National Institute for Health and Care Excellence

Final

Subarachnoid haemorrhage caused by a ruptured aneurysm: diagnosis and management

[M] Evidence review for timing of interventions to prevent rebleeding

NICE guideline NG228

Methods, evidence and recommendations

November 2022

Final

National Institute for Health and Care Excellence

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1 Timing of interventions to prevent rebleeding

Evidence review underpinning recommendation 1.2.8 in the NICE guideline.

1.1 Review question: What is the optimal timing of interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?

1.2 Introduction

Treatment of a ruptured cerebral artery aneurysm in a person with subarachnoid haemorrhage aims to reduce the risk of rebleeding and prevent death and disability.

The risk of rebleeding is highest in the first few days after the initial bleed.

Current practice therefore favours early treatment of the ruptured aneurysm to avoid the potentially catastrophic consequences of rebleeding. The National Clinical Guideline for Stroke prepared by the Intercollegiate Stroke Working Party recommended that treatment to secure the culprit aneurysm should be undertaken within 48 hours of ictus for good grade patients (Hunt and Hess or World Federation of Neurological Sciences grades 1-3), or within a maximum of 48 hours of diagnosis if presentation is delayed.

Nevertheless, timing of treatment varies nationally, particularly in people with subarachnoid haemorrhage that results in unconsciousness and/or requires ventilation for more than 48 hours or people with delayed presentation. Some neurosurgeons may delay surgery in these very unwell patients until operating conditions are more favourable.

This review investigates the most clinically and cost effective timing of interventions to prevent rebleeding.

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	• Intervention ≤24 hours of ictus/admission/diagnosis • Intervention ≤48 hours of ictus/admission/diagnosis Interventions may include neurosurgical clipping or endovascular intervention.
Comparisons	Intervention at a greater time from ictus/admission/diagnosis: • >24 hours of diagnosis/admission • >48 hours of diagnosis/admission
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) • Rebleed from culprit aneurysm IMPORTANT • Subsequent subarachnoid haemorrhage • Return to usual daily activity (e.g. work) • Length of post-intervention hospital stay • Complications (any) Short term outcomes <30 days will be grouped. Outcomes will be reported monthly for the first year and grouped at yearly time-points thereafter.
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered, starting with prospective cohort studies.

1.4 Clinical evidence

1.4.1 Included studies

Two randomised controlled trials and 12 observational studies were included in the review,[13, 22, 26, 43, 44, 48, 56, 59-61, 64, 76, 82, 88] these are summarised in Table 2 below. Evidence from observational studies was considered for inclusion where no evidence for the critical outcomes of the evidence review was available from RCTs, or where the RCT evidence included for review included an indirect population and the evidence from a non-randomised study provided outcome data from a direct population. Cohort data would be prioritised for inclusion if it performed outcome adjustment for the key confounder of patient age, or if intervention and comparison groups were matched for this key confounder. As it was anticipated that there may be little evidence from randomised trials, given the potential ethical challenges of randomising participants to delayed intervention, cohort studies not accounting for key confounders would be considered for inclusion, but noted for an increased risk of bias. Evidence from these studies is summarised in the clinical evidence summary below (Table 6).

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

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review - Early (≤72 hours) Intervention versus Delayed Intervention (>72hours)

Study	Intervention and comparison	Population	Outcomes	Comments
Ohman 1989[56]	**Early Intervention:** Surgical intervention between 0 - 3 days after SAH (day of SAH = day 0). (n=71) **Intermediate Intervention:** Surgical intervention between 4 to 7 days after SAH (day of SAH = day 0). Duration long term. (n=70) **Late Intervention:** Surgical intervention after 8 days to an indefinite time after the SAH. (n=70) Follow-up: 3 months	Patients aged 16 - 65 with a ruptured aneurysm located in the anterior part of the circle of Willis and admitted in Hunt & Hess grades I to III within 72 hours from their last SAH Age - Mean (SD): Acute Surgery: 42.6 ± 10.4; Intermediate Surgery: 45.7 ± 12.1; Late Surgery: 43.8 ± 10.2 Finland RCT	• Mortality (mRS 6 – 3 months post SAH) • Dependent (Severe disability or Vegetative state at 3 months post SAH from Glasgow Outcome Scale)	There are three intervention groups: Acute; Intermediate; and Late surgery. The results for intermediate and late surgery have been combined for the purpose of this review.

Table 3: Summary of studies included in the evidence review - Early Intervention (<24 hours) versus Intervention post-stabilization

Study	Intervention and comparison	Population	Outcomes	Comments
Mitra 2015[48]	**Early Intervention:** Patient cared for by interventional neuroradiology team. Appropriate assent for the coiling procedure was then obtained. If amenable to endovascular treatment, the	Patients older than 18 years admitted to the neurosciences intensive therapy unit with WFNS grade IV or V SAH who were hemodynamically stable and	• Mortality (mRS 6 – at 6 months) • Modified Rankin Score (mRS 1 – at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	aneurysm was treated within 24 hours of randomization. (n=5) **Delayed Intervention:** patient cared for by intensive therapy unit and neurosurgical team who continued managing the patient as per local established protocol. If and when the patient's neurologic status improved to WFNS grade III or better, the aneurysm was treated appropriately. There was no specific time-delay criterion for aneurysm treatment in this arm. (n=3) Follow-up: 6 months	whose next of kin provided assent for inclusion Age - Mean (range): 53 (26-64). United Kingdom RCT		

Table 4: Summary of studies included in the evidence review - Early Intervention (<24h) versus Delayed Intervention (>24h)

Study	Intervention and comparison	Population	Outcomes	Comments
Gu 2012[22]	**Early Intervention:** Patients coiled within 24 hours of SAH. (n=56) **Delayed Intervention:** Patients coiled after 24 hours of SAH. (n=40) (Types of coils - GDC; Matrix; EDC. Types of stents - Neuroform; Leo; Enterprise)	Patients aged ≥ 70 with aSAH who received treatment with coil embolization China Age - Mean (Range): <24h: 74.5 (70-85); >24h: 75.7 (70-89)	• mRS 0-2 • mRS 3-6	Confounding factors: groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 6 months	Cohort Study		
Ibrahim Ali 2016[26]	**Early Intervention:** Aneurysmal SAH referred for coiling and treated within 24 h from presentation. (n=10) **Delayed Intervention:** Aneurysmal SAH referred for coiling and treated after 24 h from presentation. (n=20) Follow-up: 6 months	Patients with aneurysmal SAH Age - Mean (SD): <24h: 50.50 ± 15.81; >24h: 50.65 ± 12.40 Egypt Cohort Study	• Mortality • mRS 0-2 • mRS 3-5 • Rebleeding	Confounding factors: groups matched for age
Luo 2015[43]	**Early Intervention:** Patients treated <24h after SAH. (n=31) **Delayed Intervention:** Patients treated >24h after SAH. (n=14) Follow-up: 6 months	aSAH patients who received coil embolization and Hunter or Hess grade 4/5 at admission Age - Mean (Range): <24h: 62.6 (39-82); >24h: 55.6 (39-84) China Cohort Study	• mRS 0-2 • mRS 3-6	Confounding factors: statistically significant difference between study group ages. No outcome adjusting for confounding factors
Mahaney 2011[44]	**Early Intervention:** Treatment with neurosurgical clipping within 24 hours. (n=368) **Delayed Intervention:**	Non pregnant adult patients must have suffered an SAH from a radiographically demonstrated intracranial aneurysm no more than 14 days prior to surgery and must have had a WFNS score of I,II, or III at the time of enrolment and on arrival	• Complications (DIND, Hydrocephalus, other)	There are six intervention groups within the study: 0-1, 2, 3, 4, 5-6, and 7-14 days. For the purposes of this review, 2, 3, 4, 5-6 and 7-14 days are combined to represent >24 hours.

Study	Intervention and comparison	Population	Outcomes	Comments
	Treatment for SAH >24 hours with neurosurgical clipping. (n=631) Follow-up: post-operative	to the operating room. Patients were also required to have a pre-SAH Rankin score of 0 or 1. Age - Mean (SD): 52 ± 13 USA Cohort Study		For analysis in this review, the time points were also combined into <48 hours and >48 hours. Confounding factors: groups matched for age
OudShoorn 2014[59]	**Early Intervention:** Patients treated with clipping or coiling within 24 of ictus. (n=134) **Delayed Intervention:** Patients treated after 24 hours of SAH ictus. (n=180) Follow-up: 3 months	All patients with aSAH were included within the study Age - Mean (Range): <24h: 55 (47-62); >24h: 56 (47-66) Netherlands Cohort Study	• Mortality • Rebleeding • Complication (DCI) • Poor functional outcome (pooled)	This study presents results from two cohorts: Utrecht and ISAT cohort. For this review, the outcomes from the Utrecht cohort are used. The outcome of poor functional outcome is used from the pooled cohort results (including Utrecht and ISAT) as this outcome has not been previously reported. Confounding factors: groups matched for age
Park 2015[60]	**Early Intervention:** Patient treatment commenced within 24 hours. (n=442) **Delayed Intervention:** Patient treatment commenced after 24 hours. (n=423) Follow-up: during hospital stay	In this study, patients with an aneurysmal SAH were included. Age - Mean (SD): <24h: 55.7 ± 12.9 >24h: 55.5 ± 11.6 Korea	• Rebleeding	Confounding factors: groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
		Cohort study		
Phillips 2011[61]	**Early Intervention:** Treated with coiling or clipping within 24 hours of the aneurysmal SAH ictus. (n=230) **Delayed Intervention:** Coiling or clipping performed >24 hours after SAH. (n=229) Follow-up: 6 months	Only cases of proven aneurysmal SAH were included with coiling or clipping of acutely ruptured aneurysms Age - Mean (SD): <24h: 52 ± 13; >24h: 54 ± 15.6 Australia Cohort Study	• Mortality • mRS 0-2 • mRS 3-5	Confounding factors: groups matched for age
Qian 2014[64]	**Early Intervention:** Endovascular treatment within 24 hours of SAH. (n=269) **Delayed Intervention:** Endovascular treatment after 24 hours of SAH. (n=395) Follow-up: 9 months	Only cases of proven aSAH with endovascular treatment were included. Age – Mean: <24 hours: 56.2 years >24 hours: 55.5 years China Cohort Study	• Mortality • mRS 0-2 • mRS 3-5	There are four intervention groups: ultra early, early, intermediate and delayed. For the purposes of this review, the results for the groups early, intermediate and delayed are combined. Confounding factors: groups matched for age
Solomon 1991[76]	**Early Intervention:** Neurosurgical clipping within 24 hours of admission. (n=49) **Delayed Intervention:**	Patients with confirmed acute aSAH were included within this study Age: not specified	• Complication (DCI)	Confounding factors: age not reported. No outcome adjusting for confounding factors

Study	Intervention and comparison	Population	Outcomes	Comments
	Neurosurgical clipping beyond 24 hours of admission. (n=96) Follow-up: post-operative	USA Cohort Study		
Tykocki 2017[82]	**Early Intervention:** Endovascular coiling or Neurosurgical clipping within 24 hours of SAH. (n=38) **Delayed Intervention:** Endovascular coiling or Neurosurgical clipping after 24 hours of SAH. (n=41) Follow-up: unclear	Patients who had been classified with grade IV or V on WFNS scale at admission. Age - Mean (SD): <24h: 49.5 ± 6.1; >24h: 65.8 ± 7.4 Poland Cohort Study	• Mortality	Confounding factors: statistically significant difference between study group ages. No outcome adjusting for confounding factors
Wong 2012[87]	**Early Intervention:** Timing of intervention within 24 hours. (n=148) **Delayed Intervention:** Timing of aneurysm treatment after 24 hours. (n=128) Follow-up: 6 months	Patients with spontaneous SAH within 48 hours of ictus and angiographic evidence of intracranial aneurysm as the likely source of haemorrhage Age - Mean (SD): <24 hours: 55 years ± 12 >24 hours: 58 years ± 12 Hong Kong New Zealand Cohort Study	• Mortality • mRS 0-2 • mRS 3-5	Confounding factors: statistically significant difference between study group ages. No outcome adjusting for confounding factors

Table 5: Summary of studies included in the evidence review - Early Intervention (<48h) versus Delayed Intervention (>48h)

Study	Intervention and comparison	Population	Outcomes	Comments
Dorhout Mees 2012[13]	**Early Intervention:** Patients treated within 48 hours of admission. (n=891) **Delayed Intervention:** Patients treated after 48 hours of admission. (n=1215) Follow-up: 1 year	Patients were eligible for the trial if (1) they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, with the preceding 28 days; (2) they had an intercranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; (3). they were in the clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; (4). they had an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee.	• Complication (DCI) • Rebleed	There are four intervention groups: 0-2, 3-4, 5-10 & ≥ 11 days. The results for 3-4, 5-10 & ≥ 11 have been combined for the purpose of this review. Confounding factors: groups matched for age

Study	Intervention and comparison	Population	Outcomes	Comments
		Netherlands & United Kingdom Age - Mean (SD): <48h: 51 ± 11; >48h: 52.24 ± 12.09 Cohort Study		
Mahaney 2011[44]	**Early Intervention:** Treatment for SAH >24 hours with neurosurgical clipping. (n=552) **Delayed Intervention:** Neurosurgical clipping ≥ 48 hours. (n=447) Follow-up: post-operative	Non pregnant adult patients must have suffered an SAH from a radiographically demonstrated intracranial aneurysm no more than 14 days prior to surgery and must have had a WFNS score of I,II, or III at the time of enrolment and on arrival to the operating room. Patients were also required to have a pre-SAH Rankin score of 0 or 1. Age - Mean (SD): 52 ± 13 USA Cohort Study	• Complications (DIND, Hydrocephalus, other)	There are six intervention groups within the study: 0-1, 2, 3, 4, 5-6, and 7-14 days. For the purposes of this review, 2, 3, 4, 5-6 and 7-14 days are combined to represent >24 hours. For analysis in this review, the time points were also combined into <48 hours and >48 hours. Confounding factors: groups matched for age

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 6: Clinical evidence summary: Early Intervention (≤72 hours) compared to Delayed Intervention (>72hours) for interventions to prevent rebleeding in aSAH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Delayed Intervention (merged)	Risk difference with Acute Intervention (95% CI)
Mortality	202 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.57 (0.19 to 1.68)	Moderate	
				99 per 1000	43 fewer per 1000 (from 80 fewer to 67 more)
Dependent (Severe disability or Vegetative state)	202 (1 study) 3 months	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.23 (0.05 to 0.97)	Moderate	
				122 per 1000	94 fewer per 1000 (from 4 fewer to 116 fewer)

1 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: Early Intervention (<24hours) compared to post stabilization for interventions to prevent re-bleeding in aSAH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Post stabilization	Risk difference with Early Intervention (95% CI)
Mortality (mRS 6)	8 (1 study) 6 months	⊕⊕⊖⊖ LOW1 due to imprecision	RR 1.2 (0.48 to 2.99)	Moderate	
				667 per 1000	133 more per 1000 (from 347 fewer to 1000 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Post stabilization	Risk difference with Early Intervention (95% CI)
Modified Rankin Score (mRS 1) Scale 0-6; high score represents poor outcome	8 (1 study) 6 months	⨁⨁⊖⊖ LOW1 due to imprecision	RR 0.6 (0.06 to 6.44)	Moderate	
				333 per 1000	133 fewer per 1000 (from 313 fewer to 1000 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 8: Clinical evidence summary: Early Intervention (<24 hours) compared to Delayed Intervention (>24 hours) for Interventions to prevent rebleeding in aSAH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with >24 hours	Risk difference with <24 hours (95% CI)
Mortality	1620 (6 studies) 0-6 months	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.87 (0.50 to 1.51)	Moderate	
				95 per 1000	12 fewer per 1000 (from 47 fewer to 48 more)
mRS 0 - 2 - Endovascular Coil Scale 0-6; high score represents poor outcome	684 (4 studies)	⨁⊖⊖⊖ VERY LOW1,3,4 due to risk of bias, imprecision	RR 1.31 (1.18 to 1.45)	Moderate	
				537 per 1000	166 more per 1000 (from 97 more to 242 more)
mRS 0 - 2 - Mixed Intervention Scale 0-6; high score represents poor outcome	684 (2 studies)	⨁⨁⊖⊖ LOW1,3,4 due to risk of bias	RR 1.07 (0.99 to 1.16)	Moderate	
				725 per 1000	51 more per 1000 (from 7 fewer to 116 more)
mRS 3 – 5 Scale 0-6; high score represents poor outcome	1227 (4 studies) 1-9 months	⨁⨁⊖⊖ LOW1 due to risk of bias	RR 0.59 (0.46 to 0.76)	Moderate	
				297 per 1000	122 fewer per 1000 (from 71 fewer to 160 fewer)
mRS 3 – 6				Moderate	

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with >24 hours	Risk difference with <24 hours (95% CI)
Scale 0-6; high score represents poor outcome	141 (2 studies) 6 months	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 0.48 (0.3 to 0.76)	543 per 1000	282 fewer per 1000 (from 130 fewer to 380 fewer)
Poor Functional Outcome	1195 (1 study) 6 months	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 1.54 (1.26 to 1.88)	Moderate	
				251 per 1000	136 more per 1000 (from 65 more to 221 more)
Rebleed	1209 (3 studies)	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.60 (0.07 to 4.94)	Moderate	
				64 per 1000	26 fewer per 1000 (from 60 fewer to 252 more)
Complication (DCI)	1458 (3 studies)	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.69 (0.26 to 1.80)	Moderate	
				190 per 1000	59 fewer per 1000 (from 141 fewer to 152 more)
Complication (Hydrocephalus)	999 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 0.42 (0.26 to 0.68)	Moderate	
				124 per 1000	72 fewer per 1000 (from 40 fewer to 92 fewer)
Complications (Other)	999 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 0.33 (0.26 to 0.41)	Moderate	
				555 per 1000	372 fewer per 1000 (from 327 fewer to 411 fewer)

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 due to 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
4 Heterogeneity, I2=50%, p=0.04, explained by subgroup analysis by method of intervention.

Table 9: Clinical evidence summary: Early Intervention (<48 hours) compared to Delayed Intervention (>48 hours) for Interventions to prevent rebleeding in aSAH

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with >48 hours	Risk difference with <48 hours (95% CI)
Rebleed	2106 (1 study)	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.37 (0.15 to 0.91)	Moderate	
				18 per 1000	11 fewer per 1000 (from 2 fewer to 15 fewer)
Complication (DCI)	3105 (2 studies)	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 0.79 (0.69 to 0.91)	Moderate	
				242 per 1000	51 more per 1000 (from 22 fewer to 75 fewer)
Complication (Hydrocephalus)	999 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 0.48 (0.32 to 0.71)	Moderate	
				137 per 1000	71 fewer per 1000 (from 40 fewer to 93 fewer)
Complications (Other)	999 (1 study)	⊕⊕⊖⊖ LOW1 due to risk of bias	RR 0.47 (0.39 to 0.56)	Moderate	
				506 per 1000	268 fewer per 1000 (from 223 fewer to 309 fewer)

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 due to Heterogeneity, I2<50%, p=0.04, unexplained by subgroup analysis.

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 G:.

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee considered the critical outcomes for decision making to be mortality, health and social-related quality of life, degree of disability (modified Rankin scale, Glasgow outcome scale) and rebleed of the culprit aneurysm. Subsequent subarachnoid haemorrhage, return to daily activity, length of hospital stay and complications of intervention are important outcomes.

No evidence was identified for subsequent subarachnoid haemorrhage, return to daily activities or length of hospital stay.

1.6.1.2 The quality of the evidence

The quality of evidence that was suitable for GRADE analysis ranged from very low to moderate. The majority of evidence is graded at very low quality. This was mostly due to risk of bias, inconsistency and imprecision. The majority of evidence was from cohort studies with increased risk of selection bias and confounding bias. The majority of observational data included demonstrated that participants were matched for the key confounder of age but none of the outcome evidence was adjusted to account for age or any other potentially confounding factors. A small amount of data from cohort studies showed a statistically significant difference between groups for age and were considered to be poorer quality due to this increased risk of bias.

Two randomised controlled trials were available but 1 was considered outdated and the second trial had few patients. Both studies provided an indirect comparison of timing intervals to those stated in the review protocol. Non-randomised studies that met the protocol and provided a direct comparison for the chosen timing intervals were therefore included. In the observational studies patients could have been selected for either arm of the study based on their clinical presentation. For example, patients with a 'good grade' subarachnoid haemorrhage may have been chosen for earlier treatment, whereas those with 'poor grade' subarachnoid haemorrhage (typically characterised by the aneurysmal subarachnoid haemorrhage resulting in unconsciousness and/or needing ventilation for more than 48 hours) could have been delayed to later treatment. Overall, the rates of rebleeding are higher in patients with a 'poor grade' subarachnoid haemorrhage. Patients with 'good grade' subarachnoid haemorrhages are less likely to have complications and will have better outcomes post-intervention. The committee recognised this selection and confounding bias and the subsequent downgrading in the overall quality of evidence.

The committee agreed the evidence was not of sufficient quality to draw any conclusion about the optimum timing of intervention but decided to made a consensus recommendation that treatment should be carried out as soon as possible. The committee agreed this was in line with current practice.

The committee discussed whether a research recommendation should be made but concluded the established practice of carrying out treatment as soon as the patient is stable is widely accepted because not doing so could result in serious adverse outcomes for the patient. Therefore the committee did not consider this a priority area for future research.

1.6.1.3 Benefits and harms

The aim of treatment is to prevent re-bleeding and associated morbidity and mortality. As re-bleed can occur within 24 hours, earlier treatment is generally considered preferable.

Mortality and degree of disability was reported in the two randomised controlled trials. One study comparing early intervention (≤72 hours) to delayed Intervention (>72 hours) showed a clinically important reduction in mortality and rate of severe disability or vegetative state. A second trial comparing early Intervention (<24hours) to intervention post stabilization found clinically important increase in risk of mortality and rate of disability with early intervention. The committee considered that these 2 RCTs were of low quality with few events and that the evidence could not support a recommendation.

The evidence from 12 observational studies comparing interventions performed within 24 hours of ictus to over 24 hours was reviewed by the committee. The results suggested no clinically important difference in the rate of mortality between groups. Earlier intervention was associated with clinically important lower level of disability when compared to later intervention. Subgroup analysis of 6 studies reporting the rate of low-level disability compared to higher levels of disability showed a clinically important benefit with early intervention (<24 hours) for patients undergoing endovascular coiling as reported by 4 studies, however two studies that included populations who may have received clipping or coiling found no clinically important difference between early or delayed (>24 hours) intervention. As the participants in the mixed intervention groups could have received either clipping or coiling, the committee were unable to determine if the observed lack of benefit in this group for degree of disability was due to the provision of clipping over coiling. One study assessed functional outcome, which reported a clinically important increase in the number of people with a poor functional outcome at 6 months if intervention was performed within 24 hours. The committee agreed the evidence showed no difference in rebleeding, rate of DCI or hydrocephalus with timing of intervention. The committee discussed the findings of this evidence base but agreed that the low quality of the evidence did not allow for any conclusions.

The committee also discussed the evidence from two cohort studies comparing early treatment (<48 hours) compared to delayed treatment (>48 hours) for interventions to prevent rebleeding in aSAH. The committee agreed that the evidence showed now clinically important difference between intervention timings for rate of rebleed, rate of DCI or rate of hydrocephalus. The committee noted that the evidence did show a clinically important reduction in the rate of complications with early intervention, although agreed that the evidence overall was of insufficient quality and quantity to directly inform any recommendations.

The committee discussed that from their experience, delaying treatment for aSAH is generally associated with an increased risk of rebleeding, which is then associated with poorer outcomes. Since a delay may increase risk of re-bleed and cause significant harm, a consensus recommendation that treatment should be carried out as soon as possible. The committee agreed that the implications of the recommendation are that all patients assessed as suitable for treatment should be transferred to a neurosurgical centre as soon as possible.

1.6.2 Cost effectiveness and resource use

No published economic evaluations were identified assessing the timing of intervention for people with aneurysmal subarachnoid haemorrhage.

The committee discussed from their experience that people who experience aneurysm re-bleeds often have worse clinical outcomes with associated long term disabilities. This will have both a significant detriment on quality of life for the patient as well as a high long term cost of care. Therefore, the committee considered that people with aneurysmal subarachnoid haemorrhage should undergo intervention without delay after their clinical condition has been stabilised.

Usually a person who has had an aneurysmal subarachnoid haemorrhage will be admitted to a hospital ward for 5 to 7 days post intervention, and some patients require care in an ICU. The committee discussed that this is very costly, and therefore if intervention is required and the person is stable, the sooner the intervention is undertaken, the shorter their overall length of stay is likely to be and therefore the lower the cost of the admission overall.

The committee discussed that in current practice most people, if they are stable, will receive intervention within 48 hours. However, access to treatment may be influenced by the availability of interventional neuroradiologists, vascular neurosurgeons and hospital facilities. The committee stated that interventions to prevent rebleeding should be done in a timely manner irrespective of day or time of presentation. The committee acknowledged that this may require a change in current practice for some areas due to the need for additional staff and the increased cost of clinicians working over the weekend. On the other hand, the committee noted that endovascular services are becoming more common over the weekend due to the need to deliver thrombectomy for patients with ischaemic stroke, so some of these costs have already been mitigated. Overall, this recommendation was not considered to have a substantial resource impact for the NHS.

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Appendices

Appendix A: Review protocols

Table 10: Review protocol: Timing of interventions to prevent re-bleeding

ID	Field	Content
0.	PROSPERO registration number	CRD42019132507
1.	Review title	What is the optimal timing of interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?
2.	Review question	What is the optimal timing of interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?
3.	Objective	To determine the optimal timing of intervention to prevent rebleeding for subarachnoid haemorrhage.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • 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	• Intervention ≤24 hours of ictus/admission/diagnosis • Intervention ≤48 hours of ictus/admission/diagnosis Interventions may include neurosurgical clipping or endovascular intervention.
8.	Comparator/Reference standard/Confounding factors	Comparator: • Intervention at a greater time from ictus/admission/diagnosis: ○ >24 hours of diagnosis/admission ○ >48 hours of diagnosis/admission
9.	Types of study to be included	• Randomised controlled trials (RCTs), systematic reviews of RCTs. • If insufficient RCT evidence is available, non-randomised studies will be considered, 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) • Rebleed from culprit aneurysm
13.	Secondary outcomes (important outcomes)	• Subsequent subarachnoid haemorrhage • Return to usual daily activity (e.g. work) • Length of post-intervention hospital stay • Complications (any) 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	Subgroups (if heterogeneity):
		• Type of intervention
		• Aneurysmal SAH grade
		  ○ Good grade
		  ○ Poor grade

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		
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 11: 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.[54] **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 reviews;

- What is the optimal timing of interventions to prevent rebleeding (such as clipping and coiling) in adults (16 and older) with a confirmed subarachnoid haemorrhage caused by a ruptured aneurysm?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual[54]

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 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 June 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 26 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.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	limit 27 to English language
29.	Embolization, Therapeutic/
30.	(coil* or hydrocoil* or Guglielmi* or GDC*).ti,ab.
31.	endovascular procedures/
32.	(((neuroendovascular or endovascular or intrasaccular or intra-saccular) adj3 (treatment* or intervention* or procedure* or therap* or device* or surgery)) or EVT).ti,ab.
33.	blood vessel prosthesis implantation/
34.	vascular surgical procedures/
35.	blood vessel prosthesis/
36.	emboli?at*.ti,ab.

37.	(clip* or microsurg*).ti,ab.
38.	Neurosurgery/
39.	neurosurgical procedures/
40.	(web or woven endobridge* or bridg*).ti,ab.
41.	((flow adj (diver* or disrupt*)) or FRED or pipeline).ti,ab.
42.	or/29-41
43.	28 and 42
44.	Epidemiologic studies/
45.	Observational study/
46.	exp Cohort studies/
47.	(cohort adj (study or studies or analys* or data)).ti,ab.
48.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
49.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
50.	Controlled Before-After Studies/
51.	Historically Controlled Study/
52.	Interrupted Time Series Analysis/
53.	(before adj2 after adj2 (study or studies or data)).ti,ab.
54.	exp case control study/
55.	case control*.ti,ab.
56.	Cross-sectional studies/
57.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	or/44-57
59.	Meta-Analysis/
60.	exp Meta-Analysis as Topic/
61.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
62.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
63.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
64.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
65.	(search* adj4 literature).ab.
66.	(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.
67.	cochrane.jw.
68.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
69.	or/59-68
70.	randomized controlled trial.pt.
71.	controlled clinical trial.pt.
72.	randomi#ed.ti,ab.
73.	placebo.ab.
74.	randomly.ti,ab.
75.	Clinical Trials as topic.sh.
76.	trial.ti.
77.	or/70-76
78.	43 and (58 or 69 or 77)

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.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
25.	23 not 24
26.	limit 25 to English language
27.	exp artificial embolization/
28.	(coil* or hydrocoil* or Guglielmi* or GDC*).ti,ab.
29.	exp endovascular surgery/
30.	(((neuroendovascular or endovascular or intrasaccular or intra-saccular) adj3 (treatment* or intervention* or procedure* or therap* or device* or surgery)) or EVT).ti,ab.
31.	blood vessel transplantation/
32.	vascular surgery/
33.	exp aneurysm surgery/
34.	blood vessel prosthesis/
35.	emboli?at*.ti,ab.
36.	(clip* or microsurg*).ti,ab.
37.	neurosurgery/
38.	(web or woven endobridge* or bridg*).ti,ab.
39.	((flow adj (diver* or disrupt*)) or FRED or pipeline).ti,ab.
40.	or/27-39
41.	26 and 40

42.	Clinical study/
43.	Observational study/
44.	family study/
45.	longitudinal study/
46.	retrospective study/
47.	prospective study/
48.	cohort analysis/
49.	follow-up/
50.	cohort*.ti,ab.
51.	49 and 50
52.	(cohort adj (study or studies or analys* or data)).ti,ab.
53.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
54.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
55.	(before adj2 after adj2 (study or studies or data)).ti,ab.
56.	exp case control study/
57.	case control*.ti,ab.
58.	cross-sectional study/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/42-48,51-59
61.	random*.ti,ab.
62.	factorial*.ti,ab.
63.	(crossover* or cross over*).ti,ab.
64.	((doubl* or singl*) adj blind*).ti,ab.
65.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
66.	crossover procedure/
67.	single blind procedure/
68.	randomized controlled trial/
69.	double blind procedure/
70.	or/61-69
71.	systematic review/
72.	meta-analysis/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(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.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/71-80
82.	41 and (60 or 70 or 81)

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: [Embolization, Therapeutic] explode all trees
#8.	(coil* or hydrocoil* or Guglielmi* or GDC*):ti,ab
#9.	MeSH descriptor: [Endovascular Procedures] explode all trees
#10.	(((neuroendovascular or endovascular or intrasaccular or intra-saccular) near/3 (treatment* or intervention* or procedure* or therap* or device* or surgery)) or EVT):ti,ab
#11.	MeSH descriptor: [Blood Vessel Prosthesis Implantation] explode all trees
#12.	MeSH descriptor: [Vascular Surgical Procedures] explode all trees
#13.	MeSH descriptor: [Blood Vessel Prosthesis] explode all trees
#14.	emboli?at*:ti,ab
#15.	(clip* or microsurg*):ti,ab
#16.	MeSH descriptor: [Neurosurgery] explode all trees
#17.	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#18.	(web or woven endobridge* or bridg*):ti,ab
#19.	((flow next (diver* or disrupt*)) or FRED or pipeline):ti,ab
#20.	(or #7-#19)
#21.	#6 and #20

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 13: 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

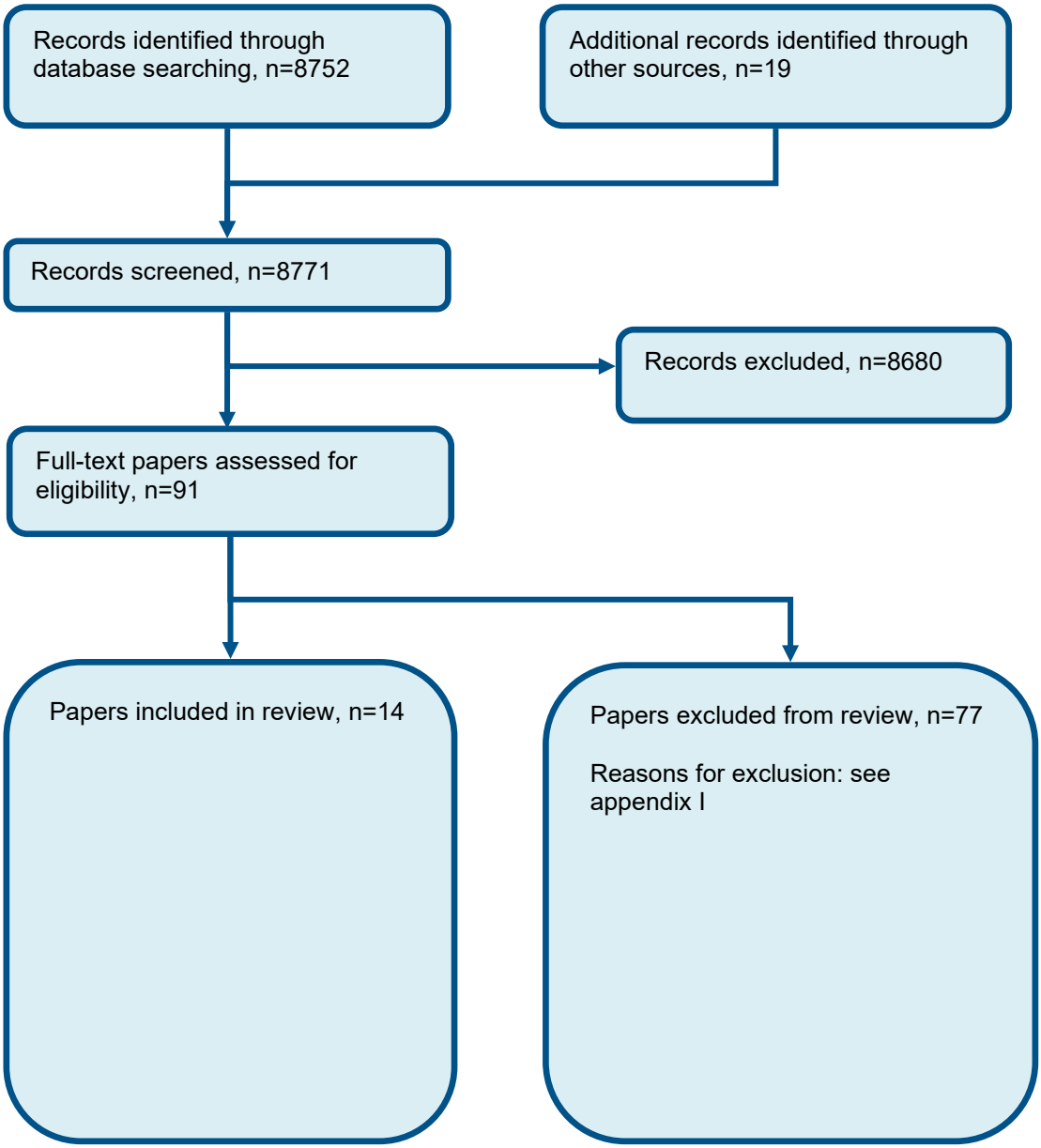
39.	24 and 38

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 timing of interventions to prevent rebleeding



Appendix D: Clinical evidence tables

Study	**Mitra 2015[48]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=8)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients older than 18 years admitted to the neurosciences intensive therapy unit with WFNS grade IV or V SAH who were hemodynamically stable and whose next of kin provided assent for inclusion
Exclusion criteria	Exclusion criteria were the following: 1) age older than 75 years, 2) signs of brain stem death not promptly reversed by anticerebral oedema treatment, 3) pure intraventricular haemorrhage, 4) large intracerebral hematoma requiring immediate clot evacuation, 5) lack of clinical equipoise (i.e., the treating clinician believed that there was a much greater benefit to be gained for that patient by one or the other of the treatment arms), and 6) pregnancy
Recruitment/selection of patients	Patients selected from those admitted with poor-grade subarachnoid haemorrhage on admission
Age, gender and ethnicity	Age - Mean (range): 53 (26-64). Gender (M:F): 4/4. Ethnicity:
Further population details	1. aSAH grade: Poor grade (Grade IV: 3; Grade V: 5). 2. Type of intervention: Endovascular intervention
Indirectness of population	No indirectness
Interventions	(n=5) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. If the patient was randomized to the early treatment arm, the result of randomization was communicated to the interventional neuroradiology team. Appropriate assent for the coiling procedure was then obtained. If amenable to endovascular treatment, the aneurysm was treated within 24 hours of randomization. Duration immediate. Concurrent medication/care: NA. Indirectness: No indirectness

	(n=3) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. If the patient was randomized to the treatment after clinical improvement arm, the result was communicated to the intensive therapy unit and neurosurgical team who continued managing the patient as per local established protocol. If and when the patient's neurologic status improved to WFNS grade III or better, the aneurysm was treated appropriately. There was no specific time-delay criterion for aneurysm treatment in this arm. . Duration treatment after neurological recovery. Concurrent medication/care: NA. Indirectness: Serious indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EARLY TREATMENT versus TREATMENT AFTER CLINICAL IMPROVEMENT Protocol outcome 1: Mortality - Actual outcome: Modified Rankin Score (mRS 6 - death) at 6 months; Group 1: 4/5, Group 2: 2/3; Comments: 6 patients died in total (mRS 6) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear time point for treatment after clinical improvement; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Modified Rankin Score (mRS 1) at 6 months; Group 1: 1/5, Group 2: 1/3 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear time point for treatment after clinical improvement; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health and social quality of life; Rebleed of culprit aneurysm; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Complications; Length of post-intervention stay

Study	Ohman 1989[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=216)
Countries and setting	Conducted in Finland; Setting: Helsinki University Central Hospital, Finland.
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aged 16 - 65 with a ruptured aneurysm located in the anterior part of the circle of Willis and admitted in Hunt & Hess grades I to III within 72 hours from their last SAH
Exclusion criteria	associated intracerebral hematoma and a decreased level of consciousness or severe neurological deficit. Pregnancy; hepatic or renal insufficiency; severe cardiac decompensation; and cardiac arrhythmia.
Recruitment/selection of patients	aged 16 - 65 with a ruptured aneurysm located in the anterior part of the circle of Willis
Age, gender and ethnicity	Age - Mean (SD): Acute: 42.6 ± 10.4; IS: 45.7 ± 12.1; LS: 43.8 ± 10.2 . Gender (M:F): 105/106. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (Hunt & Hess grades I to III). 2. Type of intervention: Neurosurgical clipping (Not specified).
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: Intervention >24 hours - Intervention >24 hours from admission. Surgical intervention between 0 - 3 days after SAH (day of SAH = day 0). Duration long term. Concurrent medication/care: betamethasone, 4mg four times daily IM. No antifibrinolytic agents, hypertensive therapy, or volume expansion was used. Indirectness: No indirectness (n=70) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Surgical intervention between 4 to 7 days after SAH (day of SAH = day 0). Duration long term. Concurrent medication/care: betamethasone, 4mg four times daily IM. No antifibrinolytic agents, hypertensive therapy, or volume expansion was used. Indirectness: No indirectness (n=70) Intervention 3: Intervention >24 hours - Intervention >24 hours from admission. Surgical intervention after 8 days to an indefinite time after the SAH . Duration long term. Concurrent medication/care:

	betamethasone, 4mg four times daily IM. No antifibrinolytic agents, hypertensive therapy, or volume expansion was used. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUTE SURGERY versus INTERMEDIATE SURGERY

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 3 months post SAH; Group 1: 4/71, Group 2: 4/67
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: Dependent - Severe disability or vegetative state (Glasgow Outcome Scale) at 3 months post SAH; Group 1: 2/71, Group 2: 11/67
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; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUTE SURGERY versus LATE SURGERY

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 3 months post SAH; Group 1: 4/71, Group 2: 9/64
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: Dependent - Severe disability or vegetative state (Glasgow Outcome Scale) at 3 months post SAH; Group 1: 2/71, Group 2: 5/64
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERMEDIATE SURGERY versus LATE SURGERY

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 3 months post SAH; Group 1: 4/67, Group 2: 9/64
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 ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures)
- Actual outcome: Dependent - Severe disability or vegetative state (Glasgow Outcome Scale) at 3 months post SAH; Group 1: 11/67, Group 2: 5/64

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; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health and social quality of life; Rebleed of culprit aneurysm; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Complications; Length of post-intervention stay

Study	**Dorhout Mees 2012[13]**
Study type	Cohort study
Number of studies (number of participants)	(n=2143)
Countries and setting	Conducted in Netherlands, United Kingdom; Setting: 43 neurological centres
Line of therapy	1st line
Duration of study	Follow up (post intervention): Patients followed up from ISAT study
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for the trial if:1. they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, with the preceding 28 days; 2. they had an intercranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; 3. they were in the clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; 4. they had an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee. If a patient was not competent to give consent (because of his or her cognitive state), assent from relatives was obtained if the ethics committee regarded it as an acceptable alternative.
Exclusion criteria	Patients were not eligible if any of the following criteria were: 1. SAH occurred more than 28 days before randomization; 2 the patient was regarded as unsuitable for one or both treatments; consent was refused or 4. the patient was participating in another randomized clinical trial of a treatment for subarachnoid haemorrhage
Recruitment/selection of patients	2143 patients with ruptured intracranial aneurysms were enrolled between 1994 and 2002

Age, gender and ethnicity	Age - Mean (SD): <48h: 51 ± 11; >48h: 52.24 ± 12.09. Gender (M:F): 822/1321. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear 2. Type of intervention: Not stated / Unclear (endovascular coiling treatment or neurosurgical clipping of the ruptured aneurysm).
Indirectness of population	No indirectness
Interventions	(n=891) Intervention 1: Intervention ≤48 hours - Intervention ≤48 hours from admission. Patients treated within 48 hours of admission. Duration Time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=1215) Intervention 2: Intervention >48 hours - Intervention >48 hours from admission. Patients treated after 48 hours of admission. Duration Time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Other (This study was partly sponsored by the Netherlands Heart Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVETNION ≤48 HOURS FROM ADMISSION versus INTERVETNION >48 HOURS FROM ADMISSION Protocol outcome 1: Rebleed of culprit aneurysm - Actual outcome: Rebleeding at Unclear; Group 1: 6/891, Group 2: 22/1215; Comments: Results for >48h combined. Risk of bias: All domain – Very High, Selection - High, Confounding – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 2: Complications - Actual outcome: Delayed Cerebral Ischemia (DCI) at Unclear; Group 1: 218/891, Group 2: 293/1215; Comments: Results for >48h combined Risk of bias: All domain – Very High, Selection - High, Confounding – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
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); Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Length of post-intervention stay

Study	Gu 2012[22]
Study type	Cohort study
Number of studies (number of participants)	(n=96)
Countries and setting	Conducted in China; Setting: Department of Neurosurgery, Southern Medical University, Zhujiang Hospital, China
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged ≥ 70 with aSAH who received treatment with coil embolization
Exclusion criteria	Fusiform, dissecting aneurysms and aneurysms associated with brain AV malformations were excluded
Recruitment/selection of patients	Aged ≥ 70 with aSAH who received treatment with coil embolization between January 2003 - December 2010
Age, gender and ethnicity	Age - Mean (range): <24h: 74.5 (70-85); >24h: 75.7 (70-89). Gender (M:F): 43/53. Ethnicity:
Further population details	1. aSAH grade: Not applicable (WFNS 1-2: 57; WFNS 3-4: 39). 2. Type of intervention: Endovascular intervention (Coiling or stent assisted coiling).
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Patients coiled within 24 hours of SAH (types of coils - GDC; Matrix; EDC. Types of stents - Neuroform; Leo; Enterprise). Duration time to intervention. Concurrent medication/care: na. Indirectness: No indirectness (n=40) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Patients coiled after 24 hours of SAH (types of coils - GDC; Matrix; EDC. Types of stents - Neuroform; Leo; Enterprise). Duration time to intervention. Concurrent medication/care: na. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION	

Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS 0 - 2 at 6 months postoperatively; Group 1: 49/56, Group 2: 28/40 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 - Actual outcome: mRS 3 - 6 at 6 months postoperatively; Group 1: 7/56, Group 2: 12/40 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Rebleed of culprit aneurysm; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Complications; Length of post-intervention stay

Study	Ibrahim Ali 2016[26]
Study type	Cohort study
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Egypt; Setting: Alexandria University Hospital and Insurance Main Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with aneurysmal SAH
Exclusion criteria	not specified
Recruitment/selection of patients	patients with aneurysmal SAH presenting to the Alexandria University Hospital and Insurance Main Hospital during the period from February 2013 to May 2014.
Age, gender and ethnicity	Age - Mean (SD): <24h: 50.50 ± 15.81; >24h: 50.65 ± 12.40. Gender (M:F): 15/15. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (WFNS 1: 11; WFNS 2:9; WFNS 3: 7; WFNS 4: 2; WFNS 5: 1). 2. Type of intervention: Endovascular intervention (framing coil).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. aneurysmal SAH referred for coiling and treated within 24 h from presentation. Duration time to intervention. Concurrent medication/care: The treatment of vasospasm was managed by Triple-H therapy (induced hypertension, hypervolemia, and haemodilution) and endoluminal angioplasty. Post-endovascular evaluation included postoperative CT of the brain to exclude any postoperative complications (intra-cerebral and/or intra-ventricular haemorrhage, brain oedema, or cerebral infarction). (n=20) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. aneurysmal SAH referred for coiling and treated after 24 h from presentation. Duration time to intervention. Concurrent medication/care: The treatment of vasospasm was managed by Triple-H therapy (induced hypertension, hypervolemia, and haemodilution) and endoluminal angioplasty. Post-endovascular evaluation included postoperative CT of the brain to exclude any postoperative complications (intra-cerebral and/or intra-

	ventricular haemorrhage, brain oedema, or cerebral infarction).. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION Protocol outcome 1: Mortality - Actual outcome: Mortality at unclear; Group 1: 0/10, Group 2: 1/20 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Good Outcome (mRS 0 - 2) at 30 days postoperatively; Group 1: 9/10, Group 2: 9/20 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 - Actual outcome: High Morbidity (mRS 3 - 5) at 30 days postoperatively; Group 1: 1/10, Group 2: 10/20 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 3: Rebleed of culprit aneurysm - Actual outcome: Rebleed at unclear; Group 1: 0/10, Group 2: 8/20 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Health and social quality of life; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Complications; Length of post-intervention stay

Study	IHAST trial: Mahaney 2011[44]
Study type	Cohort study
Number of studies (number of participants)	(n=999)
Countries and setting	Conducted in USA; Setting: University of Iowa Hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Non pregnant adult patients must have suffered an SAH from a radiographically demonstrated intracranial aneurysm no more than 14 days prior to surgery and must have had a WFNS score of I,II, or III at the time of enrolment and on arrival to the operating room. Patients were also required to have a pre-SAH rankin score of 0 or 1.
Exclusion criteria	BMI>35kg/m²; had any potentially cold related disorders; or who were endotracheally intubated at the time of enrolment
Recruitment/selection of patients	Patients from the IHAST trial
Age, gender and ethnicity	Age - Mean (SD): 52 ± 13. Gender (M:F): 339/660. Ethnicity:
Further population details	1. aSAH grade: Not applicable (WFNS I: 660; WFNS II: 290; WFNS III:50). 2. Type of intervention: Neurosurgical clipping
Indirectness of population	No indirectness
Interventions	(n=368) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. treatment with neurosurgical clipping within 24 hours. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=631) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Treatment for SAH >24 hours with neurosurgical clipping. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=552) Intervention 3: Intervention ≤48 hours - Intervention ≤48 hours from admission. Treatment commenced within 48 hours . Duration time to intervention. Concurrent medication/care: NA. Indirectness: No

	indirectness (n=447) Intervention 4: Intervention >48 hours - Intervention >48 hours from admission. Neurosurgical clipping ≥ 48 hours. Duration time to intervention. Concurrent medication/care: NA . Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVETNION ≤24 HOURS FROM ADMISSION versus INTERVETNION >24 HOURS FROM ADMISSION

Protocol outcome 1: Complications
- Actual outcome: Delayed Ischemic Neurological Deficit at Postoperatively; Group 1: 22/368, Group 2: 110/631
Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0- Actual outcome: Hydrocephalus at Postoperatively; Group 1: 19/368, Group 2: 78/631
Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0
- Actual outcome: Complications (General and Cardiovascular) at Postoperatively; Group 1: 67/368, Group 2: 350/631
Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVETNION ≤48 HOURS FROM ADMISSION versus INTERVETNION >48 HOURS FROM ADMISSION

Protocol outcome 1: Complications
- Actual outcome: Delayed Ischemic Neurological Deficit at Postoperatively; Group 1: 45/552, Group 2: 109/447
Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0

- Actual outcome: Hydrocephalus at Postoperatively; Group 1: 36/552, Group 2: 61/447
Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0
- Actual outcome: Complications (General and Cardiovascular) at Postoperatively; Group 1: 130/552, Group 2: 226/447

Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
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); Rebleed of culprit aneurysm; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Length of post-intervention stay

Study	IMASH - Intravenous Magnesium Sulphate after aSAH trial: Wong 2012[87]
Study type	Cohort study
Number of studies (number of participants)	(n=276)
Countries and setting	Conducted in Hong Kong (China), New Zealand; Setting: Tertiary Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with spontaneous SAH within 48 hours of ictus and angiographic evidence of intracranial aneurysm as the likely source of haemorrhage
Exclusion criteria	death within 48 hours after admission was anticipated; major hepatic, pulmonary, or cardiac disease; recent myocardial infarction (within 6 months of ictus); significant renal impairment; clinical indication or contraindication to magnesium infusion; pre-existing disability from stroke, dementia, or other neurological disease; or concurrent participation in another clinical trial.
Recruitment/selection of patients	Patients with spontaneous SAH within 48 hours of ictus
Age, gender and ethnicity	Age - Mean (SD): 56 ± 12. Gender (M:F): 99/177. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (WFNS 1 - 2: 154; WFNS 3 - 5: 122). 2. Type of intervention: Not applicable (Endovascular coiling or Craniotomy and clipping).
Indirectness of population	No indirectness
Interventions	(n=148) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Timing of intervention within 24 hours. Duration time to intervention. Concurrent medication/care: NA . Indirectness: No indirectness (n=128) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Timing of aneurysm treatment after 24 hours. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION Protocol outcome 1: Mortality - Actual outcome: Mortality at Unclear; Group 1: 19/148, Group 2: 12/128 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS 0 - 2 at Unclear; Group 1: 94/148, Group 2: 76/128 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0- Actual outcome: mRS 3 - 5 at Unclear; Group 1: 35/148, Group 2: 40/128 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Health and social quality of life; Rebleed of culprit aneurysm; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Complications; Length of post-intervention stay

Study	**Luo 2015[43]**
Study type	Cohort study
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in China; Setting: The Military general Hospital of Beijing, China
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	aSAH patients who received coil embolization and Hunter or Hess grade 4/5 at admission
Exclusion criteria	Untypical aneurysms such as aneurysms associated with AV malformations or moyamoya disease were excluded. Those poor grade patients with large haematoma who were more suitable for clipping were not included in the study.
Recruitment/selection of patients	aSAH patients who received coil embolization between January 2011 and June 2013
Age, gender and ethnicity	Age - Mean (range): <24h: 62.6 (39-82); >24h: 55.6 (39-84). Gender (M:F): 19/26. Ethnicity:
Further population details	1. aSAH grade: Poor grade (Hunter Hess Grade 4: 41; Hunter Hess Grade 5: 3). 2. Type of intervention: Endovascular intervention (Coiling).
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Patients treated <24h after SAH. Duration time to intervention. Concurrent medication/care: na. Indirectness: No indirectness (n=14) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Patients treated >24h after SAH. Duration time to intervention. Concurrent medication/care: na. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION	

Protocol outcome 1: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS 0 - 2 at 6 months postoperatively; Group 1: 18/31, Group 2: 3/14 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0- Actual outcome: mRS 3 - 6 at 6 months postoperatively; Group 1: 13/31, Group 2: 11/14 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Mortality; Health and social quality of life; Rebleed of culprit aneurysm; Return to daily activity (e.g. work); Subsequent subarachnoid haemorrhage; Complications; Length of post-intervention stay

Study	Oudshoorn 2014[59]
Study type	Cohort study
Number of studies (number of participants)	(n=314)
Countries and setting	Conducted in Netherlands; Setting: University Medical centre Utrecht, Netherlands
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	all patients with aSAH
Exclusion criteria	Imminent death; untreatable aneurysms; age <16 years.
Recruitment/selection of patients	all patients with aSAH admitted between January 2008 - January 2012
Age, gender and ethnicity	Age - Median (IQR): <24h: 55 (47-62); >24h: 56 (47-66) . Gender (M:F): 95/219. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear 2. Type of intervention: Not stated / Unclear (Clipping and Coiling).
Extra comments	This study compares the Utrecht cohort to the ISAT cohort. Individual results are compared to pooled Utrecht and ISAT results.
Indirectness of population	No indirectness
Interventions	(n=134) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Patients treated with clipping or coiling within 24 of ictus. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=180) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Patients treated after 24 hours of SAH ictus. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION	

>24 HOURS FROM ADMISSION Protocol outcome 1: Mortality - Actual outcome: Case fatality at Unclear; Group 1: 20/134, Group 2: 13/180 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: Poor Functional Outcome at 3 months post treatment; Pooled functional outcome for Utrecht Cohort and ISAT Cohort (poor functional outcome is defined as Glasgow Outcome Scale of 1-3 after ictus OR modified Rankin Scale score of 3-6 two months after SAH) <24h: 83/217 >24h: 246/980 ; Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 3: Rebleed of culprit aneurysm - Actual outcome: Rebleed at between admission and treatment; Group 1: 14/134, Group 2: 5/180 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0 Protocol outcome 4: Complications - Actual outcome: Delayed Cerebral Ischemia (DCI) at Unclear; Group 1: 37/134, Group 2: 36/180 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
Protocol outcomes not reported by the study	Health and social quality of life ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Length of post-intervention stay

Study	**Park 2015[60]**
Study type	Cohort study
Number of studies (number of participants)	(n=865)
Countries and setting	Korea
Line of therapy	1st line
Duration of study	Intervention time: 2001-2011
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with an aneurysmal SAH
Exclusion criteria	Unclear
Recruitment/selection of patients	patients with an aneurysmal SAH managed at the present tertiary referral centre (Kyungpook National University Hospital)
Age, gender and ethnicity	Age - Mean (SD): <24h: 55.7 ± 12.9; >24h: 55.5 ± 11.6. Gender (M:F): 274/591. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (WFNS Grade 4 or 5: 137). 2. Type of intervention: Not stated / Unclear (Clipping or Coiling).
Indirectness of population	No indirectness
Interventions	(n=442) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Patient treatment commenced within 24 hours between 2008 and 2011. Duration time of intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=423) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Patient treatment commenced after 24 hours between 2001 and 2004. Duration time of intervention. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION	

Protocol outcome 1: Rebleed of culprit aneurysm - Actual outcome: Rebleeding at in hospital; Group 1: 8/442, Group 2: 27/423 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
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) ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Complications ; Length of post-intervention stay

Study	Phillips 2011[61]
Study type	Cohort study
Number of studies (number of participants)	(n=459)
Countries and setting	Conducted in Australia; Setting: The Royal Melbourne Hospital, Melbourne, Victoria, Australia
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Only cases of proven aneurysmal SAH were included with coiling or clipping of acutely ruptured aneurysms
Exclusion criteria	Cases of SAH due to arterial dissection, trauma, arteriovenous malformation rupture, perimesencephalic venous haemorrhage, or unknown aetiology were excluded. Patients who died in the first 24 hours before treatment were also excluded.
Recruitment/selection of patients	Consecutive cases of coiling or clipping of acutely ruptured aneurysms
Age, gender and ethnicity	Age - Mean (SD): <24h: 52 ± 13; >24h: 54 ± 15.6. Gender (M:F): 162/297. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear (WFNS 1 - 3: 354; WFNS 4 - 5: 104). 2. Type of intervention: Not stated / Unclear (Clipping and Coiling).
Indirectness of population	No indirectness
Interventions	(n=230) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from diagnosis. treated with coiling or clipping within 24 hours of the aneurysmal SAH ictus. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=229) Intervention 2: Intervention >24 hours - Intervention >24 hours from diagnosis. coiling or clipping was performed > 24 hours after SAH. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Other (source of funding not stated)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM DIAGNOSIS versus INTERVENTION >24 HOURS FROM DIAGNOSIS Protocol outcome 1: Mortality - Actual outcome: Mortality (mRS 6) at 6 months postoperatively; Group 1: 8/199, Group 2: 15/209 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 31, Reason: not specified; Group 2 Number missing: 20, Reason: not specified Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS 0 - 2 at 6 months postoperatively; Group 1: 183/199, Group 2: 179/209 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 31, Reason: not specified; Group 2 Number missing: 20, Reason: not specified - Actual outcome: mRS 3 - 5 at 6 months postoperatively; Group 1: 8/199, Group 2: 16/209 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 31, Reason: not specified; Group 2 Number missing: 20, Reason: not specified	
Protocol outcomes not reported by the study	Health and social quality of life ; Rebleed of culprit aneurysm ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Complications ; Length of post-intervention stay

Study	**Qian 2014[64]**
Study type	Cohort study
Number of studies (number of participants)	(n=664)
Countries and setting	Conducted in China; Setting: Beijing Tiantan Hospital, Capital Medical University, China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Only cases of proven aSAH with endovascular treatment were included.
Exclusion criteria	Cases of aneurysmal SAH who underwent clipping, cases due to hypertension, trauma, moyamoya, AV malformation, dural AV fistula, arterial dissection, or unknown aetiology were excluded.
Recruitment/selection of patients	patients selected from those who had endovascular treatment as the primary treatment modality for ruptured aneurysms.
Age, gender and ethnicity	Age - Other: 55.8. Gender (M:F): 289/375. Ethnicity:
Further population details	1. aSAH grade: Not applicable (Hunter and Hess grade 1-2: 516; Hunter and Hess grade 3-5 : 148). 2. Type of intervention: Endovascular intervention (endovascular treatment only).
Indirectness of population	No indirectness
Interventions	(n=269) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Endovascular treatment within 24 hours of SAH. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness (n=395) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Endovascular treatment after 24 hours of SAH. Duration time to intervention. Concurrent medication/care: NA. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION	

>24 HOURS FROM ADMISSION Protocol outcome 1: Mortality - Actual outcome: Mortality (mRS 6) at 9 months postoperatively; Group 1: 13/204, Group 2: 29/309 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness ; Group 1 Number missing: 65; Group 2 Number missing: 86 Protocol outcome 2: Degree of disability or dependence in daily activities, (e.g. Modified Rankin Scale and patient-reported outcome measures) - Actual outcome: mRS 0 - 2 at 9 months postoperatively; Group 1: 160/204, Group 2: 193/309 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness ; Group 1 Number missing: 65; Group 2 Number missing: 86 - Actual outcome: mRS 3 - 5 at 9 months postoperatively; Group 1: 31/204, Group 2: 87/309 Risk of bias: All domain – Very High, Selection - High, Confounding - High Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness ; Group 1 Number missing: 65; Group 2 Number missing: 86	
Protocol outcomes not reported by the study	Health and social quality of life ; Rebleed of culprit aneurysm ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Complications ; Length of post-intervention stay

Study	Solomon 1991[76]
Study type	Cohort study
Number of studies (number of participants)	(n=145)
Countries and setting	Conducted in USA; Setting: Columbia-Presbyterian Medical Centre, Columbia University College, New York
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 – 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Confirmed acute aSAH
Exclusion criteria	Not specified
Recruitment/selection of patients	consecutive series of 145 patients with acute aSAH
Age, gender and ethnicity	Age - Other: Not specified. Gender (M:F): Not specified. Ethnicity:
Further population details	1. aSAH grade: Not stated / Unclear 2. Type of intervention: Neurosurgical clipping
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Neurosurgical clipping within 24 hours of admission . Duration time to intervention. Concurrent medication/care: Prior to surgery patients were maintained euvolemic. At surgery all patients received mannitol and generous CSF drainage from a spinal catheter for brain relaxation. For patients with DCI aggressive volume expansion hemodilution was instituted. . Indirectness: No indirectness (n=96) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Neurosurgical clipping beyond 24 hours of admission . Duration time to intervention. Concurrent medication/care: Prior to surgery patients were maintained euvolemic. At surgery all patients received mannitol and generous CSF drainage from a spinal catheter for brain relaxation. For patients with DCI aggressive volume expansion hemodilution was instituted. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION Protocol outcome 1: Complications - Actual outcome: Delayed Cerebral Ischemia at postoperatively ; Group 1: 8/49, Group 2: 23/96 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
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) ; Rebleed of culprit aneurysm ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Length of post-intervention stay

Study	**Tykocki 2017[82]**
Study type	Cohort study
Number of studies (number of participants)	(n=79)
Countries and setting	Conducted in Poland; Setting: Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw Poland
Line of therapy	1st line
Duration of study	Intervention time: 2011 - 2013
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who had been classified with grade IV or V on WFNS scale at admission.
Exclusion criteria	not specified
Recruitment/selection of patients	patients with aSAH treated between 2011 and 2013
Age, gender and ethnicity	Age - Mean (SD): <24h: 49.5 ± 6.1; >24h: 65.8 ± 7.4. Gender (M:F): unclear. Ethnicity:
Further population details	1. aSAH grade: Poor grade (WFNS 4: 49; WFNS 5: 30). 2. Type of intervention: Not applicable (Clipping or Coiling).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Intervention ≤24 hours - Intervention ≤24 hours from admission. Endovascular coiling or Neurosurgical clipping within 24 hours of SAH. Duration time to intervention. Concurrent medication/care: na. Indirectness: No indirectness (n=41) Intervention 2: Intervention >24 hours - Intervention >24 hours from admission. Endovascular coiling or Neurosurgical clipping after 24 hours of SAH. Duration time to intervention. Concurrent medication/care: na. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERVENTION ≤24 HOURS FROM ADMISSION versus INTERVENTION >24 HOURS FROM ADMISSION	

Protocol outcome 1: Mortality - Actual outcome: Mortality at Unclear; Group 1: 5/38, Group 2: 14/41; Comments: p value 0.023 Risk of bias: All domain – Very High, Selection - High, Confounding - Flawed Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Comparative results from ISAT study; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing:0	
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 culprit aneurysm ; Return to daily activity (e.g. work) ; Subsequent subarachnoid haemorrhage ; Complications ; Length of post-intervention stay

Appendix E: Forest plots

E.1 Early (≤72 hours) Intervention versus Delayed Intervention (>72hours)

Figure 2: Mortality

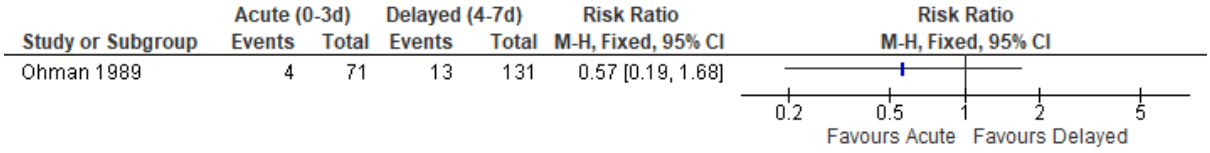
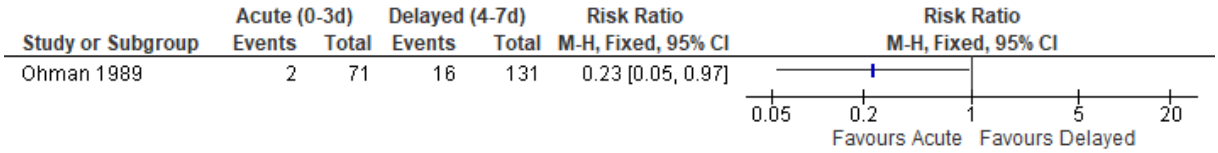


Figure 3: Dependent (Severe disability or Vegetative state)



E.2 Early Intervention (<24 hours) versus Intervention post-stabilization

Figure 4: Mortality

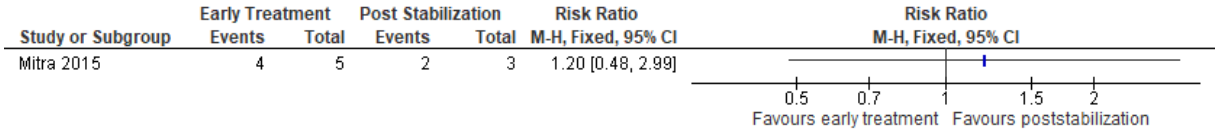
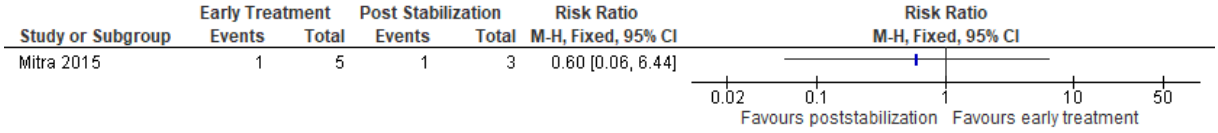


Figure 5: Modified Rankin Score (mRS 1). Scale 0-6; high score represents poor outcome



E.3 Early Intervention (<24h) versus Delayed Intervention (>24h)

Figure 6: Mortality

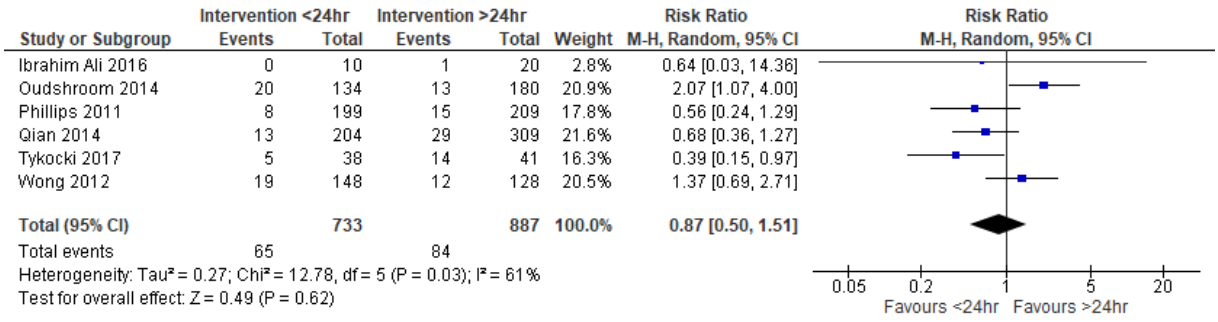


Figure 7: mRS 0 – 2. Scale 0-6; high score represents poor outcome

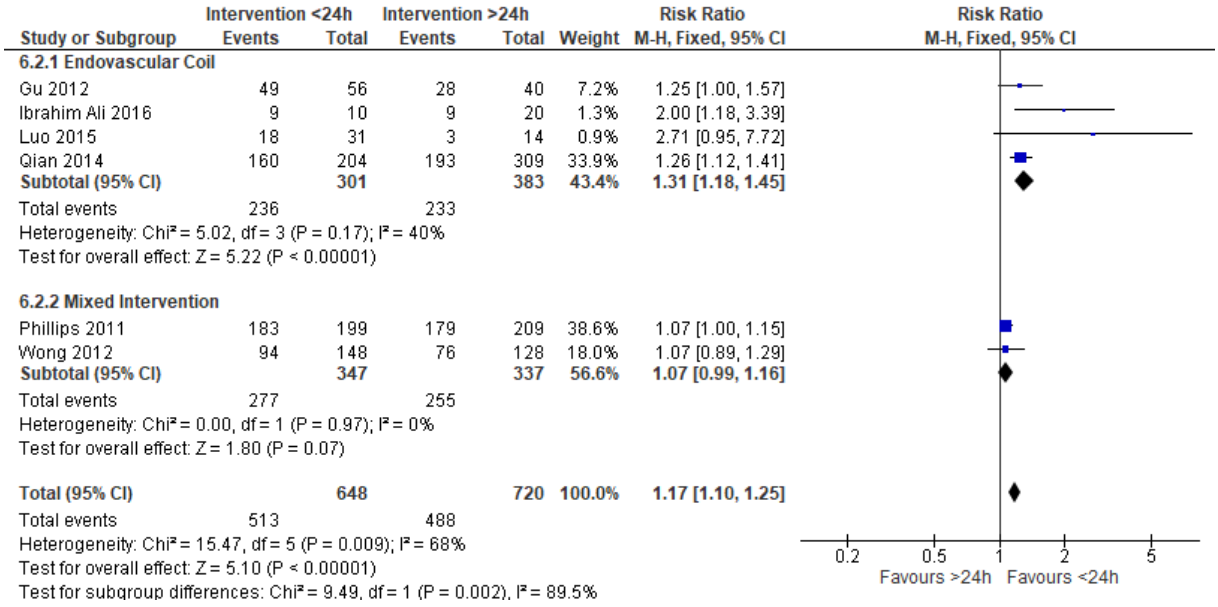


Figure 8: mRS 3 – 5. Scale 0-6; high score represents poor outcome

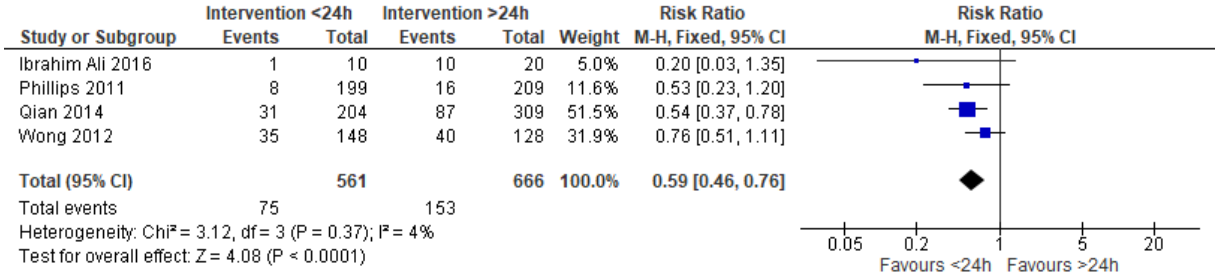


Figure 9: mRS 3 – 6. Scale 0-6; high score represents poor outcome

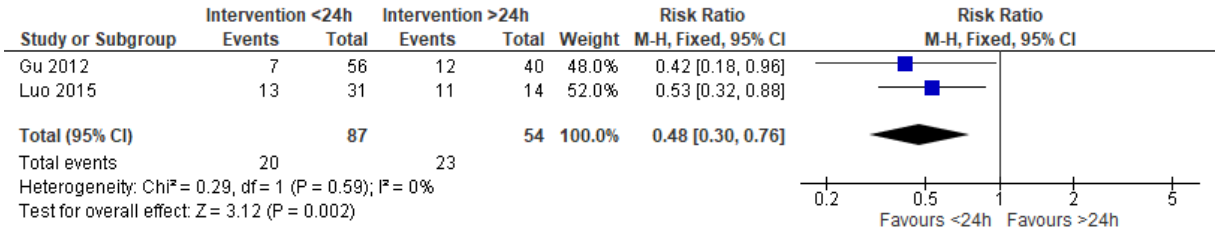


Figure 10: Poor Functional Outcome

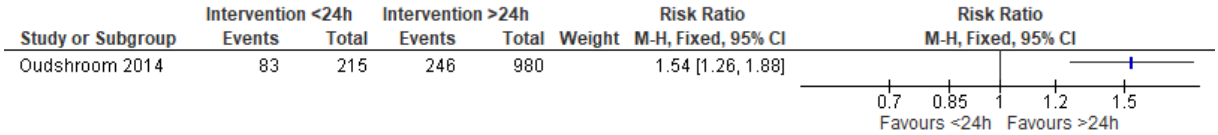


Figure 11: Rebleed

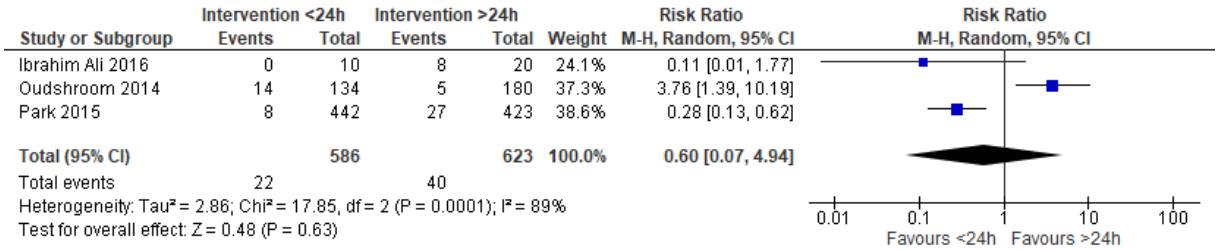


Figure 12: Complication (DCI)

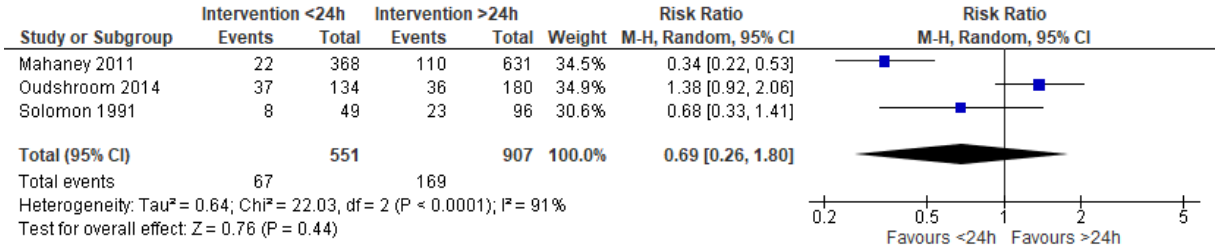


Figure 13: Complication (Hydrocephalus)

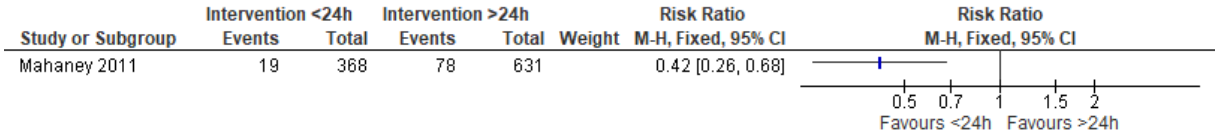
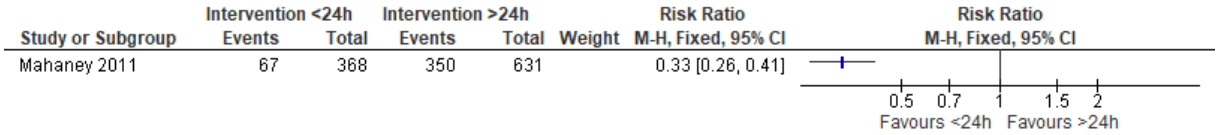


Figure 14: Complications (other)



E.4 Early Intervention (<48h) versus Delayed Intervention (>48h)

Figure 15: Rebleed

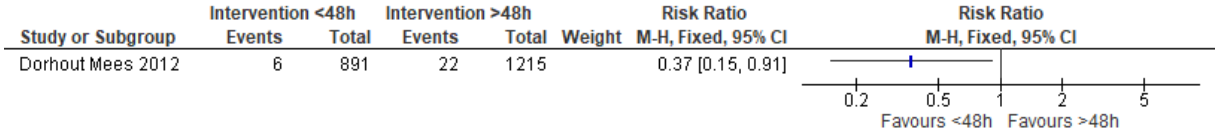


Figure 16: Complication (DCI)

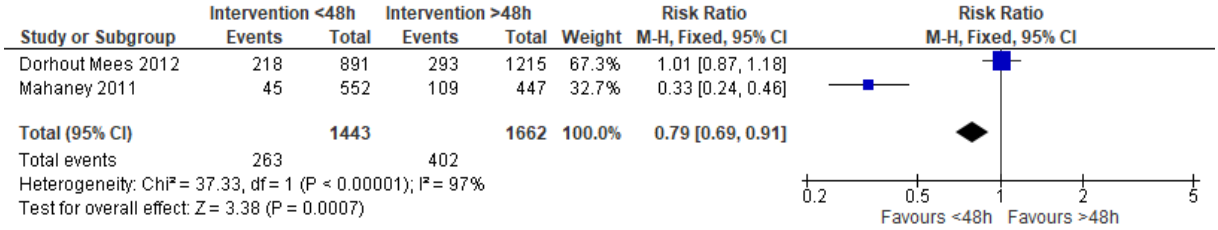


Figure 17: Complication (Hydrocephalus)

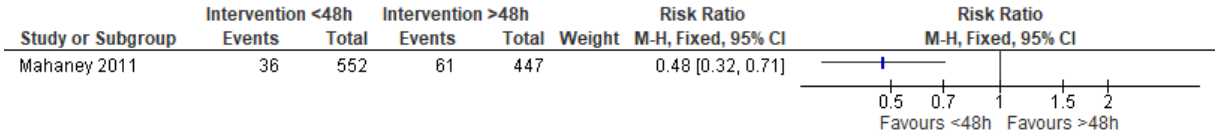
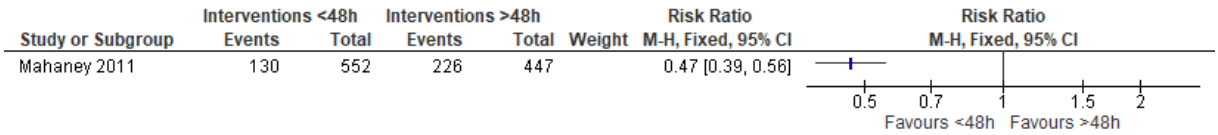


Figure 18: Complications (other)



Appendix F: GRADE tables

Table 14: Clinical evidence profile: Early Intervention (≤72 hours) compared to Delayed Intervention (>72hours)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acute surgery	Delayed surgery (merged)	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	4/71 (5.6%)	9.9%	RR 0.57 (0.19 to 1.68)	43 fewer per 1000 (from 80 fewer to 67 more)	⊕⊕OO LOW	CRITICAL
Dependent (Severe disability or Vegetative state) (follow-up 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/71 (2.8%)	12.2%	RR 0.23 (0.05 to 0.97)	94 fewer per 1000 (from 4 fewer to 116 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 15: Clinical evidence profile: Early Intervention (<24 hours) versus Intervention post stabilization

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Post stabilization	Relative (95% CI)	Absolute		
Mortality (mRS 6) (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/5 (80%)	66.7%	RR 1.2 (0.48 to 2.99)	133 more per 1000 (from 347 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Modified Rankin Score (mRS 1) (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/5 (20%)	33.3%	RR 0.6 (0.06 to 6.44)	133 fewer per 1000 (from 313 fewer to 1000 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

Table 16: Clinical evidence profile: Early Intervention (<24 hours) compared to Delayed Intervention (>24 hours)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**<24 hours**	**>24 hours**	**Relative (95% CI)**	**Absolute**		
Mortality (follow-up 0-6 months)												
6	observational studies[1]	very serious[2]	serious[3]	no serious indirectness	very serious[4]	none	65/733 (8.9%)	9.5%	RR 0.87 (0.50 to 1.51)	12 fewer per 1000 (from 47 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL
mRS 0 - 2 - Endovascular Coil												

4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious	none	236/301 (78.4%)	53.7%	RR 1.31 (1.18 to 1.45)	166 more per 1000 (from 97 more to 242 more)	⊕OOO VERY LOW	CRITICAL
mRS 0 - 2 - Mixed Intervention												
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	277/347 (79.8%)	72.5%	RR 1.07 (0.99 to 1.16)	51 more per 1000 (from 7 fewer to 116 more)	⊕⊕OO LOW	CRITICAL
mRS 3 - 5 (follow-up 1-9 months)												
4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/561 (13.4%)	29.7%	RR 0.59 (0.46 to 0.76)	122 fewer per 1000 (from 71 fewer to 160 fewer)	⊕⊕OO LOW	CRITICAL
mRS 3 - 6 (follow-up 6 months)												
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	20/87 (23%)	54.3%	RR 0.48 (0.3 to 0.76)	282 fewer per 1000 (from 130 fewer to 380 fewer)	⊕⊕OO LOW	CRITICAL
Poor Functional Outcome (follow-up 6 months)												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/215 (38.6%)	25.1%	RR 1.54 (1.26 to 1.88)	136 more per 1000 (from 65 more to 221 more)	⊕⊕OO LOW	CRITICAL
Rebleed												
3	observational studies[1]	very serious[2]	very serious[3]	no serious indirectness	very serious[4]	none	22/586 (3.8%)	6.4%	RR 0.60 (0.07 to 4.94)	26 fewer per 1000 (from 26 fewer to 252 more)	⊕OOO VERY LOW	IMPORTANT
Complication (DCI)												

3	observational studies[1]	very serious[2]	very serious[3]	no serious indirectness	very serious[4]	none	67/551 (12.2%)	19%	RR 0.69 (0.26 to 1.80)	59 fewer per 1000 (from 141 fewer to 152 fewer)	⊕OOO VERY LOW	IMPORTANT
Complication (Hydrocephalus)												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	19/368 (5.2%)	12.4%	RR 0.42 (0.26 to 0.68)	72 fewer per 1000 (from 40 fewer to 92 fewer)	⊕⊕OO LOW	IMPORTANT
Complications (Other)												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	67/368 (18.2%)	55.5%	RR 0.33 (0.26 to 0.41)	372 fewer per 1000 (from 327 fewer to 411 fewer)	⊕⊕OO LOW	IMPORTANT

[1] The majority of the evidence was from studies with observational/non-randomised study design.
[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
[3] Downgraded by 1 or 2 increments because: o The point estimate varies widely across studies, unexplained by subgroup analysis. o The confidence intervals across studies show minimal or no overlap, unexplained by subgroup analysis o Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: Early Intervention (<48 hours) compared to Delayed Intervention (>48 hours)

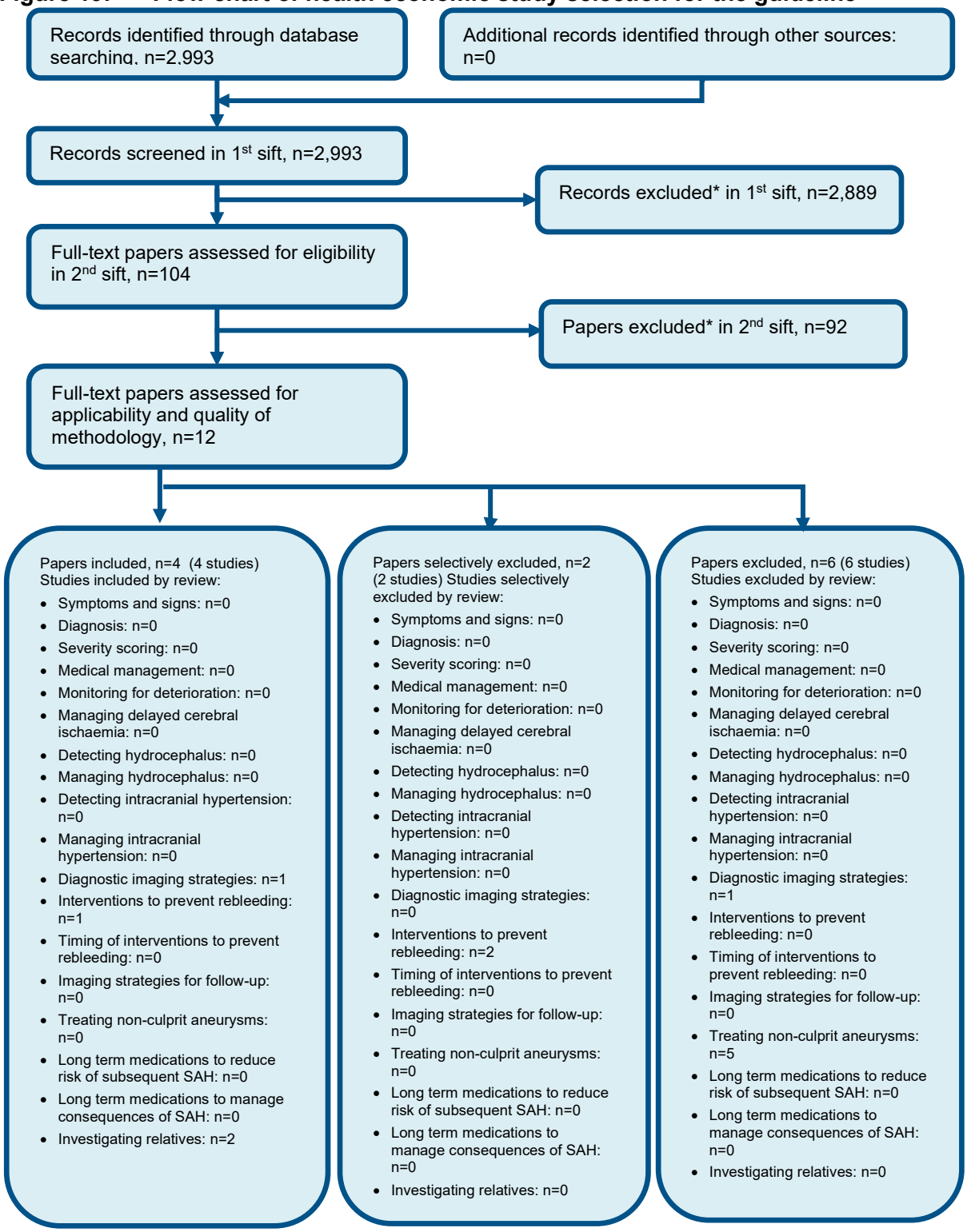
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**<48 hours**	**>48 hours**	**Relative (95% CI)**	**Absolute**		
Rebleed												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	strong association	6/891 (0.67%)	1.8%	RR 0.37 (0.15 to 0.91)	11 fewer per 1000 (from 2 fewer to 15 fewer)	⊕OOO VERY LOW	IMPORTANT

Complication (DCI)												
2	observational studies[1]	very serious[2]	very serious[5]	no serious indirectness	serious[3]	none	263/1443 (18.2%)	24.2%	RR 0.79 (0.69 to 0.91)	51 fewer per 1000 (from 22 fewer to 75 fewer)	⊕OOO VERY LOW	IMPORTANT
Complication (Hydrocephalus)												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	36/552 (6.5%)	13.7%	RR 0.48 (0.32 to 0.71)	71 fewer per 1000 (from 40 fewer to 93 fewer)	⊕⊕OO LOW	IMPORTANT
Complications (Other)												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	130/552 (23.6%)	50.6%	RR 0.47 (0.39 to 0.56)	268 fewer per 1000 (from 223 fewer to 309 fewer)	⊕⊕OO LOW	IMPORTANT

[1] The majority of the evidence was from studies with observational/non-randomised study design
[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
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 or 2 increments because of heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.

Appendix G: Health economic evidence selection

Figure 19: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 18: Studies excluded from the clinical review

Reference	Reason for exclusion
Abe 1992[1]	Inappropriate intervention – no relevant outcomes
Al-Jehani 2018[2]	Inappropriate intervention – early investigation
Attenello 2014[3]	Inappropriate comparison – <3 days compared to >3 days
Baltsavias 2000[4]	Inappropriate comparison – <3 days compared to >3 days
Bir 2016[5]	Inappropriate population – arteriovenous malformations
Brilstra 1999[6]	Inappropriate study design – citation
Byrne 2001[7]	Inappropriate comparison - <6 days compared to >6 days
Cherian 2011[8]	Inappropriate study design – non comparative
Chyatte 1988[9]	Inappropriate comparison – 0 – 3 days, 4 – 9 days or >10 days
Dalbayrak 2011[10]	Inappropriate comparison – intervention <72 hours compared to >72 hours
De Gans 2002[11]	Systematic review – references screened
Deguchi 2018[12]	Inappropriate population – stroke
Dorsch 1984[14]	Inappropriate study design – no relevant outcomes
Dorsch 1989[15]	Inappropriate comparison – early (3 days) compared to late (>4 days)
Dossani 2019[16]	Systematic review – references screened
Egashira 2013[17]	Inappropriate comparison – intervention within 72h for all patients
Egge 2002[18]	Inappropriate study design – non comparative study
Ferch 2003[19]	Inappropriate comparison – 0-4 days compared to >8 days
Golchin 2012[20]	Inappropriate comparison – <4 days compared to >7 days
Gruber 1998[21]	Inappropriate study design – non comparative study
Hafez 2017[23]	Inappropriate population – arteriovenous malformations
Haley Jr 1992[24]	Inappropriate comparison – <3 days compared to >3 days
Hashemi 2011[25]	Inappropriate comparison – <4 days compared to >7 days
Inamasu 2016[27]	Inappropriate study design – non comparative study
Jiang 2018[28]	Inappropriate comparison – <3 days compared to >3 days
Jung 2013[29]	Inappropriate population – intra-arterial treatment for ischaemic stroke
Jussen 2015[30]	Inappropriate study design – non comparative study
Kameda-Smith 2018[31]	Inappropriate comparison – timing of complication
Kassell 1981[32]	Inappropriate intervention – grouped by admission times
Kassell 1981[33]	Inappropriate comparison – early compared to late (not clear)
Kawakami 1987[34]	Inappropriate comparison – review of intracranial aneurysms
Kayama 1978[35]	Inappropriate study design – non comparative study
Khan 2015[36]	Inappropriate comparison – assessment of service reorganization
Lamb 2011[37]	Inappropriate study design – audit
Lavine 1997[38]	Inappropriate intervention – assessment of IV brain protection
Lawson 2010[39]	Inappropriate comparison – <3 days compared to >3 days

Reference	Reason for exclusion
Lee 1991[40]	Inappropriate study design – non comparative
Linzey 2018[41]	Inappropriate comparison – rebleed compared to no rebleed
Ljunggren 1982[42]	Inappropriate study design – non comparative
Mavaddat 1999[45]	Inappropriate comparison – <3 days compared to >3 days
McLaughlin 2006[46]	Inappropriate study design – non comparative
Milhorat 1986[47]	Inappropriate comparison – immediate surgery compared to late surgery (>1 week)
Miyaoka 1993[49]	Inappropriate comparison – <3 days compared to >3 days
Mizukami 1982[50]	Inappropriate study design – non comparative
Mogollon 2018[51]	Inappropriate intervention – assessment of neuro-interventional radiology
Mordasini 2005[52]	Inappropriate comparison – assessment of endovascular technique
Mutoh 2010[53]	Inappropriate comparison – successful surgery compared to unsuccessful surgery
Nieuwkamp 2005[55]	Inappropriate comparison – 0 – 3 days, 4 – 7 days or >7 days
Okada 2016[57]	Inappropriate comparison – ruptured compared to unruptured aneurysms
Olkowski 2015[58]	Inappropriate intervention – early mobilization
Piepgras 1998[62]	Inappropriate comparison – <3 days compared to >3 days
Prat 2007[63]	Inappropriate study design – non comparative
Ritz 2002[65]	Inappropriate comparison – prognostic assessment
Roos 1997[66]	Inappropriate comparison – <3 days compared to >3 days
Ross 2002[67]	Inappropriate intervention – early embolization compared to surgery
Ross 2002[68]	Inappropriate comparison – <3 days compared to >3 days
Sagoh 1997[69]	Inappropriate comparison – <3 days compared to >3 days
Samson 1979[70]	Inappropriate comparison – <8 days compared to >8 days
Sano 1994[71]	Inappropriate study design – non comparative study
Satzger 1995[72]	Inappropriate comparison – <3 days compared to >3 days
Seifert 1990[74]	Inappropriate comparison – grade IV compared to V aneurysm
Seifert 1988[73]	Inappropriate comparison – <3 days compared to >3 days
Shigematsu 2016[75]	Inappropriate comparison – predictors of early shunt insertion
Stolke 1988[77]	Not in English
Tamasauskas 2000[78]	Inappropriate study design – non comparative study
Tan 2014[79]	Inappropriate comparison – surgery <3 days compared to post neuro-stabilization
Taneda 1982[80]	Inappropriate comparison – surgery within 48 hours +/- clot removal compared to surgery >10 days
Tucker 1987[81]	Inappropriate comparison – <3 days compared to >3 days
Van Der Jagt 2009[83]	Inappropriate comparison – early surgery (<72h) compared to late surgery (day 12)
Vieira 2012[84]	Inappropriate comparison – intervention techniques
Weir 1981[85]	Inappropriate study design – non comparative
Whitfield 2001[86]	Systematic review: references screened
Yamamoto 1992[89]	Inappropriate study design – non comparative study
Yoshimoto 1999[90]	Inappropriate study design – non comparative study
Zhang 2013[91]	Inappropriate study design – study protocol
Zhao 2017[92]	Systematic review: references screened

Reference	Reason for exclusion
Zhou 2014[93]	Inappropriate comparison – <3 days compared to >3 days

I.2 Excluded health economic studies

None. 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 19: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	