11 or #14)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of medical management strategies.



Appendix D: Clinical evidence tables

Study	**Allen 1983[4]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=121)
Countries and setting	Conducted in USA; Setting: university centres
Line of therapy	Not applicable
Duration of study	Intervention time: 21 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Neurologically normal patients with intracranial aneurysmal subarachnoid haemorrhage.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 46 (17-79). Gender (M:F): 41/80. Ethnicity: not reported
Further population details	1. aSAH grade: Poor grade (73% grade 3 CAT scan (out of 4)). 2. Location of aneurysm: (to be reported) (majority internal carotid).
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Nimodipine - Nimodipine. Initial dose of 0.7mg/kg-1 nimodipine within 96 hours of SAH, before 0.35 mg/kg-1 given every four hours for 21 full days. Duration 21 days. Concurrent medication/care: Medical and surgical management determined by patient physician. Surgery could not be performed before 24 hours administration of study drug. Indirectness: No indirectness

	(n=63) Intervention 2: No treatment - Placebo. Matched placebo given for 21 days. Duration 21 days. Concurrent medication/care: Medical and surgical management determined by patient physician. Surgery could not be performed before 24 hours administration of study drug. Indirectness: No indirectness
Funding	Study funded by industry (Funded by Niles Pharmaceuticals)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 21 days; Group 1: 3/56, Group 2: 7/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3 - Actual outcome for Pre-surgical/endovascular intervention: Degree of disability at 21 days; Mean; , Comments: Unvalidated measure of neurological deficit.; Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 2: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 21 days; Group 1: 7/56, Group 2: 9/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Health and social quality of life ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH ; Return to daily activity (e.g. work) ; Major complications: DCI, hydrocephalus, intracranial ; Length of stay

Study (subsidiary papers)	Anderson 2006[8] (Todd 2005[211])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1001)
Countries and setting	Conducted in USA; Setting: Multicentre study, settings not reported
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing surgical aneurysm clipping within 14 days after an acute aneurysmal SAH
Exclusion criteria	Patients could not be endotracheally intubated at the time of preoperative assessment.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 52 (12). Gender (M:F): 345/656. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear 2. Location of aneurysm: Not applicable
Indirectness of population	No indirectness
Interventions	(n=499) Intervention 1: Temperature control. Intraoperative hypothermia (33°C). Patients were covered with a forced-air blanket connected to heating/cooling unit. The use of a circulating water mattress and/or intravenous cold saline as cooling aids was optional. Duration Intraoperative. Concurrent medication/care: Other medications (e.g., nondepolarizing relaxants, mannitol, and vasoactive agents) were used as needed. Indirectness: No indirectness (n=501) Intervention 2: Temperature control. Intraoperative normothermia (37°C). Patients were covered with a forced-air blanket connected to heating/cooling unit. The use of a circulating

	water mattress and/or intravenous cold saline as cooling aids was optional. Duration Intraoperative. Concurrent medication/care: Other medications (e.g., nondepolarizing relaxants, mannitol, and vasoactive agents) were used as needed. Indirectness: No indirectness
Funding	Academic or government funding (National Institute of Neurological Disease and Stroke)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TEMPERATURE CONTROL (HYPOTHERMIA) versus TEMPERATURE CONTROL (NORMOTHERMIA)

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months; Group 1: 29/499, Group 2: 32/501
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All study personnel, except the anaesthesiologists involved in intraoperative care, were blinded to treatment assignment.;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: Unimpaired at 3 months; Group 1: 375/439, Group 2: 345/434
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All study personnel, except the anaesthesiologists involved in intraoperative care, were blinded to treatment assignment.; Group 1 Number missing: 60; Group 2 Number missing: 67
- Actual outcome for Pre-surgical/endovascular intervention: Impaired at 3 months; Group 1: 64/439, Group 2: 89/434
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All study personnel, except the anaesthesiologists involved in intraoperative care, were blinded to treatment assignment.; Group 1 Number missing: 60; Group 2 Number missing: 67

Protocol outcome 3: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Pre-surgical/endovascular intervention: Cerebral infarction at 3 months; Group 1: 26/499, Group 2: 30/502
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All study personnel, except the anaesthesiologists involved in intraoperative care, were blinded to treatment assignment.;
- Actual outcome for Pre-surgical/endovascular intervention: DCI at 3 months; Group 1: 23/499, Group 2: 22/502
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All study personnel, except the anaesthesiologists involved in intraoperative care, were

blinded to treatment assignment.; Protocol outcome 4: Length of stay - Actual outcome for Pre-surgical/endovascular intervention: Length of hospital stay at n/a; Group 1: mean 16 days (SD 9); n=499, Group 2: mean 16 days (SD 11); n=501 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All study personnel, except the anaesthesiologists involved in intraoperative care, were blinded to treatment assignment.;	
Protocol outcomes not reported by the study	Health and social quality of life ; Change in grade of aSAH ; Rebleed of index aneurysm ; Return to daily activity (e.g. work)

Study	**Bercker 2018[21]**
Study type	Retrospective cohort study
Number of studies (number of participants)	(n=276)
Countries and setting	Conducted in Germany; Setting: university of Leipzig Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: post-operatively
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with SAH as primary diagnosis in the hospital information system.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): 54 years. Gender (M:F): n/a Ethnicity: n/a
Further population details	1. aSAH grade: good grade (WFNS 2). 2. Location of aneurysm: not reported.

	Confounding factors – groups matched for age. No outcome adjustment.
Indirectness of population	No indirectness
Interventions	(n=183) Intervention 1: Colloid. SAH patients admitted to our ICU before February 2012 received HES 10% continuously via infusion system to prevent hypovolaemia. The standard fluid dose of HES 10% was 1,000 ml/24h and was started immediately after surgical or endovascular therapy. HES 6% was administered additionally as repetitive bolus application to treat hypovolaemia at the discretion of the attending physician until July 2013. Target MAP was 65 mmHg (in absence of increased intracerebral pressure) and norepinephrine was added to the therapy if it was not achieved by fluid therapy alone. (n=93) Intervention 2: Crystalloid. Patients received exclusively crystalloid. Application of crystalloids aimed at avoiding hypovolaemia and at maintaining a well-adjusted fluid balance.
Funding	Study funded by academic institution (Funding was received from the University Hospital Leipzig in using materials and collecting data during working hours)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COLLOID versus CRYSTALLOID Protocol outcome 1: Complication (vasospasm) - Actual outcome for post-surgical/endovascular intervention: vasospasm post-operatively; Group 1: 62/183, Group 2: 16/93 Risk of bias: All domain – Very High, Selection - High, Confounding – High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: n/a; Group 2 Number missing: n/a	
Protocol outcomes not reported by the study	Health and social quality of life ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH ; Return to daily activity (e.g. work) ; Major complications: DCI, hydrocephalus, intracranial ; Length of stay

Study	Chandra 1978[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=39)
Countries and setting	Conducted in Indonesia; Setting: Department of Neurology, University of Airlangga school of medicine, Indonesia
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with subarachnoid haemorrhage resulting from ruptured intracranial aneurysm (acute onset of headache, evidence of meningeal irritation, blood stained CSF not due to trauma, angiographic demonstration of intracranial aneurysm, fresh SAH not older than 7 days)
Exclusion criteria	Not specified
Recruitment/selection of patients	Patients with subarachnoid haemorrhage resulting from ruptured intracranial aneurysm
Age, gender and ethnicity	Age - Other: 30-39: 7; 40-49: 12; 50-59: 14; 60-69: 6. Gender (M:F): 21/18. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable (I: 5; 2:19; 3: 11; 4:2; 5:2). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Antifibrinolytic - Tranexamic acid. Patients received IV tranexamic acid, 6 gm daily for 14 to 21 days. . Duration 14 - 21 days. Concurrent medication/care: -. Indirectness: No indirectness (n=19) Intervention 2: No treatment - Placebo. Patients received conventional therapy of bedrest and dexamethasone when cerebral edema developed, plus isotonic saline. Duration 14 - 21 days. Concurrent

	medication/care: -. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at <30 days; Group 1: 1/20, Group 2: 5/19 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Protocol outcome 2: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at <30 days; Group 1: 1/20, Group 2: 4/19 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Return to daily activity (e.g. work); Major complications: DCI, hydrocephalus, intracranial ; Length of stay

Study (subsidiary papers)	**Fodstad 1981[50] (Fodstad 1980[49], Fodstad 1982[47], Fodstad 1982[48], Fodstad 1978[51])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=59)
Countries and setting	Conducted in Sweden; Setting: Umea University Hospital
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT, LP or angiogram
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted to hospital within 3 days after a SAH due to ruptured aneurysm. and whom treatment was started within 3 days.
Exclusion criteria	TXA received before admission
Recruitment/selection of patients	Consecutive patients recruited
Age, gender and ethnicity	Age - Mean (range): 52 (19-72). Gender (M:F): 25/34. Ethnicity: not reported
Further population details	1. aSAH grade: Good grade (Botterell grade 1 (36), grade 2 (12), grade 3 (7), grade 4 (4), grade 5 (0)). 2. Location of aneurysm: (to be reported) (ICA (18), MCA (17), ACA (19), PA (1), VA (4)).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Antifibrinolytic - Tranexamic acid. Conservative management (bedrest and sedation) and TXA given as hourly infusion, 1g in 100ml saline every 4 hours during week 1 and every 6 hours during week 2. During 3rd to 6th week 1.5g given orally every hours. Duration 6 weeks. Concurrent medication/care: Unclear. Indirectness: No indirectness (n=29) Intervention 2: No treatment - Standard care. Conservative management (bedrest and sedation) only . Duration 6 weeks. Concurrent medication/care: Unclear. Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus STANDARD CARE

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 6 weeks; Group 1: 10/30, Group 2: 7/29; Comments: Trial 2
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Deemed unethical to use placebo; Group 1 Number missing: 0; Group 2 Number missing: 1
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 6 weeks; Group 1: 5/23, Group 2: 5/23; Comments: Trial 1
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Deemed unethical to use placebo; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 2: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 6 weeks; Group 1: 6/30, Group 2: 7/29; Comments: Trial 2
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Deemed unethical to use placebo; Group 1 Number missing: 0; Group 2 Number missing: 1
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 6 weeks; Group 1: 1/23, Group 2: 9/23; Comments: Trial 1
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Deemed unethical to use placebo; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 3: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Pre-surgical/endovascular intervention: Death from DCI at 6 weeks; Group 1: 5/30, Group 2: 2/29; Comments: Trial 2
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Deemed unethical to use placebo; Group 1 Number missing: 0; Group 2 Number missing: 1
- Actual outcome for Pre-surgical/endovascular intervention: Death from DCI at 6 weeks; Group 1: 2/23, Group 2: 0/23
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Deemed unethical to use placebo; Group 1 Number missing: 0; Group 2 Number missing:

1	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH ; Return to daily activity (e.g. work) ; Length of stay

Study	Gelmers 1980[58]
Study type	Randomised comparative study
Number of studies (number of participants)	(n=57)
Countries and setting	Conducted in Netherlands; Setting: University medical centre, Netherlands
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of SAH made on the basis of haemorrhagic spinal fluid, not caused by lumbar puncture and severe headache of acute onset
Exclusion criteria	Not specified
Recruitment/selection of patients	confirmed SAH
Age, gender and ethnicity	Age - Other: ≤19: 1; 20-39: 23; 40-59: 27; >60: 6. Gender (M:F): 26/31. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable (Botterell grade I: 23; II: 9; III: 15; IV: 3; V: 7). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	--
Interventions	(n=31) Intervention 1: Antifibrinolytic - Tranexamic acid. Tranexamic acid within 3 days of ictus, 4g/day over 4 doses, mostly by IV but on occasion orally. . Duration Mean duration of intervention 17 days. Concurrent medication/care: -. Indirectness: No indirectness (n=26) Intervention 2: No treatment - Placebo. Patients allocated to control group received no antifibrinolytic therapy.

	Duration Mean duration of intervention 17 days. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months; Group 1: 2/31, Group 2: 5/26 Risk of bias: All domain – Very High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 3 months; Group 1: 5/31, Group 2: 9/26 Risk of bias: All domain – Very High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH ; Return to daily activity (e.g. work) ; Major complications: DCI, hydrocephalus, intracranial ; Length of stay

Study	**Girvin 1973[65]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in Canada; Setting: not specified
Line of therapy	Not applicable
Duration of study	Intervention time + follow-up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Ruptured intracranial aneurysm, within 7 days of bleeding to admission
Exclusion criteria	not specified
Recruitment/selection of patients	Ruptured intracranial aneurysm
Age, gender and ethnicity	Age - Other: not specified. Gender (M:F): not specified. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Antifibrinolytic - Aminocaproic acid. Preoperative treatment with aminocaproic acid (dose not specified) Duration not specified. Concurrent medication/care: -. Indirectness: No indirectness (n=27) Intervention 2: No treatment - Standard care. The control group received no aminocaproic acid. Duration not specified. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMINOCAPROIC ACID versus STANDARD CARE	

Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at <30 days; Group 1: 14/39, Group 2: 4/27 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Pre-surgical/endovascular intervention: Mortality at <30 days; Group 1: 7/39, Group 2: 4/27 Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Rebleed of index aneurysm; Return to daily activity (e.g. work) ; Major complications: DCI, hydrocephalus, intracranial; Length of stay

Study	Haley 1993[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=906)
Countries and setting	Conducted in USA; Setting: 50 hospitals in 41 centres in the United States and Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged over 18; SAH diagnosed by patient medical history and confirmed by CT or LP; angiography demonstrated a saccular aneurysm; patient could begin therapy at the participating hospital between days 0 and 7.
Exclusion criteria	the aneurysm were fusiform, traumatic or mycotic; the presence of severe or complicating medical illness where in the clinical judgement of the treating physician, the concomitant illness would affect assessment of ongoing therapy or therapy might adversely affect the illness; prior use of a calcium antagonist drug at the time of haemorrhage or prior to randomization; history of another neurological or psychiatric illness that might confound the neurological examination; history of allergy to or intolerance of calcium antagonist drugs; patient known to be or suspected of being pregnant; inability to gain consent.
Recruitment/selection of patients	Selected from those with SAH
Age, gender and ethnicity	Age - Mean (SD): Nicardipine: 49.7 (13.9); Placebo: 50.1 (13.5). Gender (M:F): 328/578. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear (WFNS I: 431; II:132; III: 78; IV: 94; V: 171). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=449) Intervention 1: Control of hypertension - Calcium channel blockers. High dose nicardipine; received 0.15 mg/kg/hr of nicardipine by continuous infusion for up to 14 days following haemorrhage.

	Duration up to 14 days following haemorrhage. Concurrent medication/care: - (n=457) Intervention 2: No treatment - Placebo. Patients received placebo by continuous infusion for up to 14 days following haemorrhage. Duration up to 14 days following haemorrhage. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NICARDIPINE versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Post-surgical/endovascular intervention: Death at 3 months; Group 1: 76/449, Group 2: 82/457 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Good recovery - Glasgow outcome scale at 3 months; Group 1: 247/449, Group 2: 256/457 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Moderate disability - Glasgow outcome scale at 3 months; Group 1: 54/449, Group 2: 55/457 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Severe Disability - Glasgow outcome scale at 3 months; Group 1: 40/449, Group 2: 32/457 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Vegetative state - Glasgow outcome scale at 3 months; Group 1: 4/449, Group 2: 14/457 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH ; Rebleed of index aneurysm ; Return to daily activity (e.g. work) ; Major complications: DCI, hydrocephalus, intracranial ; Length of stay

Study	Hillman 2002[87]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=505)
Countries and setting	Conducted in Sweden; Setting: Neurosurgical departments at three centres across Sweden (Linkping, Lund and Gothenburg)
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients suffering from CT verified SAH within 48 hours prior to the first hospital admission
Exclusion criteria	pregnancy, age <15 years, and history of thromboembolic disease
Recruitment/selection of patients	Patients suffering from CT verified SAH
Age, gender and ethnicity	Age - Range: 15-29: 14; 30-49: 142; 50-69:288; ≥70: 61. Gender (M:F): Unclear. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear (HH I: 52; HH II:205; HH III:130; IV: 96; V: 21). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=254) Intervention 1: Antifibrinolytic - Tranexamic acid. 1-g dose of tranexamic acid was given intravenously as soon as diagnosis of SAH had been verified in the local hospitals (before the patients were transported), followed by doses of 1 g every 6 hours until the aneurysm was occluded; this treatment did not exceed 72 hours. Duration Maximum 72 hours. Concurrent medication/care: -. Indirectness: No indirectness (n=251) Intervention 2: No treatment – usual care. Control group received no tranexamic acid. Duration

	maximum 72 hours. Concurrent medication/care: - Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Post-surgical/endovascular intervention: Mortality at 6 months; Group 1: 137/254, Group 2: 135/251
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Post-surgical/endovascular intervention: Vegetative state - Glasgow outcome scale 4 at 6 months; Group 1: 53/254, Group 2: 42/251
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Post-surgical/endovascular intervention: Severe disability - Glasgow outcome scale 3 at 6 months; Group 1: 26/254, Group 2: 31/251
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Post-surgical/endovascular intervention: Moderate disability - Glasgow outcome scale 2 at 6 months; Group 1: 5/254, Group 2: 2/251
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Post-surgical/endovascular intervention: Good recovery - Glasgow outcome scale 1 at 6 months; Group 1: 33/254, Group 2: 41/251
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Rebleed of index aneurysm
- Actual outcome for Post-surgical/endovascular intervention: Rebleed at <30 days; Group 1: 6/254, Group 2: 27/251
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Post-surgical/endovascular intervention: DCI at Postoperative; Group 1: 17/254, Group 2: 15/251 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	Ibrahim 2013[100]
Study type	Non-randomised comparative study
Number of studies (number of participants)	(n=123)
Countries and setting	Conducted in Canada; Setting: Division of Neurosurgery, St. Michael's Hospital, Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: post-intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who received colloids (plasma, dextran, starch and or albumin) as well as those who had a mean positive fluids balance during the DNID risk (3-14) days were identified.
Exclusion criteria	Not specified
Recruitment/selection of patients	Patients with computed tomography (CT)-confirmed SAH were admitted to the respective neurosurgical units.
Age, gender and ethnicity	Age - Mean (SD): Colloids: 55.3 ± 9.6; No colloids: 55.8 ± 9.6. Gender (M:F): 25/98. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear (WFNS I-III: 83; WFNS IV-V: 40). 2. Location of aneurysm: (to be reported) (ACA: 51; ICA: 38; MCA:21, Posterior circulation 7). Confounding factors: propensity matching between groups
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Fluid management - Colloid. Received colloid (plasma, dextran, starch, and/or albumin) administration for fluid balance management during DIND risk period. Duration 3-14 days. Concurrent medication/care: -. Indirectness: No indirectness (n=82) Intervention 2: Fluid management - Crystalloid. Matched patients who did not receive colloids during DNID risk period. unclear if other fluids were received. Duration 3 - 14 days. Concurrent medication/care: - . Indirectness: No indirectness

Funding	Study funded by industry (Actelion Pharmaceuticals, Ltd., was the sponsor of the CONSCIOUS-1 trial; the company provided the authors with the trial dataset, but had no role in this exploratory analysis nor the development of the article. The data analysis and writing are the work of the authors. R. Loch Macdonald is a chief scientific officer at Edge Therapeutics, Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COLLOID versus NO COLLOID Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome for Post-surgical/endovascular intervention: mRS <4 at post-treatment; Group 1: 34/41, Group 2: 62/82; Comments: p value 0.49 Risk of bias: All domain – Very High, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Key confounders: age, gender, pre-existing heart conditions, history of hypertension, nicotine use, WFNS score, aneurysm location, clazosentan treatment, severity of angiospasm.; - Actual outcome for Post-surgical/endovascular intervention: mRS ≥4 at post-treatment; Group 1: 7/41, Group 2: 20/82 Risk of bias: All domain – Very High, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Key confounders: age, gender, pre-existing heart conditions, history of hypertension, nicotine use, WFNS score, aneurysm location, clazosentan treatment, severity of angiospasm.; Protocol outcome 2: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Post-surgical/endovascular intervention: DIND at post-treatment; Group 1: 7/41, Group 2: 18/82; Comments: p value 0.64 Risk of bias: All domain – Very High, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Key confounders: age, gender, pre-existing heart conditions, history of hypertension, nicotine use, WFNS score, aneurysm location, clazosentan treatment, severity of angiospasm.; - Actual outcome for Post-surgical/endovascular intervention: Delayed infarcts at post-treatment; Group 1: 21/41, Group 2: 39/82; Comments: p value 0.71 Risk of bias: All domain – Very High, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Key confounders: age, gender, pre-existing heart conditions, history of hypertension, nicotine use, WFNS score, aneurysm location, clazosentan treatment, severity of angiospasm.;	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life ; Change in grade of aSAH ; Rebleed of index aneurysm ; Return to daily activity (e.g. work) ; Length of stay

Study	Juvela 1990[104]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=41)
Countries and setting	Conducted in Finland; Setting: Helsinki University Central Hospital
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	patients admitted <96 hours after the onset of SAH to the department of neurosurgery, who had been enrolled in a prospective double-blind placebo-controlled study of nimodipine after aneurysmal SAH.
Exclusion criteria	Patients who had used nonsteroidal anti-inflammatory drugs during the 2 weeks before admission were excluded from the study
Recruitment/selection of patients	Verified to have SAH by CT or LP
Age, gender and ethnicity	Age - Mean (SD): Nimodipine:42.3±9.7; Placebo: 43.8±11.1. Gender (M:F): 21/20. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable (I: 8; II:16; III:14; IV: 3). 2. Location of aneurysm: (to be reported) (ICA:11; ACA: 12; Pericallosal: 2; MCA:12; Vertebrobasilar artery: 4).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Nimodipine - Nimodipine. initial dose of 0.7mg/kg-1 nimodipine within 96 hours of SAH, before 0.35 mg/kg-1 given every four hours for 21 full days . Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness (n=20) Intervention 2: No treatment - Placebo. Matched placebo given for 21 days. Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Death at 6 months; Group 1: 1/21, Group 2: 3/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: Dependent - Glasgow outcome scale at 6 moths; Group 1: 4/21, Group 2: 3/20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Independent- Glasgow outcome scale at 6 moths; Group 1: 16/21, Group 2: 14/21
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;

Protocol outcome 3: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 6 months; Group 1: 1/21, Group 2: 4/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Pre-surgical/endovascular intervention: DCI at 6 months; Group 1: 4/21, Group 2: 5/20
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcomes not reported by the study	Health and social quality of life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	**Kaste 1979[107]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=64)
Countries and setting	Conducted in Finland; Setting: Department of Neurology, University of Helsinki, Finland
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	History of acute onset of severe headache accompanied by neck rigidity.
Exclusion criteria	Unconscious, acute MI within 6 months, overt renal failure, signs of disseminated intravascular coagulation, pregnancy and if it was not possible to start the treatment within 72 hours of onset of symptoms.
Recruitment/selection of patients	History of acute onset of severe headache accompanied by neck rigidity.
Age, gender and ethnicity	Age - Other: 11-20:2; 21-30:10; 31-40:18; 41-50:22; 51-60:12. Gender (M:F): 30/34. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable ((Boterell's Classification) Grade 1: 45; Grade 2: 13; Grade 3:6). 2. Location of aneurysm: (to be reported) (ACA: 17; MCA: 17; ICA: 15).
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Antifibrinolytic - Tranexamic acid. 1g IV tranexamic acid every 4 hours up until surgery or for 21 days if surgery was not feasible. Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness (n=32) Intervention 2: No treatment - Placebo. 50ml saline given as placebo. Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness

Funding	Other (Paavo Nurmi Foundation, Finland. The tranexamic acid used (Cyklokapron) was supplied by courtesy of AB Kabi, Stockholm, Sweden)	
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Post-surgical/endovascular intervention: Death at <30 days; Group 1: 4/32, Group 2: 4/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Rebleed at <30 days; Group 1: 7/32, Group 2: 6/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Change in grade of aSAH - Actual outcome for Post-surgical/endovascular intervention: Grade 1 - Boterell's classification at <30 days; Group 1: 28/32, Group 2: 25/32 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Grade 2 - Boterell's classification at <30 days; Group 1: 0/32, Group 2: 2/32 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Post-surgical/endovascular intervention: Grade 3 - Boterell's classification at <30 days; Group 1: 0/32, Group 2: 1/32 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;		
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Rebleed of index aneurysm; Return to daily activity (e.g. work); Major complications: DCI, hydrocephalus, intracranial; Length of stay	
Comments	Botterell Scale	
	1	Conscious with or without signs of blood in the subarachnoid space
	2	Drowsy without significant neurological deficit
	3	Droawsy with neurological deficit and probably intracerebral haematoma

	4	Major neurological deficit and deterioration due to large intracerebral clot, or older age with less severe neurological deficit but with pre-existing cerebrovascular disease
	5	Moribund or near moribund with failing vital centres and extensor rigidity

Study	**Katayama 2007[109]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=71)
Countries and setting	Conducted in Japan; Setting: 16 Japanese neurological centres between January 2002 and June 2003
Line of therapy	1st line

Duration of study	Intervention + follow up: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The patients admitted to hospitals within 48 hours and were available to receive the test drug within 72 hours were selected.
Exclusion criteria	Patients were excluded if they were Hunt and Kosnik Grade V or were both Hunt and Kosnik Grade I and Fisher's Class 1. Patients with cardiac disease, renal failure, hepatic failure, endocrine or mental disease, or intracranial hematomas other than SAH were excluded.
Age, gender and ethnicity	Age - Mean (range): Intervention group 58.7(34-76); placebo 55.8(29-80). Gender (M:F): 21/50. Ethnicity: Japanese
Further population details	1. aSAH grade: Not applicable (Hunt and Kosnik grade, grade 1 (intervention -4; placebo - 5); grade2 - (intervention18;placebo20); grade3(intervention-10; placebo-8); grade(intervention-4; placebo-1)). 2. Location of aneurysm: Not applicable (Anterior c.a.- (intervention - 10; placebo14); Middle c.a.(intervention - 13; placebo-9); internal carotid a. (intervention-10; placebo - 8); Other (intervention -2; placebo-5)).
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Electrolyte (management of sodium disorders) - Steroid management. Hydrocortisone was administrated intravenously at 1200 mg/d (300 mg every 6 hours) from day 0 to 10, 600 mg/d (300 mg every 12 hours) on days 11 and 12, and 300 mg/d on days 13 and 14. The management protocol was set to maintain serum sodium at _140 mmol/L, central venous pressure (CVP) within 8 to 12 cmH2O, and a positive water balance. Other steroids, drugs affecting angiotensin converting enzyme and nimodipine were not used. Angiography was done for suspected SCV,6 with angioplasty if vasospasm was seen. Duration 10 days. Concurrent medication/care: n/a. Indirectness: No indirectness (n=36) Intervention 2: No treatment - Placebo. Placebo was administrated intravenously at 1200 mg/d (300 mg every 6 hours) from day 0 to 10, 600 mg/d (300 mg every 12 hours) on days 11 and 12, and 300 mg/d on days 13 and 14. The management protocol was set to maintain serum sodium at _140 mmol/L, central venous pressure (CVP) within 8 to 12 cmH2O, and a positive water balance. Other steroids, drugs affecting

	angiotensin converting enzyme and nimodipine were not used. Duration 10 days. Concurrent medication/care: n/a. Indirectness: No indirectness
Funding	Principal author funded by industry (The authors designed the protocol for the clinical study in collaboration with the study sponsor, Nikken Chemicals.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEROID MANGEMENT versus PLACEBO Protocol outcome 1: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Post-surgical/endovascular intervention: symptomatic vasospasm at 10 days; Group 1: 5/35, Group 2: 9/36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Rebleed of index aneurysm; Return to daily activity (e.g. work); Length of stay

Study	Maurice-Williams 1978[136]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in United Kingdom; Setting: St Bartholomew's Hospital
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients admitted with a proved spontaneous subarachnoid haemorrhage who were (a) under 65 and without intercurrent disease, (b) relatively little disturbed by the first bleed (Botterell grades I-3), and (c) admitted within 96 hours of the first haemorrhage.
Exclusion criteria	Patients in whom no cause for the subarachnoid haemorrhage could be found or who had angiomas were removed from the trial after angiography.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age Not reported. Gender (M:F): Not reported. Ethnicity: not reported
Further population details	1. aSAH grade: (Not reported). 2. Location of aneurysm: (Not reported).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Antifibrinolytic - Tranexamic acid. The treated patients also received tranexamic acid 6 g/day for 42 days or until operation, by intravenous infusion for the first seven days and thereafter orally 15 g every six hours. Duration 6 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness

	(n=25) Intervention 2: No treatment - Standard care. Controls received bed rest and sedation. Duration 6 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus STANDARD CARE Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 to 33 months; Group 1: 3/25, Group 2: 11/25 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome for Pre-surgical/endovascular intervention: Disability at follow-up at 3 to 33 months; Mean; , Comments: No validation of measurement used.; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: patients who rebled at 3 to 33 months; Group 1: 6/25, Group 2: 14/25 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: Hydrocephalus at 3 to 33 months; Group 1: 4/25, Group 2: 7/25 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Health and social quality of life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	**Messeter 1987[143]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Sweden; Setting: department of neuroanesthesia and neurosurgery, University Hospital, Lund, Sweden
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	non-consecutive patients with rupture of an intracranial saccular aneurysm resulting in a major SAH
Exclusion criteria	not specified
Recruitment/selection of patients	patients with rupture of an intracranial saccular aneurysm resulting in a major SAH
Age, gender and ethnicity	Age - Mean (range): Mean age 44 (23-59). Gender (M:F): 9/11. Ethnicity: not reported
Further population details	1. aSAH grade: Good grade (Hunt & Hess I: 7; II: 10; III: 3). 2. Location of aneurysm: (to be reported) (Anterior communicating artery: 6; ICA: 1; MCA: 11; Basilar artery:1; Pericallosal artery:1).
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Nimodipine - Nimodipine. Intraoperative nimodipine 2.5x10-1 m solution to the exposed arterial segments followed by intravenous administration at 2mg/hour for at least 9 days. Duration minimum 9 days. Concurrent medication/care: - . Indirectness: No indirectness (n=7) Intervention 2: No treatment - Placebo. No nimodipine received in control group, every other aspect of care was the same. Duration Unclear. Concurrent medication/care: -. Indirectness: No indirectness

Funding	Academic or government funding (Research grants from the Swedish Medical Research council and from the medical faculty of the University of Lund)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months; Group 1: 1/13, Group 2: 2/7 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: DCI at 3 months; Group 1: 0/13, Group 2: 3/7 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH; Rebleed of index aneurysm ; Return to daily activity (e.g. work) ; Length of stay

Study (subsidiary papers)	**Mori 1999[144] (Mori 1999[145])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Japan

Line of therapy	1st line
Duration of study	Intervention + follow up: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	between July 1996 and December 1997, 30 patients admitted with ruptured intracranial aneurysms who were hospitalized in care within 1 day if the onset of symptoms (day0) and who underwent craniotomy and aneurysm clipping within 2 days (days 0 to 1) were investigated in this study
Exclusion criteria	Head trauma, known endocrinological disturbances, renal disease and congestive heart failure. In addition patients in whom intracerebral hematoma (>3 cm in diameter) was demonstrated on admission computerized tomography scans were excluded.
Recruitment/selection of patients	n/a
Age, gender and ethnicity	Age - Mean (SD): control - 56.7(10); intervention group55.3(11.7). Gender (M:F): 17/13. Ethnicity: n/a
Further population details	1. aSAH grade: Not applicable (Hunt and kosnok system Grade 1 - (control - 2, intervention - 2); Grade2 - (control 7, intervention 7); Grade3 - (control - 5, intervention - 5); Grade 4 (control 1, intervention -1)). 2. Location of aneurysm: Not applicable (Internal carotid artery - (control - 7, interv.-6); anterior cerebral - (control - 4; interv -5); middlec. artery - (control 3, interv - 3); Other - (control 1, intervention-1)).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrolyte (management of sodium disorders) - Steroid management. Fludrocortisone 0.3 mg/ day + conventional hypervolemic therapy provided by intravenous infusion.

	Duration 14days. Concurrent medication/care: during a period of 14 days after the onset of SAH, all patients underwent intravenous infusion therapy. IV infusion for extracellular fluid replacement post craniotomy was performed within 24 hours. beginning at approximately 12 hours after recovery from anaesthesia (days 1-2), all patients were encouraged to ingest to ingest fluid and foods orally, if possible.. Indirectness: No indirectness (n=15) Intervention 2: Electrolyte (management of sodium disorders) - Hypertonic saline. usual care-conventional hypervolemic therapy provided by intravenous infusion. Duration 14 days. Concurrent medication/care: during a period of 14 days after the onset of SAH, all patients underwent intravenous infusion therapy. IV infusion for extracellular fluid replacement post craniotomy was performed within 24 hours. beginning at approximately 12 hours after recovery from anaesthesia (days 1-2), all patients were encouraged to ingest to ingest fluid and foods orally, if possible. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEROID MANGEMENT versus HYPERTONIC SALINE

Protocol outcome 1: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Post-surgical/endovascular intervention: symptomatic vasospasm at 14 days; Group 1: 0/15, Group 2: 2/15
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Mortality ; Health and social quality of life ; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) ; Change in grade of aSAH ; Rebleed of index aneurysm ; Return to daily activity (e.g. work) ; Length of stay

Study	**Moro 2003[146]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)

Countries and setting	Conducted in Japan; Setting: Twenty-eight SAH patients admitted to hospital between October 1999 and July 2001 were analysed.
Line of therapy	1st line
Duration of study	Intervention + follow up: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Twenty eight SAH patients
Exclusion criteria	Patients who received endovascular surgery and patients with intracerebral hematoma were excluded.
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (range): Group1(Control) 52.1(30-72); group 2 (intervention) 51.1 (32-75). Gender (M:F): 10/18. Ethnicity: Japanese
Further population details	1. aSAH grade: Not applicable (Hunt and Kosnik Grade: control group (I - 0; II - 8; III -5; IV - 0); intervention group (I - 1; II - 10; III - 2, IV - 2)). 2. Location of aneurysm: Not applicable (Control - Anterior Cer. a. - 5; middle cerebral a. - 6; Internal carotid artery - 3; Intervention - Anterior Cer. a. - 7; middle cerebral a. - 4; Internal carotid artery - 3;).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrolyte (management of sodium disorders) - Steroid management. Hydrocortisone treatment (1200 mg/d for 10 days; n=14). Duration 10 days. Concurrent medication/care: Both groups underwent hypervolemic therapy by aggressive sodium and water replacement. The goal of the hypervolemic therapy was to maintain the serum sodium level >140 mEq/L and the central venous pressure (CVP) within 8 to 12 cm H2O. Indirectness: No indirectness (n=14) Intervention 2: No treatment. no treatment. Duration 10 days. Concurrent medication/care: Both groups underwent hypervolemic therapy by aggressive sodium and water replacement. The goal of the hypervolemic therapy was to maintain the serum sodium level >140 mEq/L and the central venous pressure

	(CVP) within 8 to 12 cm H2O.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STEROID MANGEMENT versus NO TREATMENT

Protocol outcome 1: Major complications: DCI, hydrocephalus
- Actual outcome for Post-surgical/endovascular intervention: symptomatic vasospasm. at 10 days; Group 1: 1/14, Group 2: 2/14
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcomes not reported by the study	Mortality at Define; Health and social quality of life at Define; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) at Define; Change in grade of aSAH at Define; Rebleed of index aneurysm at Define; Return to daily activity (e.g. work) at Define; Length of stay at Define

Study (subsidiary papers)	Neil dwyer 1983[156] (Neil-dwyer 1985[157])
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=204)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: 21 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting within 48 hours of an SAH confirmed by LP.
Exclusion criteria	Patients who were already moribund
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - --: Not reported. Gender (M:F): Not reported. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Control of hypertension - Beta blockers. Receiving standard management with the addition of medication with the adrenergic blocking agents propranolol and phentolamine (or propranolol alone) for 3 weeks. Duration 3 weeks. Concurrent medication/care: Anticonvulsants were given to patients having seizures and as prophylactic treatment after surgery. . Indirectness: No indirectness (n=93) Intervention 2: No treatment - Placebo. Received standard management only with matched placebo intervention.

	Duration 3 weeks. Concurrent medication/care: Anticonvulsants were given to patients having seizures and as prophylactic treatment after surgery. Indirectness: No indirectness
Funding	Other (Materials provided by Dr D Burley)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA BLOCKERS versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 1 month; Group 1: 13/111, Group 2: 21/93 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11; Group 2 Number missing: 9 - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 1 year; Group 1: 17/107, Group 2: 25/88 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11; Group 2 Number missing: 9 Protocol outcome 2: Return to daily activity (e.g. work) - Actual outcome for Pre-surgical/endovascular intervention: Able to work at 1 year; Group 1: 85/111, Group 2: 51/93 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11; Group 2 Number missing: 9	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Rebleed of index aneurysm; Major complications: DCI, hydrocephalus, intracranial; Length of stay

Study (subsidiary papers)	Neil-dwyer 1987[155] (Mee 1988[137])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in United Kingdom; Setting: Brook General Hospital, South East Thames Regional Neurosurgical Unit
Line of therapy	Not applicable
Duration of study	Intervention time: 21 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients of all neurological grades aged 18-65.
Exclusion criteria	Patients with pre-existing renal, hepatic, cardiac, or hypertensive disease were excluded.
Recruitment/selection of patients	Consecutive patients admitted were included.
Age, gender and ethnicity	Age - Mean (range): 48 (21-64). Gender (M:F): 25/50. Ethnicity: not reported
Further population details	1. aSAH grade: Poor grade (Neurological grade: majority alert.). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Nimodipine - Nimodipine. Two 30mg Nimodipine tablets given orally every 4 hours. Duration 21 days. Concurrent medication/care: All patients received standard regime of analgesics and antiemetics and postoperative anticonvulsants. Indirectness: No indirectness (n=37) Intervention 2: No treatment - Placebo. Two placebo tablets given orally every 4 hours for 21 days. Duration 21 days. Concurrent medication/care: All patients received standard regime of analgesics and antiemetics and postoperative anticonvulsants. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months; Group 1: 4/38, Group 2: 10/37 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: rebleed at 3 months; Group 1: 1/38, Group 2: 6/37 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: DCI at 3 months; Group 1: 3/38, Group 2: 5/37 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study (subsidiary papers)	**Ohman 1988[162] (Ohman 1991[163])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=213)
Countries and setting	Conducted in Finland; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 21 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with verified aneurysmal subarachnoid haemorrhage of Grades I to III (Hunt and Hess).
Exclusion criteria	Patients with an associated intracerebral hematoma and decreased level of consciousness were excluded.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 44.3 (11.2). Gender (M:F): 104/109. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear 2. Location of aneurysm: (to be reported) (22% interal carotid, 35% middle cerebral, 34% anterior communicating).
Indirectness of population	No indirectness
Interventions	(n=104) Intervention 1: Nimodipine - Nimodipine. IV nimodipine (0.5ug/kg/min) for 7 to 10 days after ictus, and orally (6omg) for a total of 21 days. . Duration 21 days. Concurrent medication/care: 97/104 underwent surgery for ruptured aneurysm. . Indirectness: No indirectness (n=109) Intervention 2: No treatment - Placebo. Received placebo in similar manner to nimodipine group.

	Duration 21 days. Concurrent medication/care: 104/109 underwent surgery for ruptured aneurysm. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months; Group 1: 10/104, Group 2: 15/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 1 year; Group 1: 13/104, Group 2: 17/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: GOS: Independent at 3 months; Group 1: 87/104, Group 2: 86/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: GOS: Dependent at 3 months; Group 1: 7/104, Group 2: 8/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: GOS: Good recovery at 1 year; Group 1: 73/104, Group 2: 77/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: GOS: moderate disability at 1 year; Group 1: 13/104, Group 2: 9/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: GOS: severe disability at 1 year; Group 1: 5/104, Group 2: 6/109
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 3 months; Group 1: 8/104, Group 2: 4/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 1 year; Group 1: 9/91, Group 2: 6/92 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: DCI at 3 months; Group 1: 1/104, Group 2: 9/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Pre-surgical/endovascular intervention: DCI at 1 year; Group 1: 13/91, Group 2: 21/92 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Health and social quality of life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	Panczykowski 2016[165]
Study type	Non-randomised cohort study
Number of studies (number of participants)	(n=353)
Countries and setting	Conducted in USA; Setting: UPMC Presbyterian Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed with a cerebral aneurysm as well as those without an identifiable aetiology for SAH on angiography were included for analysis.
Exclusion criteria	Patients were excluded if SAH was secondary to trauma, arteriovenous malformation or fistula, spontaneous intraparenchymal haemorrhage, or inflammatory vasculopathy.
Recruitment/selection of patients	Diagnosed with a cerebral aneurysm as well as those without an identifiable ethology for SAH on angiography
Age, gender and ethnicity	Age - Mean (SD): Prophylactic anti-epilepsy drugs: 52±11; no anti-epilepsy drugs: 56±13. Gender (M:F): 126/227. Ethnicity: not reported
Further population details	1. aSAH grade: Poor grade (Median Hunt - Hess score: 3 (1)). 2. Location of aneurysm: (to be reported) (Cisternal SAH, Intraventricular haemorrhage, intraparenchymal haemorrhage). Confounding factors: propensity matching between groups
Indirectness of population	No indirectness
Interventions	(n=152) Intervention 1: Seizure management/prophylaxis - Seizure prophylaxis. Prophylactic antiepileptic drug (AED) administration upon presentation for patients suffering spontaneous SAH. The dose and duration of treatment were left to the discretion of the attending neurosurgeon. Duration 7-30 days. Concurrent medication/care: -. Indirectness: No indirectness

	(n=201) Intervention 2: No treatment - Standard care. Patients who did not receive AED were analyses as controls Patients who did not receive AED were analysed as controls. Duration NA. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEIZURE PROPHLAXIS versus STANDARD CARE Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome for Pre-surgical/endovascular intervention: mRS poor outcome at 12 months; Group 1: 33/152, Group 2: 50/201; Comments: p value 0.20 Risk of bias: All domain – Very High, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: DCI at post SAH; Group 1: 51/152, Group 2: 24/201; Comments: p value 0.01 Risk of bias: All domain – Very High, Selection - High, Confounding - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Change in grade of aSAH; Rebleed of index aneurysm; Return to daily activity (e.g. work); Length of stay

Study	Petruk 1988[169]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=188)
Countries and setting	Conducted in USA; Setting: University of Health sciences centre, Canada
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients >18 who had suffered from aneurysm rupture within the previous 96 hours
Exclusion criteria	SAH outside of 96 hours, pregnancy or receiving another calcium channel blocker or any other investigative drug
Recruitment/selection of patients	suffered from aneurysm rupture within the previous 96 hours
Age, gender and ethnicity	Age - Mean (SD): Nimodipine: 53.8 (13.4); Placebo: 56.1 (12.7). Gender (M:F): 51/93. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable (SAH grade 3: 46; 4: 82; 5: 26). 2. Location of aneurysm: (to be reported) (ICA:41; MCA: 33; ACA: 59; basilar: 11; posterior circulation: 10).
Indirectness of population	No indirectness
Interventions	(n=91) Intervention 1: Nimodipine - Nimodipine. 90 mg nimodipine every 4 hours, started preoperatively and within 96 hours of ictus for 21 days. Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness (n=97) Intervention 2: No treatment - Placebo. Received placebo at the same regime as nimodipine group. Duration 21 days. Concurrent medication/care: - . Indirectness: No indirectness
Funding	Study funded by industry (Project was supported in part by a research grant to Dr Weir from Miles Pharmaceuticals, Connecticut, US)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 21 days post intervention; Group 1: 30/72, Group 2: 25/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months post intervention; Group 1: 34/72, Group 2: 32/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: Good recovery - GOS at 21 days post intervention; Group 1: 11/72, Group 2: 3/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects
- Actual outcome for Pre-surgical/endovascular intervention: Moderate Disability - GOS at 21 days post intervention; Group 1: 8/72, Group 2: 12/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects
- Actual outcome for Pre-surgical/endovascular intervention: Severe Disability - GOS at 21 days post intervention; Group 1: 12/72, Group 2: 21/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects
- Actual outcome for Pre-surgical/endovascular intervention: Vegetative state - GOS at 21 days post intervention; Group 1: 11/72, Group 2: 21/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects
- Actual outcome for Pre-surgical/endovascular intervention: Good recovery - GOS at 3 months post intervention; Group 1: 21/72, Group 2: 8/82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects - Actual outcome for Pre-surgical/endovascular intervention: Moderate Disability - GOS at 3 months post intervention; Group 1: 7/72, Group 2: 20/82 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects - Actual outcome for Pre-surgical/endovascular intervention: Severe Disability - GOS at 3 months post intervention; Group 1: 7/72, Group 2: 13/82 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects - Actual outcome for Pre-surgical/endovascular intervention: Vegetative state - GOS at 3 months post intervention; Group 1: 3/72, Group 2: 9/82 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects Protocol outcome 3: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 3 months post intervention; Group 1: 17/72, Group 2: 17/82 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: DCI at 3 months post intervention; Group 1: 33/72, Group 2: 54/82 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Protocol violation / side effects; Group 2 Number missing: 15, Reason: Protocol violation / side effects	
Protocol outcomes not reported by the study	Health and social quality of life; Change in grade of aSAH ; Return to daily activity (e.g. work) ; Length of stay

Study	Philippon 1986[170]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in France; Setting: Department of Neurology, Paris
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 21 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention:
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 15 - 65 years suffering from subarachnoid haemorrhage within 72 hours secondary to an aneurysm rupture
Exclusion criteria	Early operations (prior to day 4) or where treatment has not been started in the first 72 hours, arterial hypertension, ca
Recruitment/selection of patients	suffering from subarachnoid haemorrhage within 72 hours secondary to an aneurysm rupture
Age, gender and ethnicity	Age - Mean (SD): Nimodipine: 44.3 (13.2); Placebo: 45.6 (12.8). Gender (M:F): 30/40. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable (Hunt and Hess I: 9; II: 49; III: 12). 2. Location of aneurysm: (to be reported) (ACA: 31; ICA: 18; MCA: 13; Other: 8).
Indirectness of population	--
Interventions	(n=31) Intervention 1: Nimodipine - Nimodipine. 60 mg nimodipine every 4 hours, started preoperatively and within 72 hours of ictus for 21 days. . Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness (n=39) Intervention 2: No treatment - Placebo. Received placebo at the same regime as nimodipine group.

	. Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for Pre-surgical/endovascular intervention: Mortality at 21 days ; Group 1: 2/31, Group 2: 4/39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Rebleed of index aneurysm - Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 21 days ; Group 1: 0/31, Group 2: 3/39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: DCI at 21 days ; Group 1: 4/31, Group 2: 11/39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome for Pre-surgical/endovascular intervention: Hydrocephalus at 21 days ; Group 1: 1/31, Group 2: 1/39 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	Pickard 1989[171]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=554)
Countries and setting	Conducted in United Kingdom; Setting: Hospitals in London, Southampton, Liverpool, and Glasgow
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligibility not specified, but mentioned that patients had to be admitted within 96 hours after the onset of symptoms and signs of SAH
Exclusion criteria	pregnancy; major renal, hepatic, or pulmonary disease; pre-existing cardiac decompensation or a recent (within six months) myocardial infarction; age below 18 years; a subarachnoid haemorrhage that produced a coma in the week preceding the most recent subarachnoid haemorrhage; and the patient or relative being unwilling to give consent.
Recruitment/selection of patients	within 96 hours after the onset of symptoms and signs of SAH
Age, gender and ethnicity	Age - Mean (SD): Nimodipine: 46 (13); Placebo: 48 (12). Gender (M:F): 221/333. Ethnicity: not reported
Further population details	1. aSAH grade: Not applicable (I: 20, II:327, III:148; IV:44; V: 15). 2. Location of aneurysm: (to be reported) (ACA: 164; MCA:103; PCA:35).
Indirectness of population	No indirectness
Interventions	(n=278) Intervention 1: Nimodipine - Nimodipine. Nimodipine was given as fast release tablets containing 30 mg active compound (two tablets given orally every four hours). Treatment was started within 96 hours after ictus and routinely continued for 21 days in survivors, unless there were clinical indications for stopping. Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness

	(n=276) Intervention 2: No treatment - Placebo. Matching placebo given over the same regime Duration 21 days. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Death at 6 months; Group 1: 43/278,
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Health and social quality of life
- Actual outcome for Pre-surgical/endovascular intervention: Good Recovery - Glasgow outcome score at 3 months; Group 1: 199/278, Group 2: 169/276
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Moderate disability - Glasgow outcome score at 3 months; Group 1: 24/278, Group 2: 16/276
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Severe disability - Glasgow outcome score at 3 months; Group 1: 11/278, Group 2: 29/276
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Vegetative state - Glasgow outcome score at 3 months; Group 1: 1/278, Group 2: 2/276
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;

Protocol outcome 3: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 6 months; Group 1: 25/278, Group 2: 38/276
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial - Actual outcome for Pre-surgical/endovascular intervention: Cerebral Infarct at 6 months; Group 1: 61/278, Group 2: 92/276 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	**Post 2020[174]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=995)
Countries and setting	Conducted in The Netherlands; Setting: 16 referring hospitals in the Netherlands
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults admitted with signs and symptoms for less than 24 hours indicating subarachnoid haemorrhage and had a non-contrast CT confirming SAH.
Exclusion criteria	Perimesencephalic bleeding pattern on CT with GCS of 13-15, and without loss of consciousness directly after ictus or focal neurological deficit on admission.
Recruitment/selection of patients	Selected from hospital admissions
Age, gender and ethnicity	Age - Mean (SD): 58.4 (4). Gender (M:F): 311/644.
Indirectness of population	No indirectness

Interventions	(n=480) Intervention 1: Tranexamic acid – Bolus of 1g TXA was given intravenously immediately following randomisation, directly followed by 1 g continuous IV infusion every 8 hours. Treatment was continued until the start of endovascular or surgical treatment of aneurysm or until a maximum of 24 hours. Duration 24 hours. Concurrent medication/care: usual care. Indirectness: No indirectness (n=475) Intervention 2: No treatment. Control group received care a usual. Duration n/a. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Fonds NutsOhra

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TXA versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Death at 30 days; Group 1: 103/475, Group 2: 104/470
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

- Actual outcome for Pre-surgical/endovascular intervention: Death at 6 months; Group 1: 128/475, Group 2: 114/470
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 6 months; Group 1: 49/475, Group 2: 66/470
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Degree of disability: mRS 0-2
- Actual outcome for Pre-surgical/endovascular intervention: mRS 0-2 at 6 months; Group 1: 229/475, Group 2: 262/470
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;. Comments: mRS 0-3 also reported, 0-2 included in line with other outcomes within review

Protocol outcome 4: Major complications: DCI
- Actual outcome for Pre-surgical/endovascular intervention: DCI at 6 months; Group 1: 108/475, Group 2: 106/470

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Major complications: Hydrocephalus - Actual outcome for Pre-surgical/endovascular intervention: hydrocephalus at 6 months; Group 1: 128/475, Group 2: 114/470 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Health related Quality of Life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	Roos 2000[188]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=462)
Countries and setting	Conducted in Netherlands; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted within 96 hours after onset of SAH, in whom treatment of the aneurysm was delayed beyond 48 hours after SAH.
Exclusion criteria	Aged <18, a lapse of more than 96 hours after SAH, planned surgery to clip the aneurysm, and planned endovascular coiling within 48 hours after admission.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 55 (14). Gender (M:F): 162/300. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear (Median GCS: 14). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=229) Intervention 1: Antifibrinolytic - Tranexamic acid. Patients received IV tranexamic acid, 6g daily (1g every 4 hours) for the first week and 6g daily PO (1.5g every 6 hours) for the second and third week. Duration 21 days. Concurrent medication/care: All patients received standard medical treatment with nimodipine for 3 weeks. Indirectness: No indirectness (n=233) Intervention 2: No treatment - Placebo. Control group followed the same regime receiving placebo.

	Duration 3 weeks. Concurrent medication/care: All patients received standard medical treatment with nimodipine for 3 weeks. Indirectness: No indirectness
Funding	Academic or government funding (Netherlands Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO

Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: GOS: poor outcome at 3 months; Group 1: 114/229, Group 2: 105/233
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 21 days; Group 1: 44/229, Group 2: 77/233
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Pre-surgical/endovascular intervention: Complications: DCI at post-operative period; Group 1: 68/229, Group 2: 74/233
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Complications: Hydrocephalus at post-operative period; Group 1: 71/229, Group 2: 62/233
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Study	**Teasdale 1989[210]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=554)
Countries and setting	Conducted in United Kingdom; Setting: UK hospitals
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Patients admitted to participating restaurants recruited
Age, gender and ethnicity	Age - Mean (SD): 47. Gender (M:F): Define. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear 2. Location of aneurysm: Not stated / Unclear
Extra comments	Diagnosis confirmed by CT in most cases. Angiography not required.
Indirectness of population	Serious indirectness: Unclear what intervention (if any) other than study drug was given for aSAH
Interventions	(n=278) Intervention 1: Nimodipine - Nimodipine. Oral nimodipine: 60mg, 4 hourly. Given as fast release tablet either swallowed with water or crushed and administered through a nasogastric tube. Duration 21 days. Concurrent medication/care: Patients monitored throughout time in hospital. Indirectness: No indirectness (n=276) Intervention 2: No treatment - Placebo. Placebo, 4 hourly. Duration 21 days. Concurrent medication/care: Patients monitored throughout time in hospital. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NIMODIPINE versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Death at 3 months; Group 1: 43/278, Group 2: 60/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: Vegetative at 3 months; Group 1: 1/278, Group 2: 2/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Severe disability at 3 months; Group 1: 11/278, Group 2: 29/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Moderate disability at 3 months; Group 1: 24/278, Group 2: 16/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Good recovery at 3 months; Group 1: 199/278, Group 2: 169/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleeds at 3 months; Group 1: 25/278, Group 2: 38/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Pre-surgical/endovascular intervention: DCI at 3 months; Group 1: 20/278, Group 2: 34/276
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcomes not reported by the study	Health and social quality of life ; Change in grade of aSAH ; Return to daily activity (e.g. work) ; Length of stay

Study	Van Rossum 1977[223]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=51)
Countries and setting	Conducted in Netherlands; Setting: three hospitals across the Netherlands
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed with SAH
Exclusion criteria	Not specified
Recruitment/selection of patients	Patients diagnosed with SAH
Age, gender and ethnicity	Age - Other: Not specified. Gender (M:F): Not specified. Ethnicity: not reported
Further population details	1. aSAH grade: Not stated / Unclear 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Antifibrinolytic - Tranexamic acid. Received IV tranexamic acid, 4 gm per day for ten consecutive days. Duration 10 days. Concurrent medication/care: - . Indirectness: No indirectness (n=25) Intervention 2: No treatment - Placebo. Control group received saline for ten consecutive days. Duration 10 days. Concurrent medication/care: -. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Tranexamic acid and placebo solutions were supplied by the manufacturer KABI, Sweden)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO Protocol outcome 1: Mortality	

- Actual outcome for Post-surgical/endovascular intervention: Mortality at 3 months; Group 1: 15/26, Group 2: 11/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Rebleed of index aneurysm - Actual outcome for Post-surgical/endovascular intervention: Rebleed at 3 months; Group 1: 5/26, Group 2: 4/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Health and social quality of life; Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures); Change in grade of aSAH; Return to daily activity (e.g. work); Major complications: DCI, hydrocephalus, intracranial; Length of stay

Study	**Vermeulen 1984[225]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=479)
Countries and setting	Conducted in Netherlands, United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Pre-surgical/endovascular intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with signs and symptoms of SAH and with confirmatory information on initial CT scan.
Exclusion criteria	Lapse of 72 hours since the presenting haemorrhage, presence of DVT, coagulation disorders, renal insufficiency, CT of cause other than aneurysm, negative angiography.
Recruitment/selection of patients	patients admitted to participating centres included.
Age, gender and ethnicity	Age - Mean (SD): 50.3. Gender (M:F): 189/290. Ethnicity: not reported
Further population details	1. aSAH grade: Good grade (Grade I: 79, Grade II: 180, Grade III: 132, Grade IV or V: 88). 2. Location of aneurysm: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=241) Intervention 1: Antifibrinolytic - Tranexamic acid. Treatment started within 72 hours of ictus with maximum duration of four weeks (IV bolus for four weeks or IV bolus for two weeks and oral for two weeks). 6g TXA per day over 6 doses for first week and 4g per day thereafter. Treatment stopped if surgery for aneurysms was undertaken. Duration 4 weeks. Concurrent medication/care: Drugs to treat hypertension were limited to clonidine, and codeine or pethidine were given for pain. Indirectness: No indirectness

	(n=238) Intervention 2: No treatment - Placebo. An equivalent placebo received for the control group. Duration 4 weeks. Concurrent medication/care: Drugs to treat hypertension were limited to clonidine, and codeine or pethidine were given for pain. Indirectness: No indirectness
Funding	Academic or government funding (Dutch Heart Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Pre-surgical/endovascular intervention: Mortality at 3 months; Group 1: 84/241, Group 2: 89/238
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome for Pre-surgical/endovascular intervention: Independent (GOS) at 3 months; Group 1: 127/241, Group 2: 126/238
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;
- Actual outcome for Pre-surgical/endovascular intervention: Dependent (GOS) at 3 months; Group 1: 30/241, Group 2: 23/238
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Rebleed of index aneurysm
- Actual outcome for Pre-surgical/endovascular intervention: Rebleed at 3 months; Group 1: 21/241, Group 2: 56/238
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Major complications: DCI, hydrocephalus, intracranial
- Actual outcome for Pre-surgical/endovascular intervention: Infarction at 3 months; Group 1: 59/241, Group 2: 36/238
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

- Actual outcome for Pre-surgical/endovascular intervention: Hydrocephalus at 3 months; Group 1: 35/241, Group 2: 29/238 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Health and social quality of life; Change in grade of aSAH; Return to daily activity (e.g. work); Length of stay

Appendix E: Forest plots

E.1 Fluid management (pre/post intervention) †

Figure 2: Complications: DCI (post-intervention)

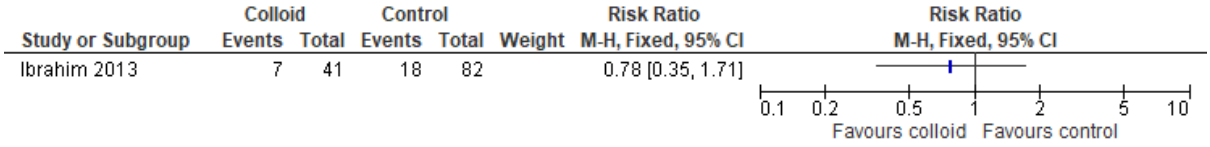


Figure 3: Complications: Cerebral infarction (post- intervention)

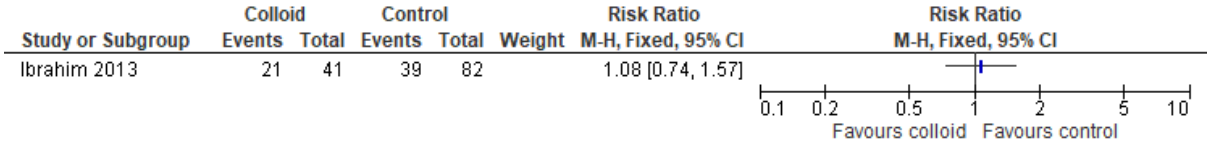


Figure 4: Degree of disability (mRS): Good (<4) (post- intervention). Scale 0-6; high score represents poor outcome.

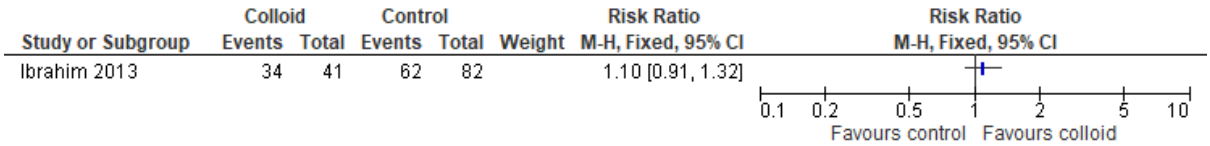
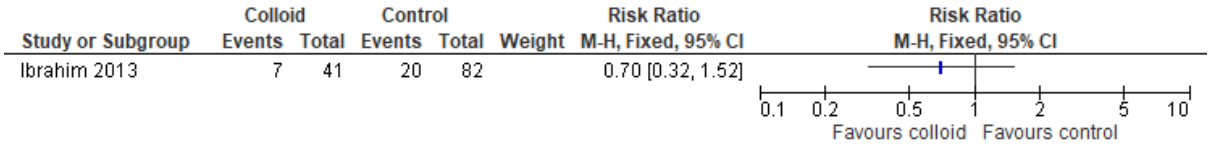


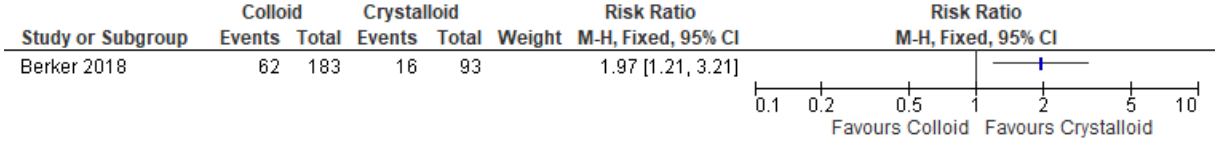
Figure 5: Degree of disability (mRS): Poor (≥4) (post- intervention). Scale 0-6; high score represents poor outcome.



†Control: Matched patients who did not receive colloids during DIND risk period. Unclear if other fluids were received.

E.2 Fluid management (post intervention)

Figure 6: Complications: Vasospasms (post- intervention)



E.3 Temperature control (perioperative)

Figure 7: Mortality at 3 months

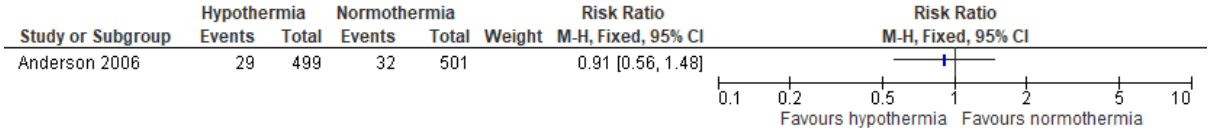


Figure 8: Degree of disability: Unimpaired at 3 months

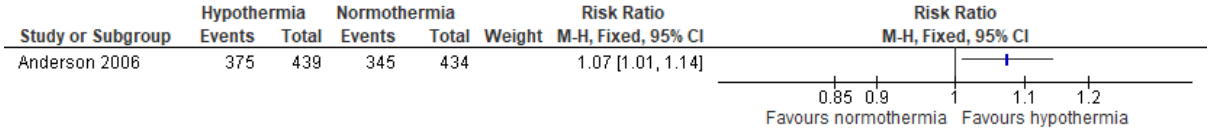


Figure 9: Degree of disability: Impaired at 3 months

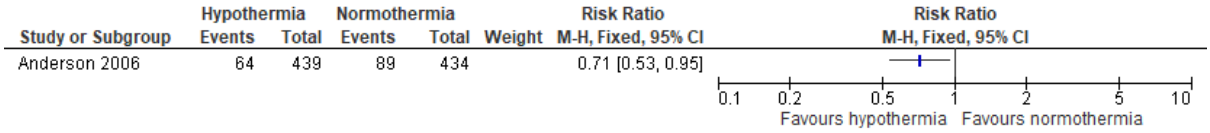


Figure 10: Complications: Cerebral infarction at 3 months

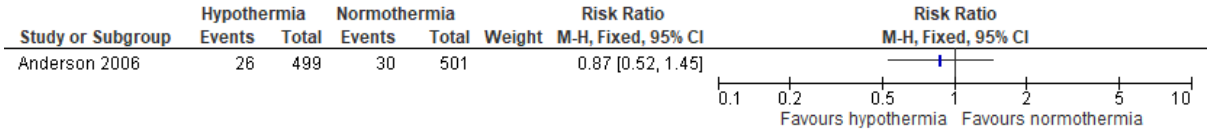


Figure 11: Complications: DCI at 3 months

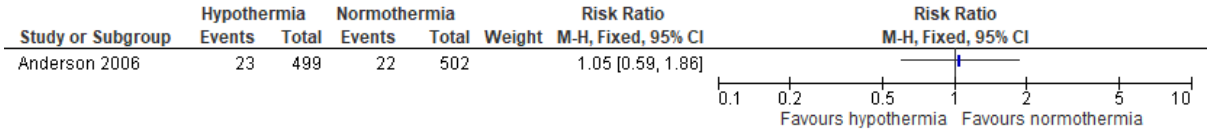
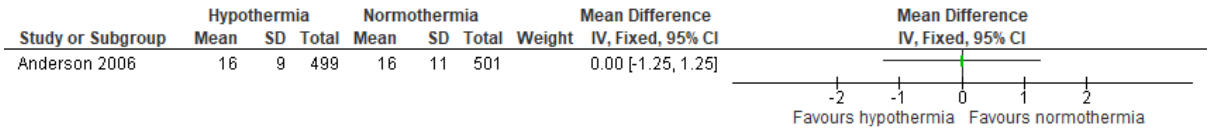


Figure 12: Length of hospital stay



E.4 Control of hypertension: β-blockers (pre-intervention)

Figure 13: Mortality at 1 month

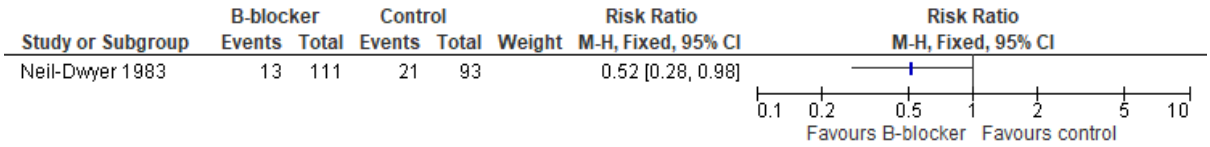


Figure 14: Mortality at 1 year

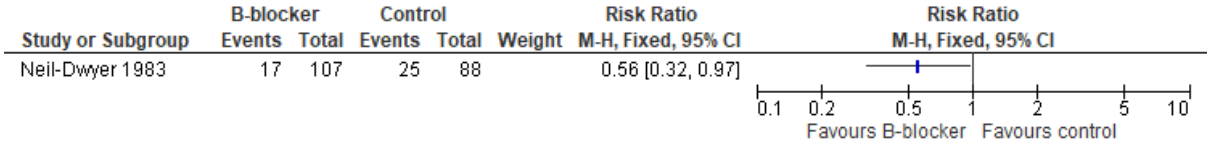
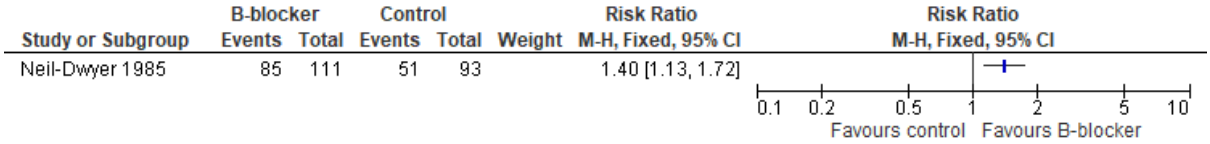


Figure 15: Return to daily activity (able to work) at 1 year



E.5 Control of hypertension: Nicardipine (pre/post-intervention)

Figure 16: Mortality at 3 months

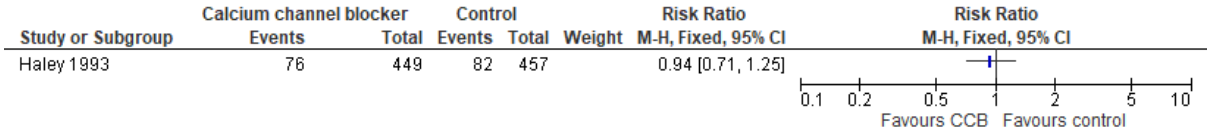


Figure 17: Degree of disability at 3 months (GOS): Good

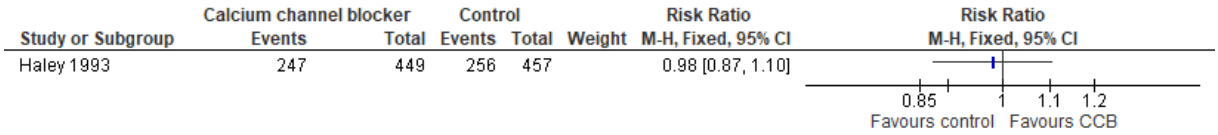


Figure 18: Degree of disability at 3 months (GOS): Moderate

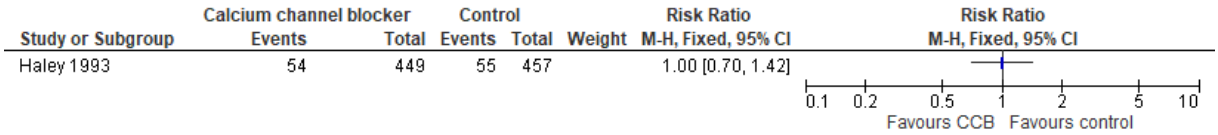


Figure 19: Degree of disability at 3 months (GOS): Severe

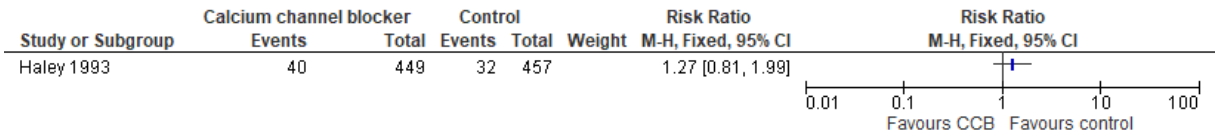
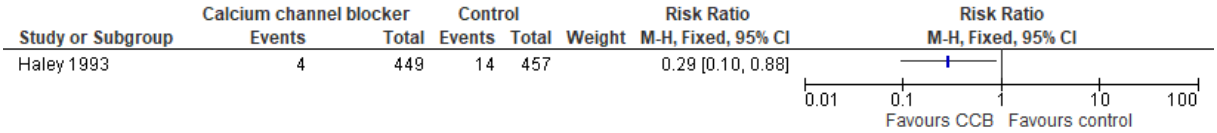


Figure 20: Degree of disability at 3 months (GOS): Vegetative



E.6 Seizure prophylaxis: (pre/post-intervention)

Figure 21: Degree of disability at 12 months (mRS ≥3): Poor. Scale 0-6; high score represents poor outcome.

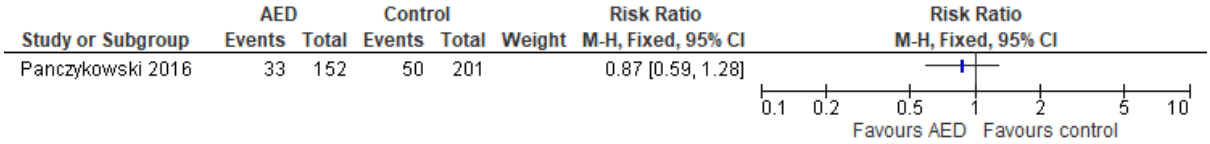
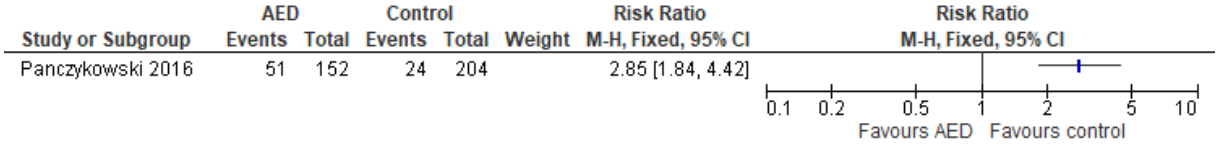


Figure 22: Complications: DCI



E.7 Nimodipine: (pre/post-intervention)

Figure 23: Mortality at 21 days

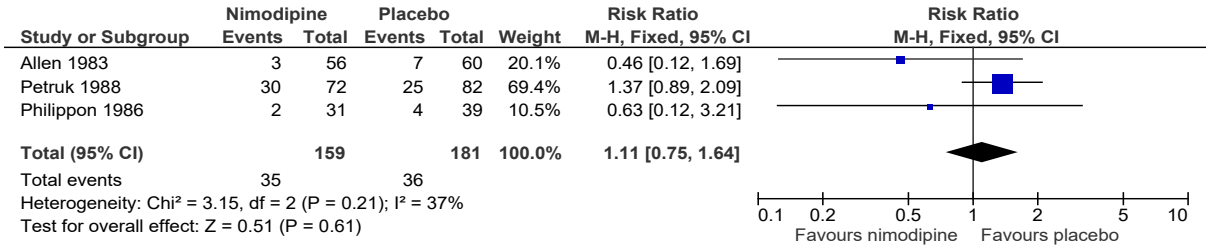


Figure 24: Mortality at 3 months

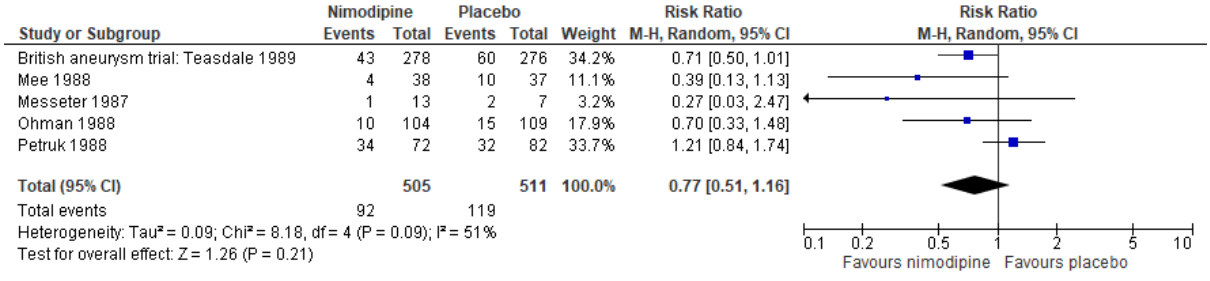


Figure 25: Mortality at 6 months

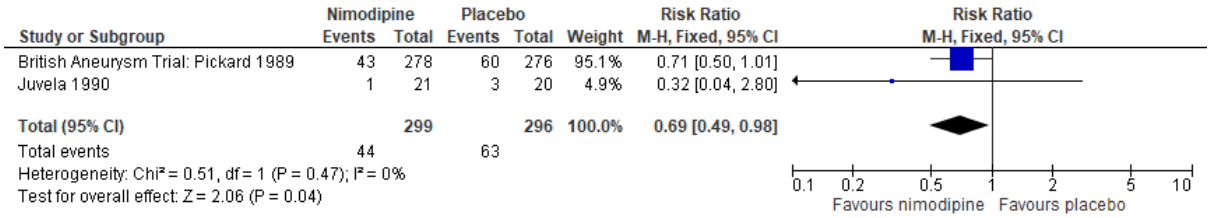


Figure 26: Mortality at 1 year

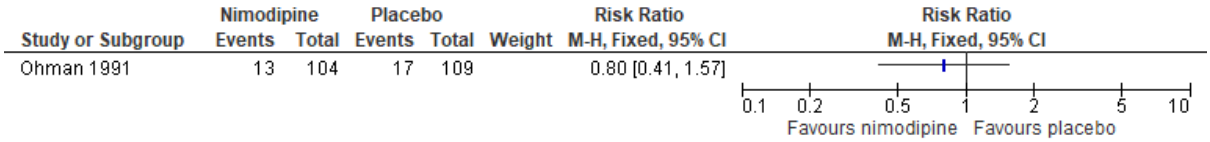


Figure 27: Rebleed at 21 days

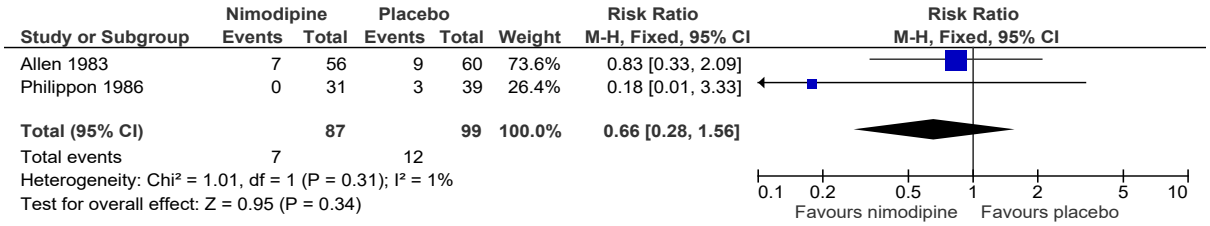


Figure 28: Rebleed at 3 months

Figure 29: Rebleed at 6 months

Figure 30: Rebleed at 1 year

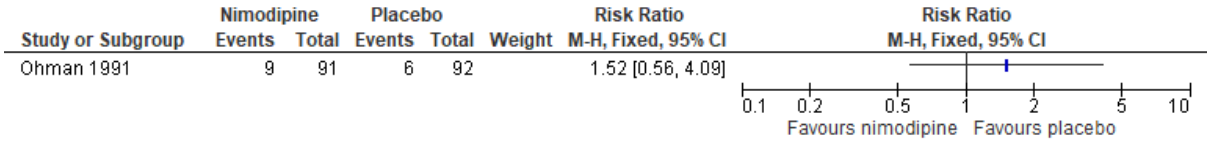


Figure 31: Degree of disability (GOS) at 21 days: Good recovery

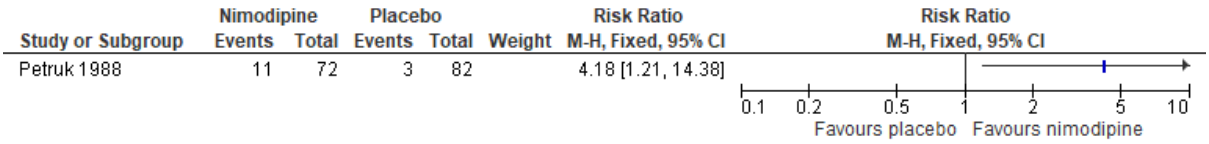


Figure 32: Degree of disability (GOS) at 21 days: Moderate disability

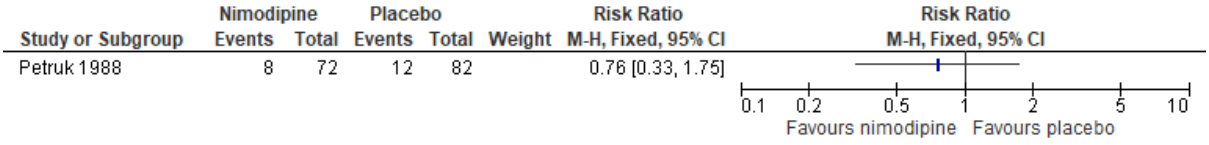


Figure 33: Degree of disability (GOS) at 21 days: Severe disability

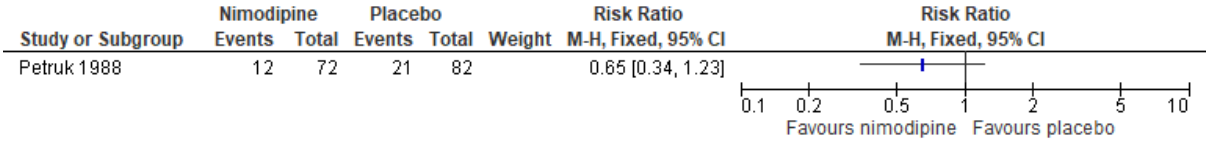


Figure 34: Degree of disability (GOS) at 21 days: Vegetative

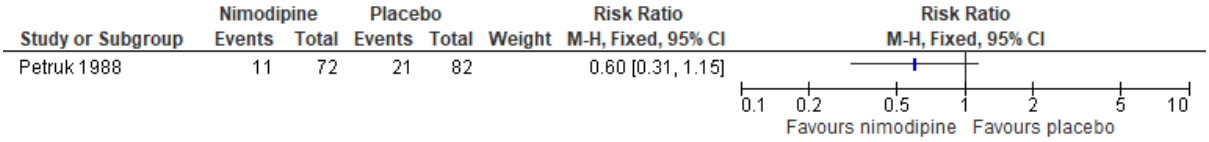


Figure 35: Degree of disability (GOS) at 3 months: Good recovery

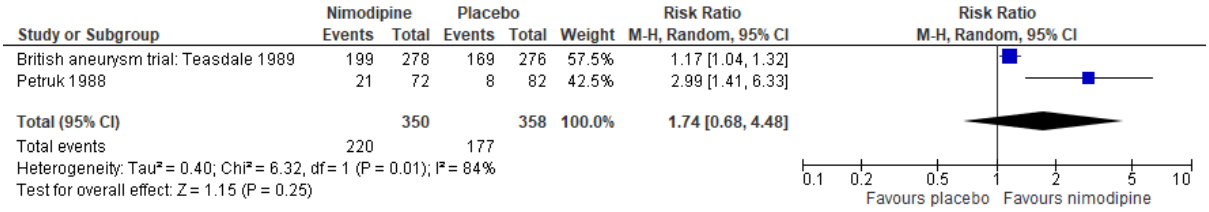


Figure 36: Degree of disability (GOS) at 3 months: Moderate disability

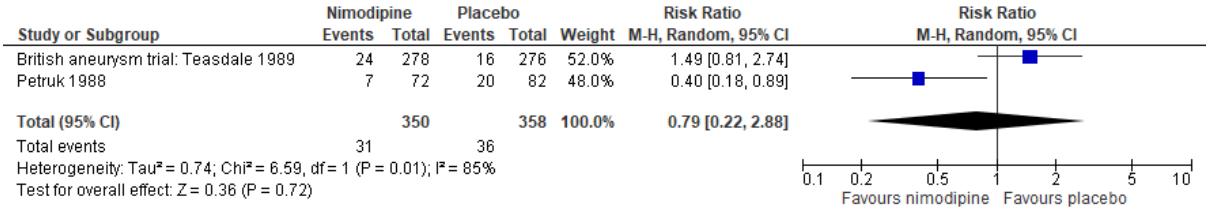


Figure 37: Degree of disability (GOS) at 3 months: Severe disability

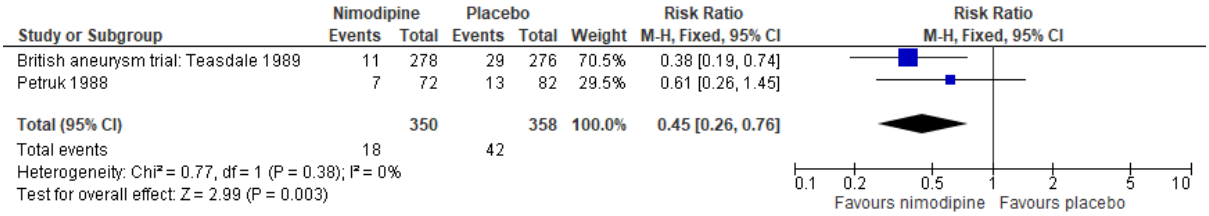


Figure 38: Degree of disability (GOS) at 3 months: Vegetative

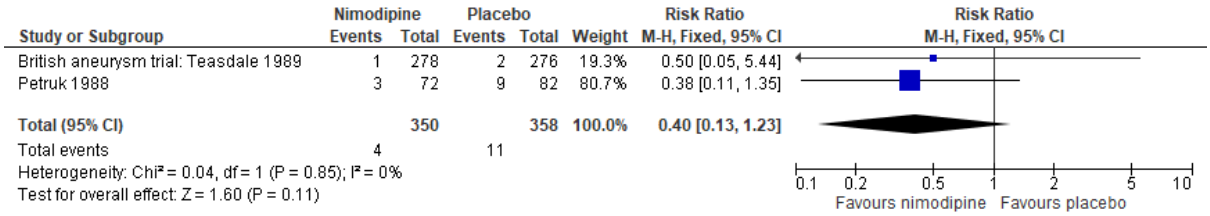


Figure 39: Degree of disability (GOS) at 3 months: Independent

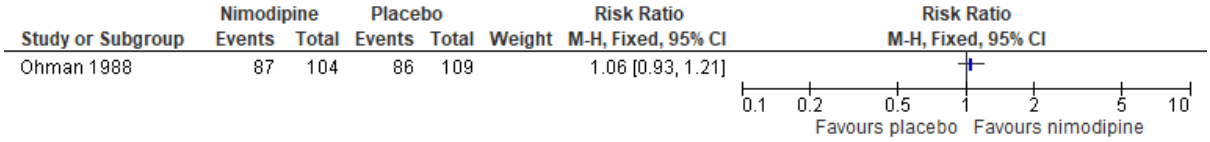


Figure 40: Degree of disability (GOS) at 3 months: Dependent

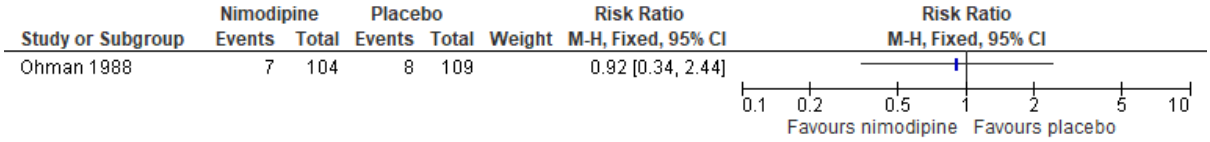


Figure 41: Degree of disability (GOS) at 6 months: Good recovery

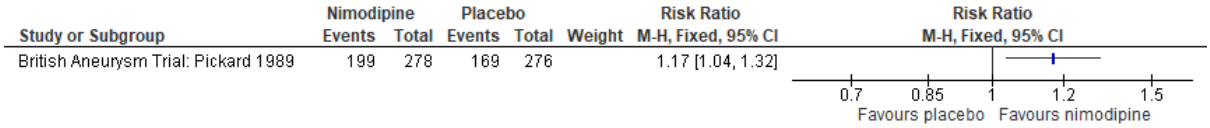


Figure 42: Degree of disability (GOS) at 6 months: Moderate disability

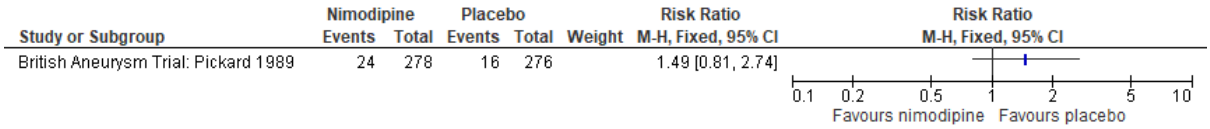


Figure 43: Degree of disability (GOS) at 6 months: Severe disability

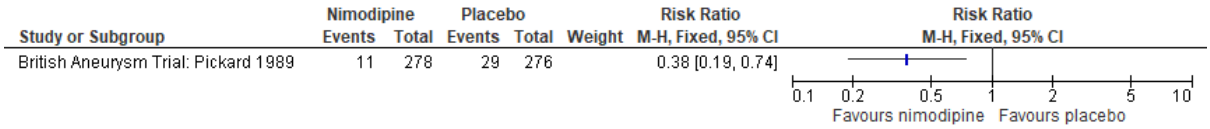


Figure 44: Degree of disability (GOS) at 6 months: Vegetative

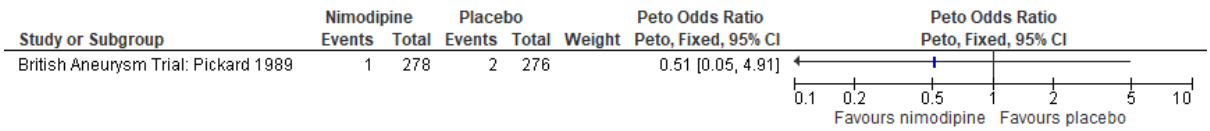


Figure 45: Degree of disability (GOS) at 6 months: Independent

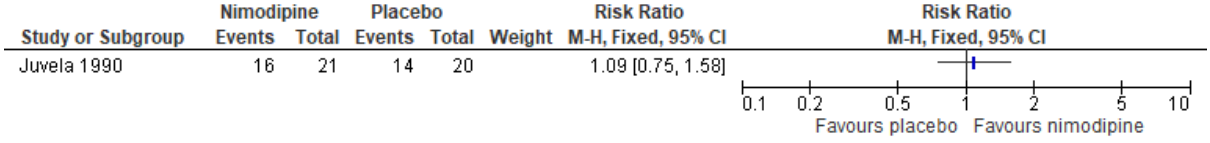


Figure 46: Degree of disability (GOS) at 6 months: Dependent

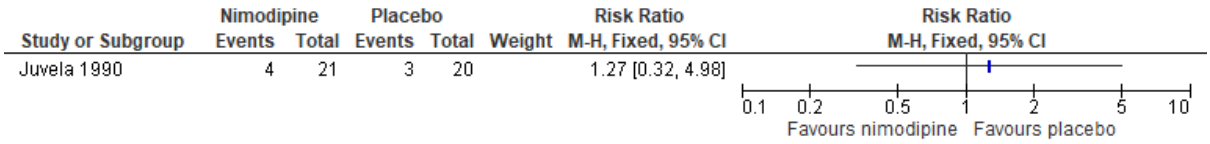


Figure 47: Degree of disability (GOS) at 1 year: Good recovery

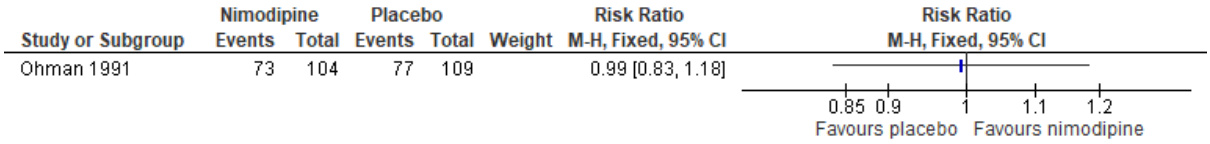


Figure 48: Degree of disability (GOS) at 1 year: Moderate disability

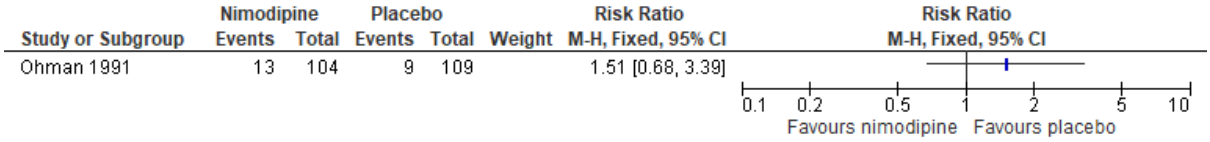


Figure 49: Degree of disability (GOS) at 1 year: Severe disability

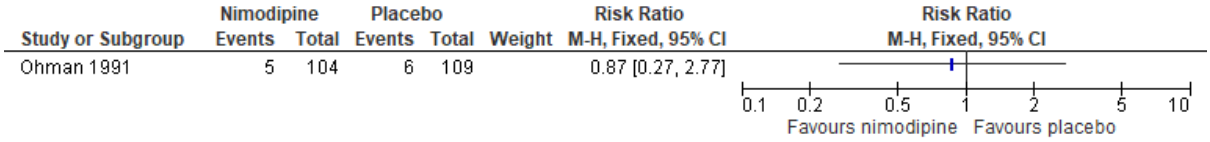


Figure 50: Complications: DCI at 21 days

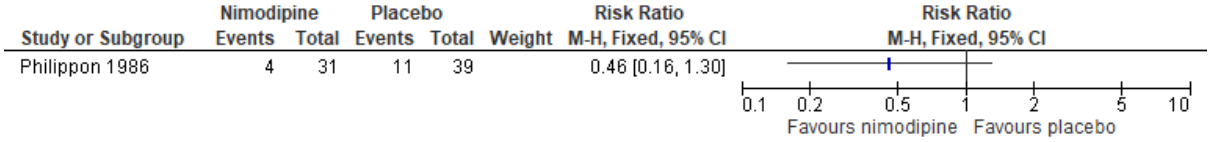


Figure 51: Complications: DCI at 3 months

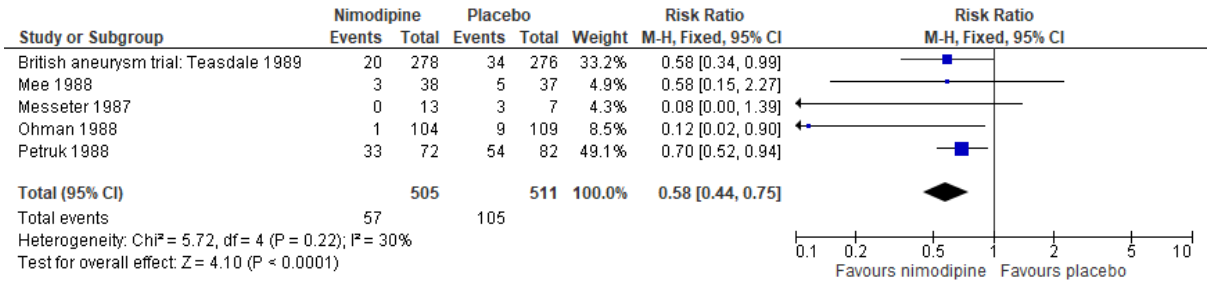


Figure 52: Complications: DCI at 6 months

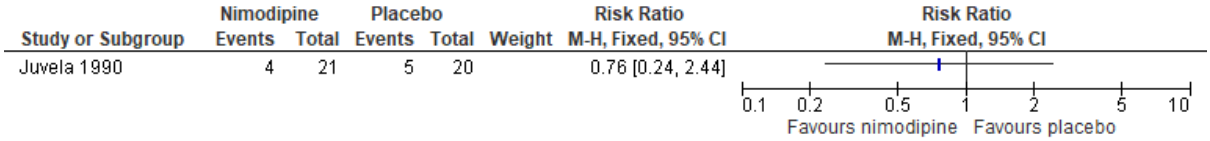


Figure 53: Complications: DCI at 1 year

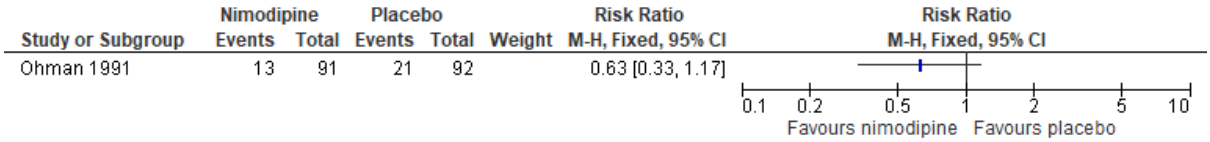


Figure 54: Complications: Cerebral infarction at 6 months

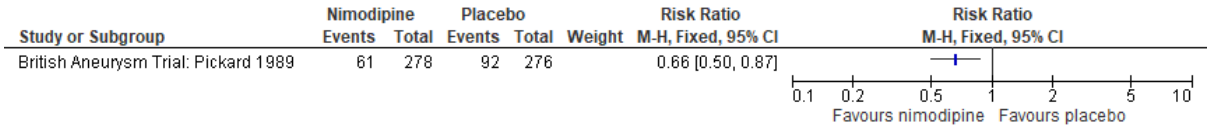


Figure 55: Complications: Hydrocephalus at 21 days

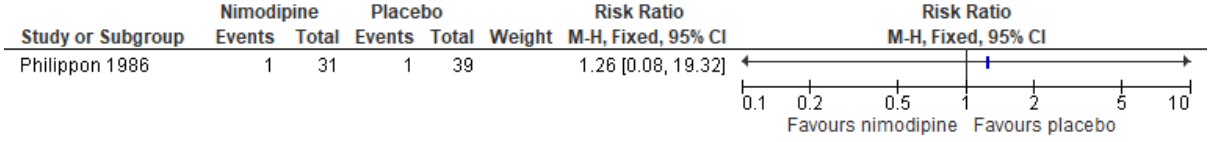
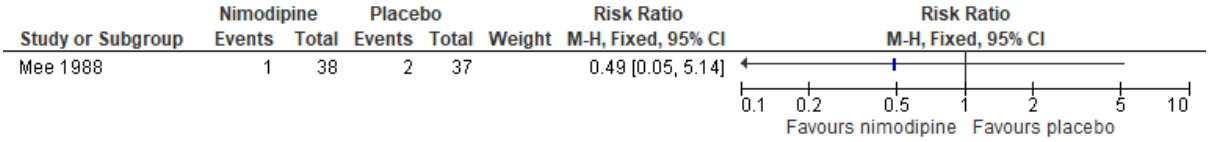


Figure 56: Complications: Hydrocephalus at 3 months


Nimodipine
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mee 1988
1
38
2
37
0.49 [0.05, 5.14]
0.1
0.2
0.5
1
2
5
10
Favours nimodipine
Favours placebo

E.8 Antifibrinolytic: Tranexamic acid (pre/post-intervention)

Figure 57: Mortality at 1 month

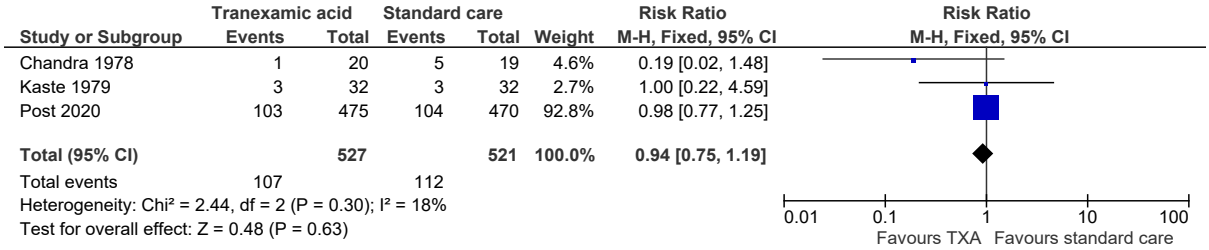


Figure 58: Mortality at 6 weeks

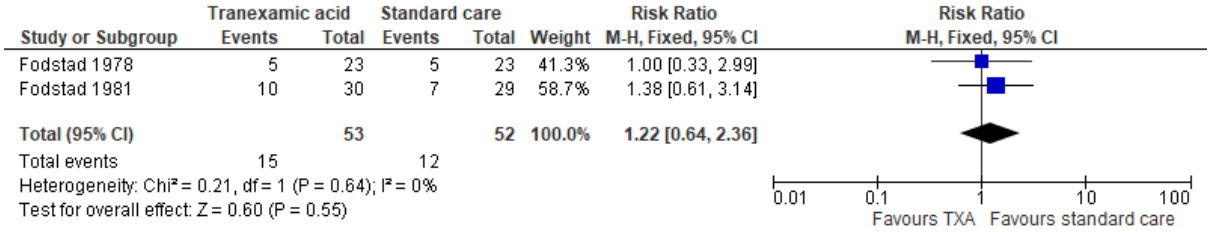


Figure 59: Mortality at 3 months

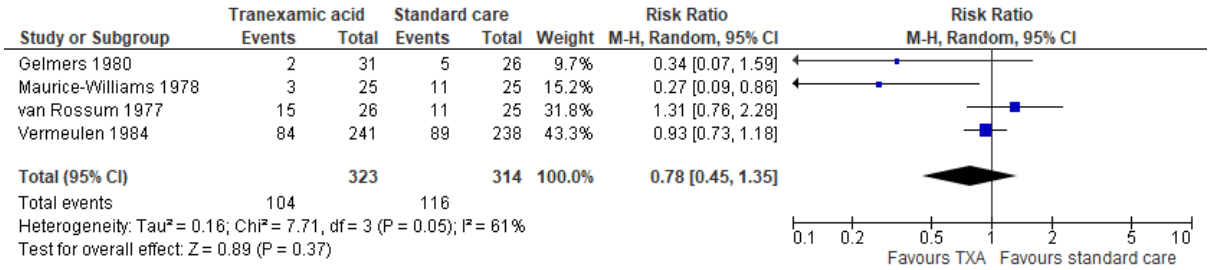


Figure 60: Mortality at 6 months

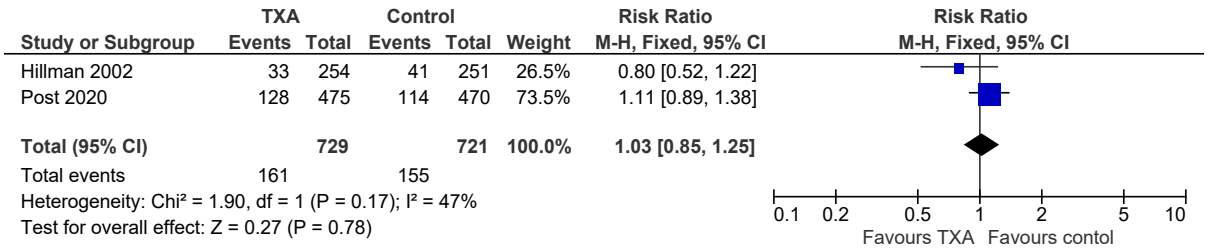


Figure 61: Rebleed at 1 month

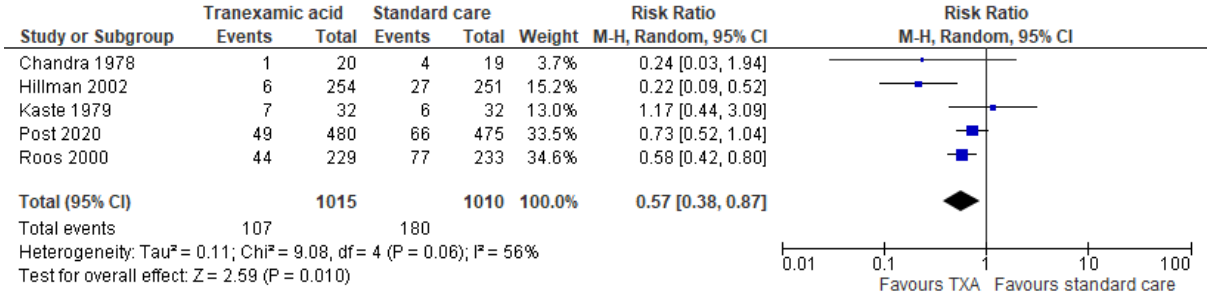


Figure 62: Rebleed at 6 weeks

Figure 63: Rebleed at 3 months

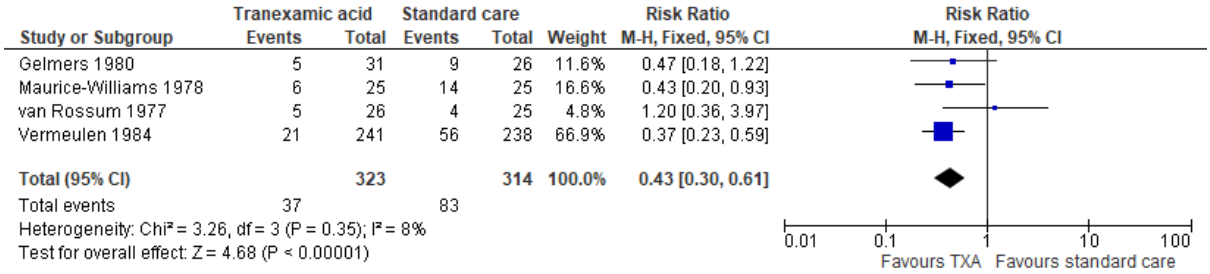


Figure 64: Degree of disability (mRS) at 6 months: good outcome (0-2); scale is 0-6, high score reflects poor outcome

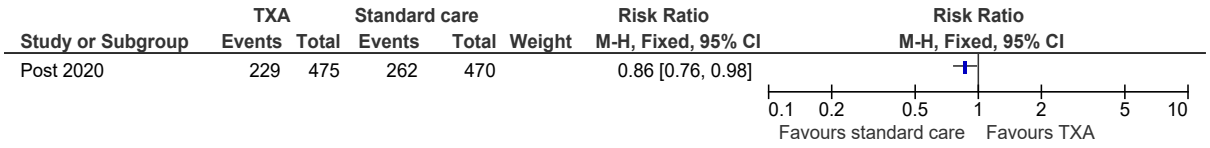


Figure 65: Degree of disability (GOS) at 3 months: Independent

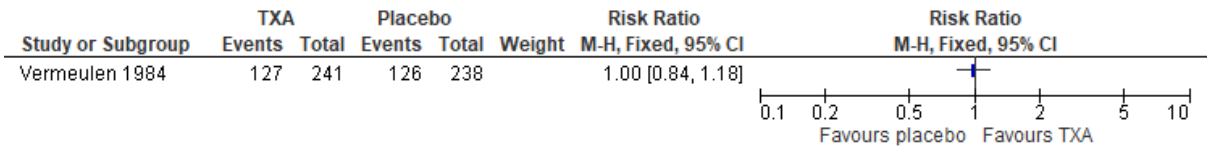


Figure 66: Degree of disability (GOS) at 3 months: Dependent

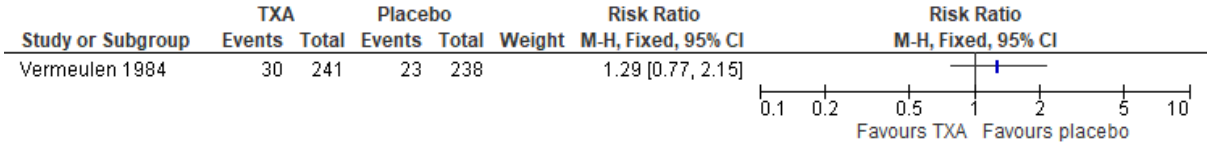


Figure 67: Degree of disability (GOS) at 3 months: Poor outcome (death, vegetative or severe disability)

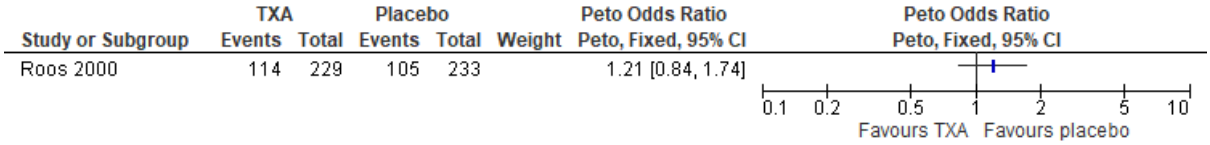


Figure 68: Degree of disability (GOS) at 6 months: Score of 5

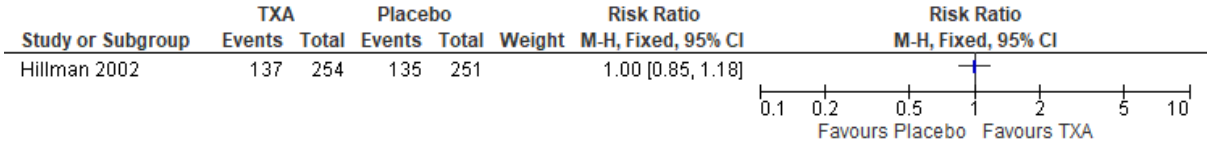


Figure 69: Degree of disability (GOS) at 6 months: Score of 4

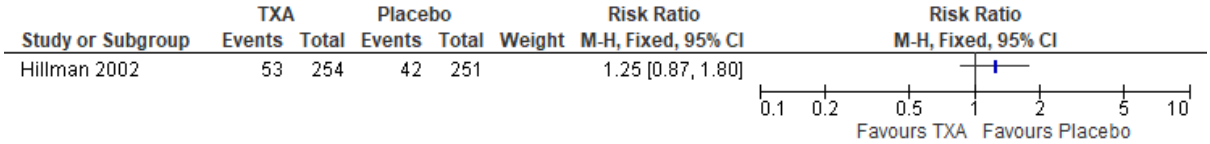


Figure 70: Degree of disability (GOS) at 6 months: Score of 3

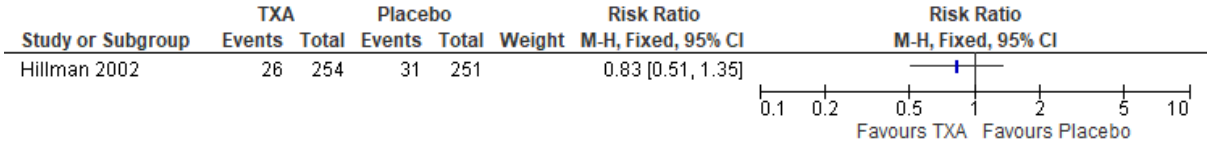


Figure 71: Degree of disability (GOS) at 6 months: Score of 2

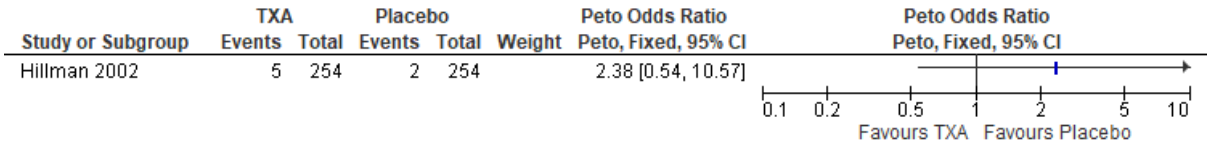


Figure 72: Grade of aSAH: Boterell's classification 1

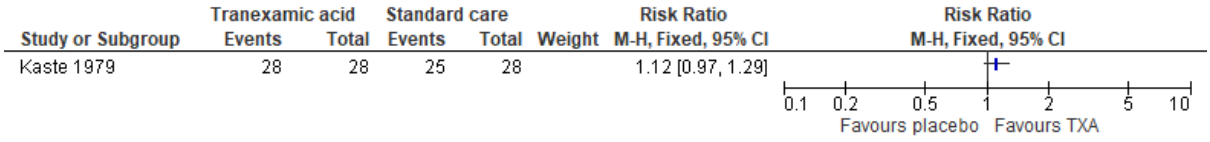


Figure 73: Grade of aSAH: Boterell's classification 2

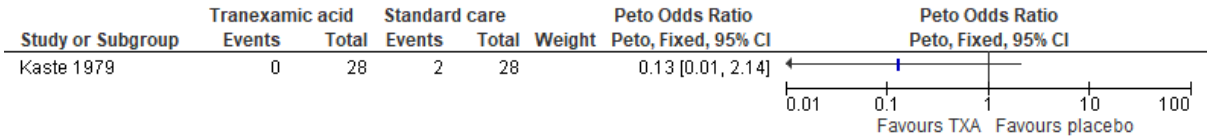


Figure 74: Grade of aSAH: Boterell's classification 3

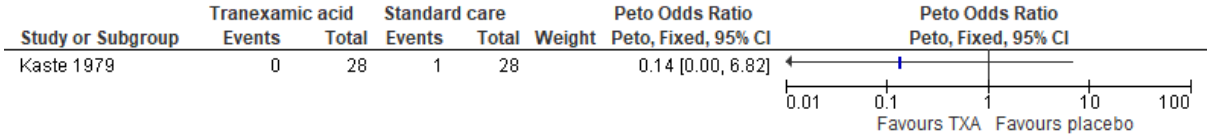


Figure 75: Complications: DCI

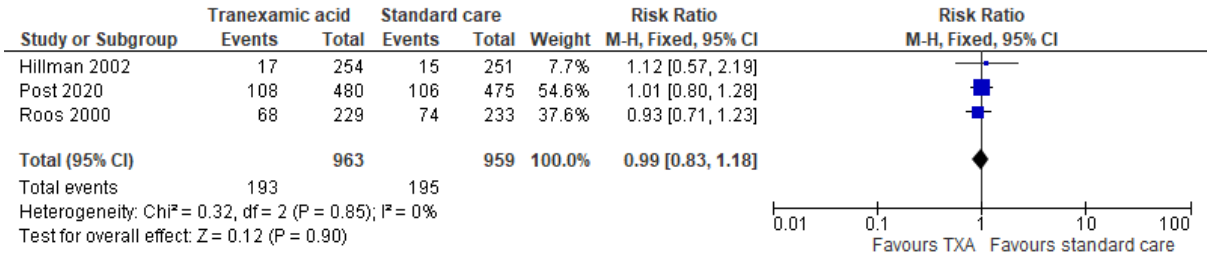


Figure 76: Complications: Death from DCI

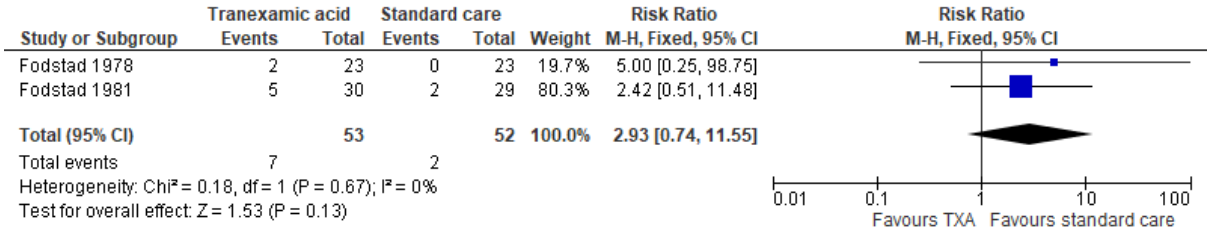


Figure 77: Complications: Cerebral infarction

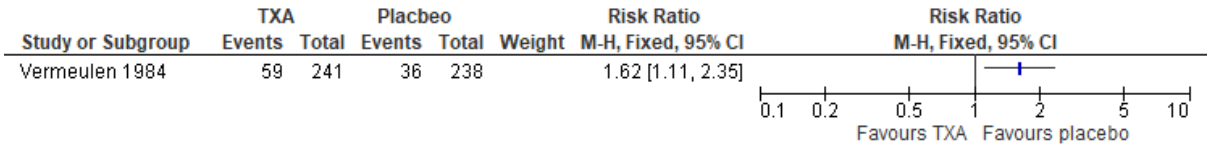
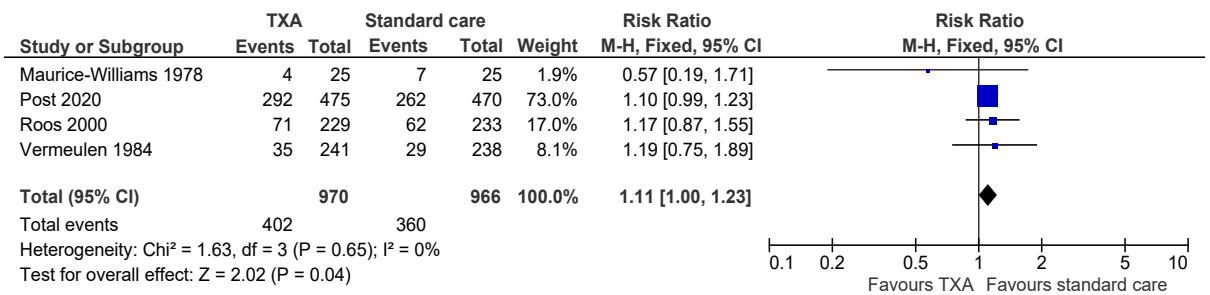


Figure 78: Complications: Hydrocephalus



E.9 Anticoagulant: Aminocaproic acid (pre/post-intervention)

Figure 79: Mortality at 1 month

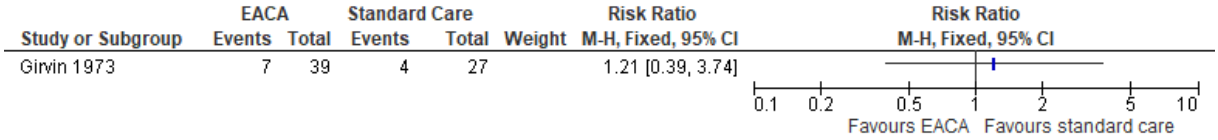
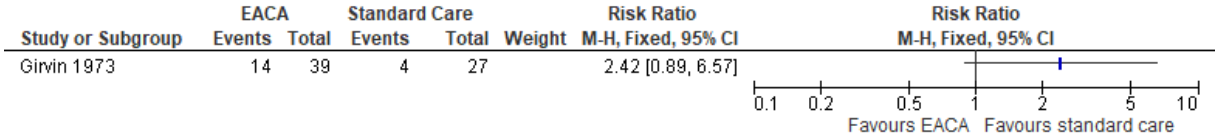


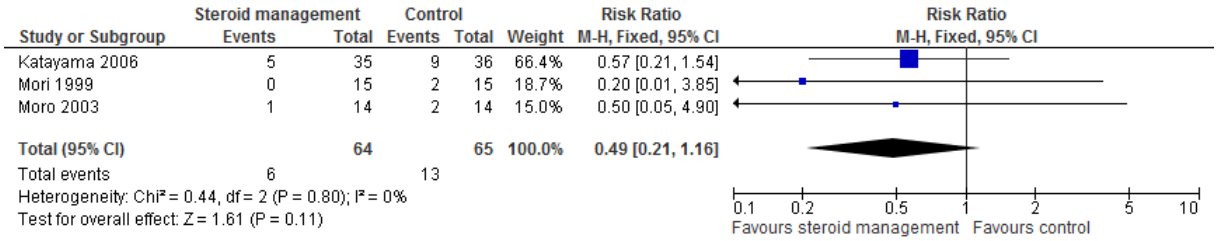
Figure 80: Rebleed at 1 month



E.10 Steroid management (post-intervention)

Figure 81: Complication: DCI

Figure 82: Complication: Symptomatic vasospasm



Appendix F:Minimal Important Difference for continuous outcomes

Table 22: Minimal important differences: Temperature control – Hypothermia versus normothermia

Outcomes	Minimally important difference (MID)
Length of hospital stay (days)	5.5

Appendix G: GRADE tables

Table 23: Clinical evidence profile: Fluid management (pre/post intervention)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre/post intervention: Colloid versus control	Control	Relative (95% CI)	Absolute		
Complication: DCI												
1	observational studies	very serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	7/41 (17.1%)	22%	RR 0.78 (0.35 to 1.71)	48 fewer per 1000 (from 143 fewer to 156 more)	⊕OOO VERY LOW	IMPORTANT
Complications: Cerebral infarction												
1	observational studies	very serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	21/41 (51.2%)	47.6%	RR 1.08 (0.74 to 1.57)	38 more per 1000 (from 124 fewer to 271 more)	⊕OOO VERY LOW	IMPORTANT
Degree of disability (MRs): Good (<4)												
1	observational studies	very serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[1]	none	34/41 (82.9%)	75.6%	RR 1.1 (0.91 to 1.32)	76 more per 1000 (from 68 fewer to 242 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (MRs): Poor (≥4)												
1	observational studies	very serious risk of bias[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	7/41 (17.1%)	24.4%	RR 0.7 (0.32 to 1.52)	73 fewer per 1000 (from 166 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL

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

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

Table 24: Clinical evidence profile: Fluid management (post intervention)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre/post intervention: Colloid	Crystalloid	Relative (95% CI)	Absolute		
Complication: Vasospasm												
1	observational studies	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	62/183 (33.9%)	17.2%	RR 1.97 (from 1.21 to 3.21	167 more per 1000 (from 36 to 380 more)	⊕OOO VERY LOW	IMPORTANT

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

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

Table 25: Clinical evidence profile: Temperature control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peri-intervention: Hypothermia versus Normothermia	Control	Relative (95% CI)	Absolute		
Mortality (follow-up 3 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	29/499 (5.8%)	6.4%	RR 0.91 (0.56 to 1.48)	6 fewer per 1000 (from 28 fewer to 31 more)	⊕⊕OO LOW	CRITICAL
Degree of disability: Unimpaired (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	375/439 (85.4%)	79.5%	RR 1.07 (1.01 to 1.14)	56 more per 1000 (from 8 more to 111 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Degree of disability: Impaired at 3 months (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	64/439 (14.6%)	20.5%	RR 0.71 (0.53 to 0.95)	59 fewer per 1000 (from 10 fewer to 96 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Complications: Cerebral infarction (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	26/499 (5.2%)	6%	RR 0.87 (0.52 to 1.45)	8 fewer per 1000 (from 29 fewer to 27 more)	⊕⊕OO LOW	IMPORTANT
Complications: DCI (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	23/499 (4.6%)	4.4%	RR 1.05 (0.59 to 1.86)	2 more per 1000 (from 18 fewer to 38 more)	⊕⊕OO LOW	IMPORTANT
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	499	501	-	MD 0 higher (1.25 lower to 1.25 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

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

Table 26: Clinical evidence profile: Control of hypertension (B-blockers)

Quality assessment						No of patients	Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-intervention: B-blocker versus control**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 1 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/111 (11.7%)	25.8%	RR 0.52 (0.28 to 0.98)	124 fewer per 1000 (from 5 fewer to 186 fewer)	⊕⊕OO LOW	CRITICAL
Mortality (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/107 (15.9%)	25/88 (28.4%)	RR 0.56 (0.32 to 0.97)	125 fewer per 1000 (from 9 fewer to 193 fewer)	⊕⊕OO LOW	CRITICAL
Return to daily activity (able to work)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	85/111 (76.6%)	54.8%	RR 1.4 (1.13 to 1.72)	219 more per 1000 (from 71 more to 395 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence profile: Control of hypertension (nicardipine)

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pere/post intervention: Calcium channel blocker versus standard care**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 3 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	76/449 (16.9%)	17.9%	RR 0.94 (0.71 to 1.25)	11 fewer per 1000 (from 52 fewer to 45 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): Good (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	247/449 (55%)	56%	RR 0.98 (0.87 to 1.1)	11 fewer per 1000 (from 73 fewer to 56 more)	⊕⊕⊕⊕ HIGH	
Degree of disability (GOS): Moderate (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	54/449 (12%)	12%	RR 1 (0.7 to 1.42)	0 fewer per 1000 (from 36 fewer to 50 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): Severe (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	40/449 (8.9%)	7%	RR 1.27 (0.81 to 1.99)	19 more per 1000 (from 13 fewer to 69 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): Vegetative (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	4/449 (0.89%)	3.1%	RR 0.29 (0.1 to 0.88)	22 fewer per 1000 (from 4 fewer to 28 fewer)	⊕⊕⊕O MODERATE	CRITICAL

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

Table 28: Clinical evidence profile: Seizure management/Seizure prophylaxis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Seizure prophylaxis versus control**	**Control**	**Relative (95% CI)**	**Absolute**		
Degree of disability (mRS): Poor (follow-up 12 months)												

1	observational studies	very serious risk of bias[3]	no serious inconsistency	serious[1]	very serious[2]	none	33/152 (21.7%)	24.9%	RR 0.87 (0.59 to 1.28)	32 fewer per 1000 (from 102 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Complication: DCI												
1	observational studies	very serious risk of bias[3]	no serious inconsistency	serious[1]	no serious imprecision	strong association[4]	51/152 (33.6%)	11.8%	RR 2.85 (1.84 to 4.42)	218 more per 1000 (from 99 more to 404 more)	⊕⊕OO LOW	IMPORTANT

[1] Matching to account for clinical covariates associated with prophylactic AED administration, not for confounding factors for SAH.
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[4] Upgraded by 1 increment if the magnitude of effect is large (RR = 2-5 or RR = 0.5-0.2)

Table 29: Clinical evidence profile: Nimodipine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre/post intervention: Nimodipine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 21 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious	none	35/159 (22%)	11.7%	RR 1.11 (0.75 to 1.64)	13 more per 1000 (from 29 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL
Mortality (follow-up 3 months)												
5	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	92/505 (18.2%)	27%	RR 0.77 (0.51 to 1.16)	62 fewer per 1000 (from 132 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
Mortality (follow-up 6 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	44/299 (14.7%)	18.4%	RR 0.69 (0.49 to 0.98)	57 fewer per 1000 (from 4 fewer to 94 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Mortality (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/104 (12.5%)	15.6%	RR 0.8 (0.41 to 1.57)	31 fewer per 1000 (from 92 fewer to 89 more)	⊕OOO VERY LOW	CRITICAL
Rebleed (follow-up 21 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/87 (8%)	11.4%	RR 0.66 (0.28 to 1.56)	39 fewer per 1000 (from 82 fewer to 64 more)	⊕⊕OO LOW	CRITICAL
Rebleed (follow-up 3 months)												
4	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	51/492 (10.4%)	15%	RR 0.88 (0.47 to 1.66)	18 fewer per 1000 (from 80 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Rebleed (follow-up 6 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	26/299 (8.7%)	16.9%	RR 0.61 (0.39 to 0.97)	66 fewer per 1000 (from 5 fewer to 103 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Rebleed (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/91 (9.9%)	6.5%	RR 1.52 (0.56 to 4.09)	34 more per 1000 (from 29 fewer to 201 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Good recovery (follow-up 21 days)												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious imprecision[3]	none	11/72 (15.3%)	3.7%	RR 4.18 (1.21 to 14.38)	118 more per 1000 (from 8 more to 495 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Moderate disability (follow-up 21 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/72 (11.1%)	12/82 (14.6%)	RR 0.76 (0.33 to 1.75)	35 fewer per 1000 (from 98 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL

Degree of disability (GOS): Severe disability (follow-up 21 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	12/72 (16.7%)	25.6%	RR 0.65 (0.34 to 1.23)	90 fewer per 1000 (from 169 fewer to 59 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): Vegetative (follow-up 21 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	11/72 (15.3%)	25.6%	RR 0.60 (0.31 to 1.15)	102 fewer per 1000 (from 177 fewer to 38 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): Good recovery (follow-up 3 months)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	220/350 (62.9%)	35.5%	RR 1.74 (0.68 to 4.48)	263 more per 1000 (from 114 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Moderate disability (follow-up 3 months)												
2	randomised trials	serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	31/350 (8.9%)	15.1%	RR 0.79 (0.22 to 2.88)	32 fewer per 1000 (from 118 fewer to 284 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Severe disability (follow-up 3 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/350 (5.1%)	13.2%	RR 0.45 (0.26 to 0.76)	73 fewer per 1000 (from 32 fewer to 98 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): Vegetative (follow-up 3 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/350 (1.1%)	5.9%	RR 0.40 (0.13 to 1.23)	35 fewer per 1000 (from 51 fewer to 14 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): Independent (follow-up 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	none	none	87/104 (83.7%)	78.9%	RR 1.06 (0.93 to 1.21)	47 more per 1000 (from 55 fewer to 166 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): Dependent (follow-up 3 months)												

1	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[3]	none	7/104 (6.7%)	7.3%	RR 0.92 (0.34 to 2.44)	6 fewer per 1000 (from 48 fewer to 105 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Good recovery (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	199/278 (71.6%)	61.2%	RR 1.17 (1.04 to 1.32)	104 more per 1000 (from 24 more to 196 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): Moderate disability (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	24/278 (8.6%)	5.8%	RR 1.49 (0.81 to 2.74)	28 more per 1000 (from 11 fewer to 101 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): Severe disability (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/278 (4%)	10.5%	RR 0.38 (0.19 to 0.74)	65 fewer per 1000 (from 27 fewer to 85 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Degree of disability (GOS): Vegetative (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/278 (0.36%)	0.7%	OR 0.51 (0.05 to 4.91)	3 fewer per 1000 (from 7 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): independent (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/21 (76.2%)	70%	RR 1.09 (0.75 to 1.58)	63 more per 1000 (from 175 fewer to 406 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): dependent (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/21 (19%)	15%	RR 1.26 (0.32 to 4.98)	39 more per 1000 (from 102 fewer to 4.98 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Good recovery (follow-up 1 years)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/104 (70.2%)	70.6%	RR 0.99 (0.83 to 1.18)	7 fewer per 1000 (from 120 fewer to 127 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): Moderate disability (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/104 (12.5%)	8.3%	RR 1.51 (0.68 to 3.39)	42 more per 1000 (from 27 fewer to 198 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): Severe disability (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/104 (4.8%)	5.5%	RR 0.87 (0.27 to 2.77)	7 fewer per 1000 (from 40 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL
DCI (follow-up 21 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/31 (12.9%)	28.2%	RR 0.46 (0.16 to 1.3)	152 fewer per 1000 (from 237 fewer to 85 more)	⊕⊕OO LOW	IMPORTANT
DCI (follow-up 3 months)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/505 (11.3%)	13.5%	RR 0.58 (0.44 to 0.75)	57 fewer per 1000 (from 34 fewer to 76 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
DCI (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/21 (19%)	25%	RR 0.76 (0.24 to 2.44)	60 fewer per 1000 (from 190 fewer to 360 more)	⊕OOO VERY LOW	IMPORTANT
DCI (follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	13/91 (14.3%)	21/92 (22.8%)	RR 0.63 (0.33 to 1.17)	84 fewer per 1000 (from 153 fewer to 39 more)	⊕⊕OO LOW	IMPORTANT
Cerebral infarct (follow-up 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	61/278 (21.9%)	33.3%	RR 0.66 (0.5 to 0.87)	113 fewer per 1000 (from 43 fewer to 167 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Complication: Hydrocephalus (follow-up 21 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/31 (3.2%)	2.6%	RR 1.26 (0.08 to 19.32)	7 more per 1000 (from 24 fewer to 476 more)	⊕⊕OO LOW	IMPORTANT
Complication: Hydrocephalus (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/38 (2.6%)	5.4%	RR 0.49 (0.05 to 5.14)	28 fewer per 1000 (from 51 fewer to 224 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Clinical evidence profile: Antifibrinolytic (tranexamic acid)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre/post intervention: Tranexamic acid**	**Standard care**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up <30 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	107/527 (20.3%)	21.3%	RR 0.94 (0.75 to 1.19)	13 fewer per 1000 (from 53 fewer to 40 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (follow-up 6 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/53 (28.3%)	22.9%	RR 1.22 (0.64 to 2.36)	50 more per 1000 (from 82 fewer to 311 more)	⊕⊕OO LOW	CRITICAL
Mortality (follow-up 3 months)												

3	randomised trials	no serious risk of bias	serious inconsistency[3]	no serious indirectness	very serious[2]	none	101/298 (33.9%)	37.4%	RR 0.78 (0.45 to 1.35)	82 fewer per 1000 (from 206 fewer to 131 more)	⊕⊕OO LOW	CRITICAL
Mortality (follow-up 6 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	161/729 (22.1%)	21.3%	RR 1.03 (0.85 to 1.25)	6 fewer per 1000 (from 32 fewer to 53 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Rebleed (follow-up <30 days)												
5	randomised trials	no serious risk of bias	serious inconsistency[3]	no serious indirectness	serious[2]	none	107/1015 (10.5%)	17.8%	RR 0.57 (0.38 to 0.87)	77 fewer per 1000 (from 23 fewer to 110 fewer)	⊕⊕OO LOW	CRITICAL
Rebleed (follow-up 6 weeks)												
2	randomised trials	no serious risk of bias	serious inconsistency[3]	no serious indirectness	serious[2]	none	7/53 (13.2%)	31.6%	RR 0.36 (0.05 to 2.82)	202 fewer per 1000 (from 300 fewer to 575 more)	⊕⊕OO LOW	CRITICAL
Rebleed (follow-up 3 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/298 (10.4%)	23.5%	RR 0.43 (0.29 to 0.64)	134 fewer per 1000 (from 85 fewer to 167 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Degree of disability (mRS): good outcome (0-3) (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	229/475 (48.2%)	55.7%	RR 0.86 (0.76 to 0.98)	78 fewer per 1000 (from 11 fewer to 134 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): independent (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	none	none	127/241 (52.7%)	52.9%	RR 1 (0.84 to 1.18)	0 fewer per 1000 (from 85 fewer to 95 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Degree of disability (GOS): dependent (follow-up 3 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	30/241 (12.4%)	9.7%	RR 1.29 (0.77 to 2.15)	28 more per 1000 (from 22 fewer to 112 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): poor outcome (death, vegetative or severe disability) (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	114/229 (49.8%)	45.1%	OR 1.21 (0.84 to 1.74)	47 more per 1000 (from 43 fewer to 137 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): 5 (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/254 (53.9%)	53.8%	RR 1 (0.85 to 1.18)	0 fewer per 1000 (from 81 fewer to 97 more)	⊕⊕⊕O MODERATE	CRITICAL
Degree of disability (GOS): 4 (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53/254 (20.9%)	16.7%	RR 1.25 (0.87 to 1.8)	42 more per 1000 (from 22 fewer to 134 more)	⊕⊕OO LOW	CRITICAL
Degree of disability (GOS): 3 (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	26/254 (10.2%)	12.4%	RR 0.83 (0.51 to 1.35)	21 fewer per 1000 (from 61 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
Degree of disability (GOS): 2 (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/254 (2%)	0.8%	Peto OR 2.38 (0.54 to 10.57)	11 more per 1000 (from 4 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Grade of aSAH: Boterell's classification 1												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	28/28 (100%)	89.3%	RR 1.12 (0.97 to 1.29)	107 more per 1000 (from 27 fewer to 259 more)	⊕⊕⊕O MODERATE	CRITICAL
Grade of aSAH: Boterell's classification 2												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	7.1%	OR 0.13 (0.01 to 2.14)	61 fewer per 1000 (from 70 fewer to 70 more)	⊕⊕OO LOW	CRITICAL
Grade of aSAH: Boterell's classification 3												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	3.6%	OR 0.14 (0 to 6.82)	31 fewer per 1000 (from 36 fewer to 167 more)	⊕⊕OO LOW	CRITICAL
Complication: DCI (follow-up Postoperative period)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193/963 (20%)	20.3%	RR 0.99 (0.83 to 1.18)	2 fewer per 1000 (from 35 fewer to 37 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Complication: death from DCI (follow-up 6 weeks)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/53 (13.2%)	3.5%	RR 2.93 (0.74 to 11.55)	68 more per 1000 (from 9 fewer to 369 more)	⊕⊕OO LOW	IMPORTANT
Complication: cerebral infarction (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	59/241 (24.5%)	15.1%	RR 1.62 (1.11 to 2.35)	94 more per 1000 (from 17 more to 204 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complication: hydrocephalus (follow-up Post-op to 6 months)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	402/970 (41.4%)	37.3%	RR 1.11 (1 to 1.23)	41 more per 1000 (from 0 fewer to 86 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p>0.04, unexplained by subgroup analysis

Table 31: Clinical evidence profile: Antifibrinolytic (aminocaproic acid)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-intervention: Aminocaproic acid	Control	Relative (95% CI)	Absolute		
Mortality (follow-up Preoperative period)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/39 (17.9%)	14.8%	RR 1.21 (0.39 to 3.74)	31 more per 1000 (from 90 fewer to 406 more)	⊕OOO VERY LOW	CRITICAL
Rebleed (follow-up Preoperative period)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/39 (35.9%)	14.8%	RR 2.42 (0.89 to 6.57)	210 more per 1000 (from 16 fewer to 824 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 32: Clinical evidence profile: Steroid management

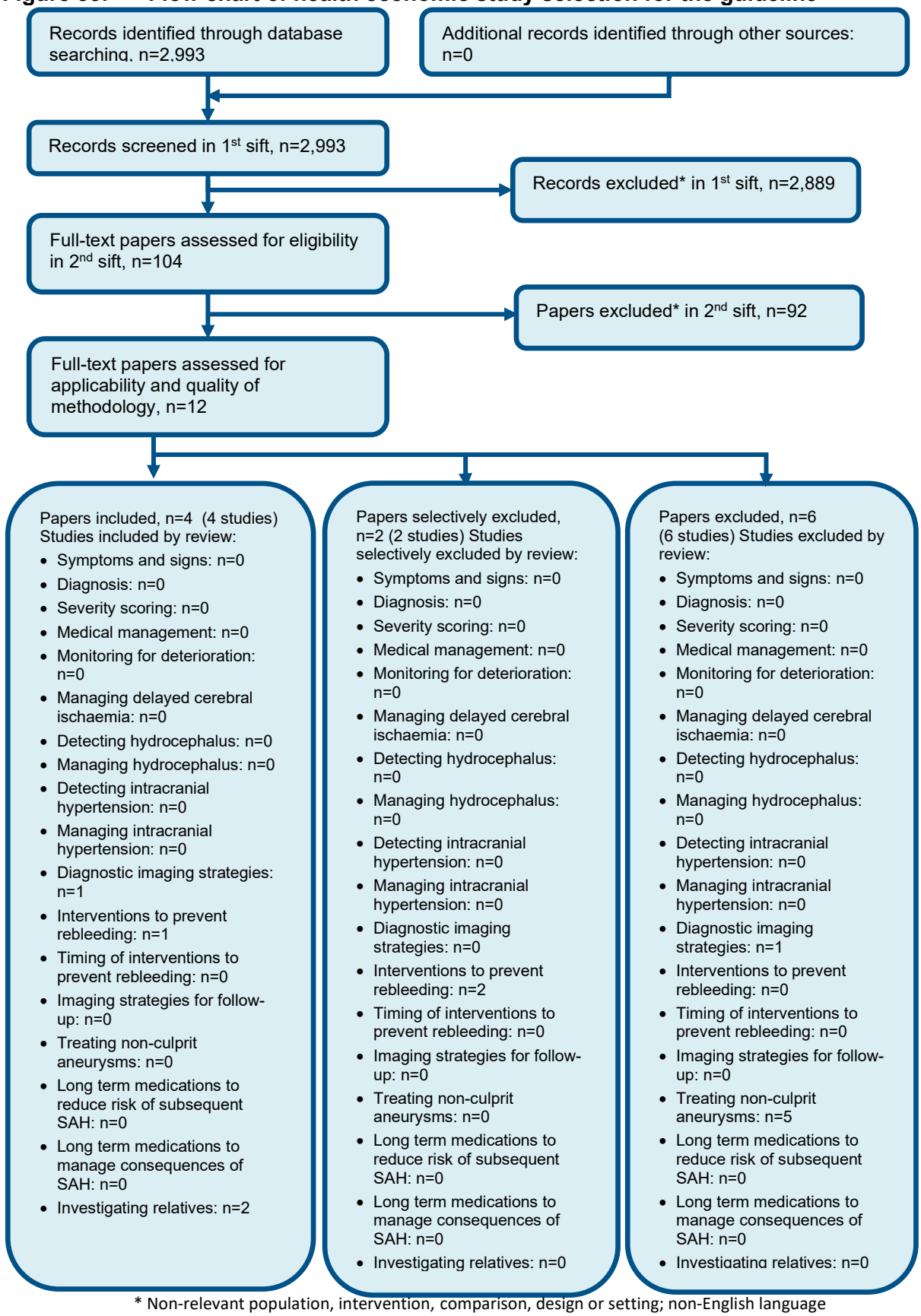
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre intervention: Steroid management	Standard care	Relative (95% CI)	Absolute		
Complication DCI (follow-up mean 28 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/46 (21.7%)	14/45 (31.1%)	RR 0.7 (0.35 to 1.4)	93 fewer per 1000 (from 202 fewer to 124 more)	⊕⊕OO LOW	CRITICAL
Complication: symptomatic vasospasm (follow-up 10-14 days)												

3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	6/64 (9.4%)	13/65 (20%)	RR 0.49 (0.21 to 1.16)	102 fewer per 1000 (from 158 fewer to 32 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Appendix H: Health economic evidence selection

Figure 83: Flow chart of health economic study selection for the guideline



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

Appendix I: Health economic evidence tables

None.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 33: Studies excluded from the clinical review

Study	Exclusion reason
Adami 2018[1]	Inappropriate study design – RCT evidence available
Adams 1981[2]	Inappropriate study design – no adjustment/matching for confounders
Ahmed 2012[3]	Inappropriate comparison – intracranial aneurysm (not SAH)
Alrahbi 2018[5]	Inappropriate comparison – comparison of BP target
Ameen 1981[6]	Inappropriate study design – RCT evidence available
Anderson 2008[7]	Inappropriate population; comparison – ICH
Anker-Moller 2017[9]	Systematic review: references screened
Anonymous 1989[10]	Inappropriate study design – narrative review
Antihypertensive Treatment of Acute Cerebral Haemorrhage 2010[11]	Inappropriate intervention – comparison of BP target
Auer 1985[12]	Inappropriate study design – literature review
Awad 2007[13]	Inappropriate study design – non comparative
Aysel 2000[14]	Inappropriate study design – RCT evidence available
Badjatia 2009[15]	Inappropriate study design – literature review
Baharoglu 2013[16]	Systematic review: references screened
Barth 2007[17]	Inappropriate intervention – not for BP control
Battey 2012[18]	Inappropriate study design – retrospective cohort for AED post ICH
Bentsen 2006[19]	Inappropriate outcome – mean ICP
Bentsen 2004[20]	Inappropriate study design – non comparative
Bhardwaj 2004[22]	Inappropriate study design – literature review
Biondi 2004[23]	Inappropriate study design – RCT evidence available
Branco 2017[24]	Inappropriate study design – literature review
Brandt 1986[25]	Inappropriate study design – RCT evidence available
Brown 2004[26]	Inappropriate study design – literature review
Cameron 1976[27]	Insufficient detail reported
Carandini 2018[28]	Inappropriate population; comparison – comparison of BP measures for ICH
Carley 2005[29]	Inappropriate study design – literature review
Chowdhary 1979[31]	Inappropriate study design - no adjustment/matching for confounders
Chwajol 2008[32]	Inappropriate study design – literature review
Corry 2014[33]	Inappropriate study design– literature review
Dankbaar 2010[34]	Systematic review: references screened
De Rooij 2013[35]	Systematic review: not review PICO
De Weijer 2017[36]	Inappropriate population; comparison – comparison of BP measures for ICH
Deogaonkar 2005[37]	Inappropriate study design – Abstract
Dewan 2012[39]	Inappropriate study design – review protocol
Dewan 2015[38]	Inappropriate study design – survey
Dhakal 2015[40]	Inappropriate study design

Study	Exclusion reason
Dmytriw 2019[41]	Inappropriate study design
Dorhout 2007[42]	Systematic review: references screened
Dorhout Mees 2007[43]	Inappropriate intervention – antiplatelets
Ekelund 1999[44]	Inappropriate study design
Feigin 1998[45]	Systematic review: references screened
Fischer 2015[46]	Inappropriate study design – risk association
Fodstad 1981[52]	Inappropriate outcome – coagulation in blood
Gaab 1984[53]	Inappropriate review population – head injury, stroke, vasospasm
Gaab 1985[54]	Inappropriate review population – head injury, stroke, DCI
Gaberel 2012[55]	Systematic review: references screened
Galvin 2015[56]	Systematic review: not review PICO
Gathier 2014[57]	Inappropriate intervention – induced hypertension
Gemma 1997[59]	Inappropriate review population – any elective neurosurgical procedures
Germans 2013[60]	Inappropriate study design – review protocol
Gibbs 1971[61]	Inappropriate study design – RCT evidence available
Gilmore 2010[62]	Inappropriate study design – literature review
Gilsbach 1990[64]	Inappropriate comparison – dose comparison
Gilsbach 1988[63]	Systematic review: references screened
Golan 2013[66]	Inappropriate study design – letter
Golfinos 1994[67]	Inappropriate study design – letter
Gong 2015[68]	Inappropriate population – not SAH
Gould 2014[69]	Inappropriate comparison – comparison of BP targets
Grande 2009[70]	Inappropriate study design – literature review
Griessenauer 2017[71]	Inappropriate population
Guggiari 1987[72]	Abstract only
Guo 2018[73]	Inappropriate comparison – propofol versus sevoflurane
Hafeez 2019[74]	Systematic review - references checked
Hajjar 2013[75]	Inappropriate population – not SAH
Haley 1990[76]	Inappropriate study design – literature review
Haley 1991[78]	Abstract only
Haley 1994[79]	Inappropriate comparison – dose comparison
Hamann 1993[80]	Inappropriate study design – RCT evidence available
Hanggi 2018[81]	Inappropriate study design – review protocol
Hauer 2011[83]	Inappropriate population – cerebrovascular disease
Hayashi 1988[84]	Inappropriate population – haemorrhagic cerebrovascular disease or systemic hypertension
Held 1993[85]	Inappropriate population – acute MI
Hertle 2016[86]	Inappropriate study design
Hindman 2010[88]	Inappropriate study design – RCT evidence available
Hinz 2007[89]	Inappropriate population – traumatic brain injury
Hoedemaekers 2007[90]	Inappropriate population – majority not SAH
Hongo 1993[91]	Inappropriate study design – literature review
Hop 2000[92]	Inappropriate intervention – Aspirin for prevention of DCI
Hu 2019[93]	Inappropriate Systematic review - references checked
Huang 2018[94]	Systematic review: not review PICO

Study	Exclusion reason
Huang 2013[95]	Systematic review: references screened
Hui 2012[96]	Inappropriate study design – no adjustment/matching for confounders
Hui 2012[97]	Inappropriate study design – no adjustment/matching for confounders
Human 2018[98]	Inappropriate comparison
Hwang 2007[99]	Inappropriate comparison
Iwata 2006[101]	Inappropriate population – craniotomy
Jordan 1985[103]	Inappropriate study design – letter
Kakarieka 1994[105]	Inappropriate study design – literature review
Kaste 1978[106]	Inappropriate study design – review summary
Kasuya 2005[108]	Inappropriate study design – RCT evidence available
Ker 2017[110]	Inappropriate study design – review protocol / plan
Khan 2013[111]	Inappropriate comparison – RCT evidence available
Kim 2009[112]	Inappropriate study design – RCT evidence available
Kinkel 2005[113]	Systematic review: references screened
Knuckey 1982[114]	Inappropriate study design – RCT evidence available; no adjustment for confounders
Kollmar 2012[115]	Inappropriate population – ICH
Kuijlen 1996[116]	Systematic review: not review PICO
Kunze 2016[117]	Inappropriate study design – risk association
Langelaar 1996[118]	Inappropriate comparison – Nimodipine + Ketamine
Lanzino 2011[119]	Inappropriate study design – literature review
Lee 1987[120]	Inappropriate study design – RCT evidence available
Lehmann 2013[121]	Inappropriate outcome – acid base disturbance; serum electrolytes
Lennihan 2000[122]	Inappropriate intervention – fluid management protocol
Li 2018[123]	Inappropriate comparison – Nimodipine +/- Edaravone
Lindsay 1981[125]	Inappropriate study design – letter
Lindsay 1989[124]	Inappropriate study design study summary
Lionel 2019[126]	No relevant outcome
Liu 2011[127]	Systematic review: references screened
Ljunggren 1987[128]	Inappropriate study design – literature review
Loan 2018[129]	Systematic review: references screened
Luo 2017[130]	Systematic review: references screened
Luo 2017[131]	Inappropriate population – elective craniotomy
Mahmoud 2017[132]	Systematic review: references screened
Malekpour 2017[133]	Inappropriate study design – RCT evidence available; no adjustment for confounders
Marigold 2013[134]	Systematic review: references screened
Massiou 1992[135]	Inappropriate comparison – dose comparison
Mee 1986[138]	Inappropriate study design – review summary
Mees 2008[139]	Systematic review: references screened
Mendelow 1982[140]	Inappropriate intervention – aspirin
Menzies 1991[141]	Inappropriate outcome – no relevant outcomes
Messe 2009[142]	Inappropriate population – not SAH
Morotti 2017[147]	Inappropriate population; comparison – comparison of BP measures for ICH
Mortazavi 2012[148]	Systematic review: not review PICO

Study	Exclusion reason
Moullaali 2019[149]	Inappropriate study design; not review population
Muizelaar 1984[150]	Inappropriate study design – abstract only
Murray 1996[151]	Inappropriate population – traumatic SAH
Naidech 2009[152]	Inappropriate outcome – no relevant outcomes
Nassiri 2016[153]	Inappropriate study design – RCT evidence available; propensity score matching
Nibbelink 1972[159]	Inappropriate comparison
Nibbelink 1975[160]	Inappropriate comparison
Oddo 2018[161]	Inappropriate study design – consensus recommendations
Oropello 1996[164]	Inappropriate study design – literature review
Pandita-Gunawardena 1999[166]	Inappropriate population – not SAH
Pasarikovski 2017[167]	Inappropriate SR: references screened
Perel 2012[168]	Inappropriate population – traumatic brain injury
Pittera 1990[172]	Inappropriate study design – RCT evidence available
Post 2019[173]	Inappropriate study design
Profeta 1975[175]	Inappropriate study design – narrative review
Qureshi 2011[176]	Inappropriate study design – review protocol
Qureshi 2016[177]	Inappropriate population; comparison – comparison of BP measures for ICH
Qureshi 2000[178]	Inappropriate study design – literature review
Rabelo 2016[179]	Inappropriate study design – literature review
Ramesh 2020[180]	Inappropriate Systematic review - references checked
Ramirez-Lassepas 1981[181]	Inappropriate SR: references screened
Ramos 2018[182]	Inappropriate study design – literature review
Ratilal 2013[184]	Inappropriate population – chronic subdural haematoma
Raper 2011[183]	Inappropriate population
Rincon 2014[185]	Inappropriate study design – review protocol
Roberts 2013[186]	Inappropriate population – traumatic brain injury
Robinson 1990[187]	Systematic review: references screened
Roos 2003[189]	Systematic review: references screened
Roos 1998[190]	Inappropriate study design – Abstract
Rosenorn 1988[191]	Inappropriate study design – no adjustment/matching for confounders
Rosenwasser 1983[192]	Inappropriate population – ruptured cerebral aneurysms
Saber 2019[193]	Inappropriate intervention – antiplatelet
Sato 2015[194]	Inappropriate study design – literature review
Schneider 2011[195]	Inappropriate study design – RCT evidence available
Seiler 1987[196]	Inappropriate study design – RCT evidence available
Senel 2005[197]	Inappropriate comparison – propofol versus midazolam
Sengupta 1976[198]	Inappropriate study design – no adjustment/matching for confounders
Shen 2017[199]	Inappropriate intervention – statin
Shibuya 1994[200]	Inappropriate study design – RCT evidence available
Shucart 1980[201]	Inappropriate study design – no adjustment/matching for confounders
Sprigg 2019[203]	Inappropriate population
Sprigg 2018[202]	Inappropriate population – stroke
Stroobandt 1998[204]	Inappropriate study design – non comparative

Study	Exclusion reason
Stullken 1984[205]	Inappropriate study design – Abstract
Stullken Jr 1985[206]	Inappropriate outcome – no relevant outcomes
Suarez 1999[207]	Inappropriate study design – before and after
Szaflarski 2010[208]	Inappropriate population – traumatic brain injury
Taquoi 1988[209]	Data already included
Toyota 1999[212]	Inappropriate study design – RCT evidence included
Tripathy 2015[213]	Inappropriate study design – literature review
Tsementzis 1992[215]	Inappropriate outcome
Tsementzis 1990[214]	Inappropriate outcome – overall complications
Tseng 2007[216]	Inappropriate study design
Tseng 2008[217]	Inappropriate study design – risk association
Ullman 1996[218]	Inappropriate study design – literature review
van den Bergh 2006[219]	Inappropriate intervention – aspirin
van der Jagt 2016[220]	Inappropriate study design – literature review
van der Werf 1985[221]	Inappropriate study design – RCT evidence available
van Rossum 1978[222]	Inappropriate study design – letter
Veldeman 2016[224]	Systematic Review: not review PICO
Vermeulen 1983[226]	Inappropriate study design – letter
Von der Brelie 2017[227]	Inappropriate study design; inappropriate comparison
Wartenberg 2017[228]	Inappropriate study design – risk association
Weir 1989[229]	Inappropriate study design – literature review
Welty 1987[230]	Systematic Review: references screened
Wijdicks 1988[231]	Inappropriate study design
Witherspoon 2017[232]	Inappropriate study design – literature review
Wong 2008[233]	Inappropriate study design
Woo 1997[234]	Inappropriate study design – literature review
Worster 2009[235]	Inappropriate comparison – comparison of BP target
Xu 2014[236]	Inappropriate population – cerebral haemorrhage
Ye 2017[237]	Inappropriate study design – review protocol
Yoon 2015[238]	Inappropriate Study design – no adjustment/matching for confounders
Zafar 2012[239]	Inappropriate population – brain injury
Zhang 2019[240]	Inappropriate population
Zheng 2014[241]	Inappropriate study design – non comparative
Zheng 2015[242]	Inappropriate study design – non comparative
Zheng 2016[243]	Inappropriate study design - risk association
Zussman 2017[244]	Inappropriate study design – review summary

J.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 34: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix K: Research recommendations

K.1 Nimodipine

Research question: What is the clinical and cost effectiveness of nimodipine in the management of aneurysmal subarachnoid haemorrhage?

Why this is important:

Nimodipine is a dihydropyridine class of calcium antagonist used widely in the acute management of aneurysmal subarachnoid haemorrhage to prevent delayed cerebral ischaemia and mortality and morbidity. The mechanism of action is unclear, evidence of utility is of poor quality and derived from studies conducted several decades ago, and few studies have examined the use of nimodipine in current clinical practice. Nimodipine is generally well-tolerated but can cause adverse effects such as hypotension. It is important to revisit the ubiquitous use of nimodipine in the management of aneurysmal subarachnoid haemorrhage to ensure that it is clinically and cost-effective.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People aged 16 or over with confirmed aneurysmal subarachnoid haemorrhage. Intervention(s): Administration of enteral nimodipine during the acute management of aSAH. Comparison: Placebo/control Outcome(s): • Mortality • Health-related quality of life • Disability or functional outcome.
Importance to patients or the population	Enteral nimodipine is used routinely in the contemporary management of patients with aSAH but evidence to support this practice is limited. Re-assessment of the use of nimodipine is important to ensure that this treatment is clinically and cost effective.
Relevance to NICE guidance	Evidence in this area will directly influence future versions of this guideline.
Relevance to the NHS	If enteral nimodipine is not shown to be cost effective, its use will rapidly decline with the potential for improved outcomes and cost saving across the NHS. If nimodipine is shown to be cost-effective current practice will continue.
National priorities	The NHS long term plan identifies stroke care as a national priority.
Current evidence base	Evidence that enteral nimodipine is effective in the acute management of aSAH is of poor quality and based on studies conducted before the introduction of neuroradiological intervention for treatment of ruptured intracranial aneurysms. The timing of neurosurgical procedures to secure the aneurysm and acute medical management of patients with aSAH has also evolved. These limitations warrant reassessment of the use of nimodipine in patients with aSAH.
Equality	No equality issues.
Study design	Double-blind randomised controlled trial
Timeframe	1 year – nimodipine is commonly used and should be able to get early data.
Feasibility	The proposed research can be carried out in a realistic timescale and at an acceptable cost.
Other comments	None

Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.