

European Stroke Organisation (ESO), European Association of Neurosurgical Societies (EANS) and European Society for Minimally Invasive Neurological Therapy (ESMINT) guideline on aneurysmal subarachnoid haemorrhage

Mervyn D. I. Vergouwen^{1,*} , Anna Ramos-Pachon² , Elena-Oana Terecoasa^{3,4} , Nicola Willett⁵ , Elisa Cuadrado-Godia⁶ , Thomas Gaberel^{7,8} , Elke Ruth Gizewski⁹ , Raimund Helbok^{10,11} , Leonard Ho¹² , Michael Hugelshofer¹³ , Miikka Korja¹⁴ , Torstein R. Meling¹⁵ , Marios-Nikos Psychogios¹⁶ , Gabriel J. E. Rinkel^{1,5} , Christian A. Taschner¹⁷ , Peter Vajkoczy¹⁸ , Nima Etminan⁵ 

¹Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

²Department of Neurology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

³Department of Neurology, University Emergency Hospital Bucharest, Bucharest, Romania

⁴Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

⁵Department of Neurosurgery, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany

⁶Department of Neurology, Hospital del Mar, Universitat Pompeu Fabra, Barcelona, Spain

⁷Department of Neurosurgery, University Hospital of Caen, Caen, France

⁸PhIND – Physiopathology and Imaging of Neurological Disorders, Inserm U1237, Institut Blood and Brain at Caen-Normandie, Cyceron, UNICAEN, Normandie University, Caen, France

⁹Department of Radiology, Medical University Innsbruck, Innsbruck, Austria

¹⁰Department of Neurology, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria

¹¹Clinical Research Institute for Neurosciences, Kepler University Hospital and Johannes Kepler University Linz, Linz, Austria

¹²European Stroke Organisation, Basel, Switzerland

¹³Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland

¹⁴Department of Neurosurgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

¹⁵Department of Neurosurgery, The National Hospital, Rigshospitalet, Copenhagen, Denmark

¹⁶Diagnostic and Interventional Neuroradiology, Clinic of Radiology and Nuclear Medicine, University Hospital Basel, Basel, Switzerland

¹⁷Department of Neuroradiology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

¹⁸Department of Neurosurgery, Charité Universitätsmedizin Berlin, Berlin, Germany

*Corresponding author: Mervyn D.I. Vergouwen, Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands (M.D.I.Vergouwen@umcutrecht.nl)

Abstract

Aneurysmal subarachnoid haemorrhage (aSAH) results from the rupture of an intracranial aneurysm. The case-fatality after aSAH is approximately 40% and those who survive often have functional, cognitive or emotional sequelae. We prepared guidelines according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology, using data from meta-analyses, randomised trials, prospective observational and case-control studies, prospective registries with external validation and single-arm cohort studies with > 50 patients with aSAH. Based on high levels of evidence, we recommend oral administration of nimodipine and regular coiling over clipping if both aneurysm treatment options are equally suitable in patients who are in good clinical condition, and recommend against the routine use of antifibrinolytic drugs prior to aneurysm treatment and against the use of tirilazad, statins, magnesium sulphate or endothelin receptor antagonists. Because of lower levels of evidence, no evidence-based recommendations can be made for the prophylactic use of antiplatelet drugs or external lumbar drainage, hypertension induction, treatment of the ruptured aneurysm with endovascular devices other than coils or endovascular treatment of vasospasm. We formulated 37 expert-consensus statements, which include, among others, the suggestions to treat aSAH patients in a dedicated neuro-ICU or high care unit in a centre that treats at least

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70 patients with aSAH per year or at least 35 patients with aSAH per year in geographically remote areas, and to treat the ruptured aneurysm within 24 h after ictus provided that the most dedicated team of experts is available. These guidelines present up-to-date recommendations and expert-consensus statements on key aspects in the management of aSAH patients.

Keywords assessment, clipping, coiling, delayed cerebral ischaemia, endovascular repair, grading of recommendations, guideline, hydrocephalus, management, medical management, rebleeding, subarachnoid haemorrhage, systematic review

Plain language summary

Intracranial aneurysms are abnormal outpouchings in the walls of intracranial arteries. They are present in approximately 3% of adults and are more common in women than in men. If an aneurysm ruptures, it causes a bleeding into the space between the brain and its surrounding membranes, known as aneurysmal subarachnoid haemorrhage. This type of stroke often occurs at a relatively young age: about half of affected patients are under 50 years old, and roughly two-thirds are women. Outcomes after aneurysmal subarachnoid haemorrhage are often poor. Approximately 40% of the patients die within 3 months, and among those who survive long term, outcomes vary widely. Roughly one-third of all patients regain independence in daily activities, while another group survives with some level of disability. Among survivors, cognitive and emotional problems are very common, including memory impairment, reduced concentration, fatigue and depression. Most survivors do not return to their pre-haemorrhage level of functioning.

How well someone recovers after aneurysmal subarachnoid haemorrhage depends on how severe the bleeding is and on complications that may happen especially in the first 2 weeks after the bleeding. The most feared complications are rebleeding of the ruptured aneurysm (occurring in approximately 40% of the patients if the ruptured aneurysm remains untreated), reduced blood flow to the brain (which can cause symptoms in approximately 20% of patients) and a build-up of fluid in the brain (in approximately 25% of patients). Hospital care is mainly focused on preventing these complications, finding them early if they occur, and treating them. The ultimate goal is to improve recovery and long-term physical, cognitive and emotional functioning.

This guideline provides recommendations based on high-quality studies from the medical literature, and opinions from experts if high-quality studies are lacking. The recommendations and expert opinions address when an aneurysm should be treated, which aneurysm treatment methods are best, and which drugs can help lower the risk of complications during hospital care. It also describes diagnostic methods that help physicians identify the cause of clinical deterioration and outlines the management of complications. In addition, it gives guidance on the appropriate hospital and specialist setting, taking into account patient volume and experience and on the timing of follow-up brain scans after aneurysm treatment.

Based on a high level of scientific evidence, this guideline recommends that patients with aneurysmal subarachnoid haemorrhage should not receive antifibrinolytic drugs to reduce the risk of rebleeding, as they do not decrease the risk of poor outcome. In patients who are awake or only mildly drowsy, with at most mild neurological deficits, coiling without adjunctive devices is preferred over microsurgical clipping to treat the ruptured aneurysm in situations where both treatment options are equally suitable. All patients should receive oral nimodipine, a drug that reduces the risk of brain damage, but not other drugs such as statins, magnesium sulphate or endothelin receptor antagonists.

Based on the opinion from experts, this guideline suggests that lowering blood pressure before the aneurysm is treated may help reduce the risk of rebleeding of the aneurysm in patients with very high blood pressure, but it remains unclear whether or not it decreases the risk of poor outcome. Blood pressure lowering should be performed slowly and in a controlled manner, ie, without undershoot, and with short-acting medications. The ruptured aneurysm should ideally be treated within 24 h, when possible, and by an experienced physician who treats at least 30 intracranial aneurysms (either ruptured or unruptured) per year. Treatment decisions should always be made by a multidisciplinary team (composed of at least 1 neurosurgeon and 1 neurointerventionalist) to consider the different aneurysm treatment options, and decide on the safest method, and the most effective and durable treatment outcome. For aneurysms that cannot be treated by regular coiling, ie, without adjunctive devices, there are no high-quality data showing that more novel endovascular techniques and devices (such as stent-assisted coiling, flow diverting stents or intra-saccular devices) decrease the risk of poor outcome compared to regular coiling. If a patient worsens due to reduced blood flow in the brain, raising blood pressure may be considered, but only after the aneurysm is secured and fluid administration has failed. Endovascular drug treatments may be used in patients with a critically reduced blood flow to the brain due to severe narrowing of the brain arteries, but treatments that widen the arteries by the use of inflatable balloons should only be considered as a last-line rescue treatment after careful multidisciplinary discussion of the potential risks and uncertain benefits. The current data are insufficient to support the use of temporary stents. Brain scans (CT and CT-perfusion) are useful when a patient's condition worsens or cannot be assessed clinically. Routine invasive brain monitoring, EEG and complex monitoring systems are not recommended because benefits are unclear. If fluid builds up in the brain (hydrocephalus), drainage is recommended when there is a reduced level of consciousness. The type of drainage

depends on the results of brain imaging and the presence of blood in the ventricles. Long-term fluid drainage devices should be used in patients with chronic hydrocephalus when temporary drainage is no longer safe. Patients should be treated in a specialised neuro-ICU in centres that treat at least 70 patients with aneurysmal subarachnoid haemorrhage per year, or at least 35 in remote areas.

After hospital discharge, follow-up brain scans can be made to investigate whether or not reopening of the aneurysm occurs after treatment. Follow-up imaging is only indicated as long as re-treatment of the aneurysm remains an option, and in the following situations that depend on type of aneurysm treatment:

- Patients treated with coils should have follow-up imaging at least once at or after 12 months after aneurysm treatment.
- Patients treated with clips usually do not need long-term follow-up imaging if imaging within 6 months after treatment shows that the aneurysm is completely occluded.
- Patients with partially occluded aneurysms or those who are treated with newer devices, such as intrasaccular devices or flow-diverting stents, need long-term follow-up.
- Patients who are at high risk of developing new aneurysms, such as those with a young age, positive family history for aneurysmal subarachnoid haemorrhage or autosomal dominant polycystic kidney disease, should have scans every 5 years to check for new aneurysms.

Key recommendations/suggestions of the Guideline

Admit or immediately transfer the patient to a dedicated neuro-ICU or high care unit in a centre that treats at least 70 patients with aSAH per year, or at least 35 patients with aSAH per year in geographically remote areas.

Do not routinely administer antifibrinolytic drugs prior to treatment of the ruptured aneurysm

Discuss all patients with aSAH in an interdisciplinary manner, with at least one neurosurgeon and one neuro-interventionalist

Treat the ruptured aneurysm by regular coiling in patients who are in good clinical condition (WFNS I-III) and who have an aneurysm of either the anterior or posterior circulation that can be treated by either regular coiling (i.e. without adjunctive devices) or microsurgical clipping.

If regular coiling is not feasible, the multidisciplinary team should discuss the safety, effectiveness, and durability of microsurgical and alternative endovascular options to determine the preferred treatment strategy.

Stent-assisted coiling should be reserved for selected cases where other treatment options are not feasible.

Flow-diversion should be reserved as a last-line treatment option for ruptured aneurysms.

Have the ruptured aneurysm treated by a neurosurgeon or neurointerventionalist who performs the treatment of choice in more than 30 patients with aneurysms (ruptured and unruptured) per year.

Treat the ruptured aneurysm within 24 hours after ictus, provided that the most dedicated team of experts is available.

Administer oral nimodipine for the prevention of delayed cerebral ischaemia and decrease the risk of poor functional outcome.

Perform head CT in combination with CT-perfusion in case of clinical deterioration.

Do not perform routine DSA to screen for macrovascular vasospasm

Perform radiological follow-up of the treated aneurysm beyond 6 months after aneurysm treatment in patients who have neck remnants or partially occluded aneurysms (irrespective of type of aneurysm treatment) as long as a potential re-treatment remains an option. In case of treatment with endovascular devices other than coils, perform radiological follow-up until at least five years after treatment as long as a potential re-treatment remains an option, regardless of the degree of occlusion, to ensure adequate long-term occlusion.

Graphical Abstract

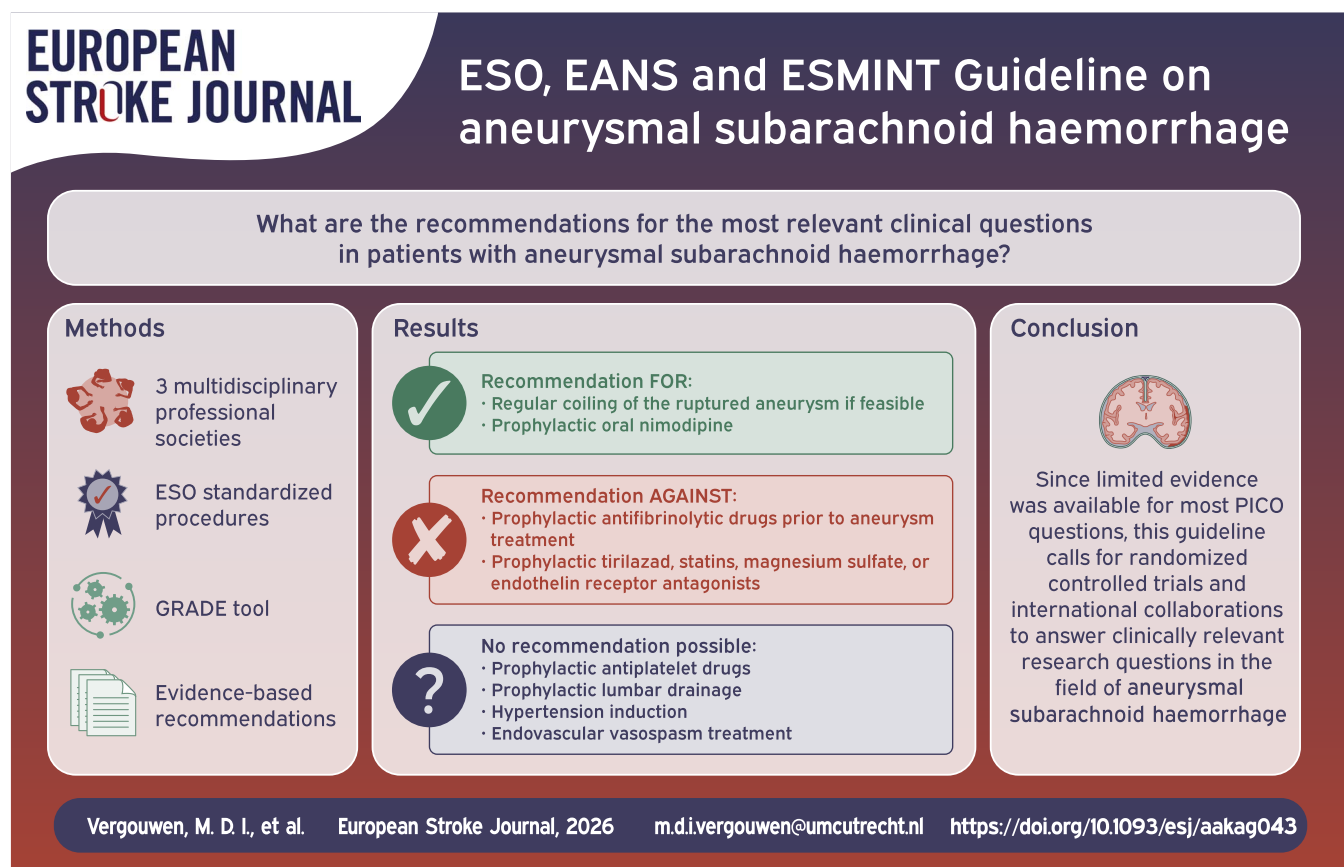


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Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) results from the rupture of an intracranial aneurysm. The median age of patients with aSAH is 52 years¹ and most patients are women. Although the global incidence of aSAH has declined from 10.2 (95% CI, 8.4–12.5) per 100,000 person-years in 1980 to 6.1 (95% CI, 4.9–7.5) in 2010,¹ the overall disease burden remains substantial, in part because of the relatively young age of affected patients. Subarachnoid haemorrhage resulted in approximately 350,000 deaths and more than 10 million disability-adjusted life years globally in 2021.²

The most important determinants of poor functional outcome after aSAH are the effects of the initial bleeding, rebleeding of the ruptured aneurysm, delayed cerebral ischaemia (DCI) and hydrocephalus.³ During hospitalisation, the management of patients with aSAH is focused on the prevention and treatment of complications resulting from aSAH to reduce the risk of death, disability and cognitive and emotional consequences. Since the publication of the European Stroke Organisation (ESO) guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage in 2013, new data have been reported regarding the diagnosis, prevention and treatment of aSAH-related complications and radiological follow-up of treated aneurysms.⁴ These include, with varying levels of evidence, the use of antifibrinolytic drugs, novel treatment options for treatment of the ruptured aneurysm, use of lumbar drains and endovascular treatment of vasospasm.

The aim of this guideline is to provide contemporary evidence-based recommendations and expert-consensus statements to guide neurosurgeons, neurologists, neurointensivists and (interventional) radiologists in the clinical management of patients with aSAH at the emergency room, during hospital admission and during follow-up, to reduce the risk of case-fatality and long-term disability.

Methods

Composition and approval of the Module Working Group

This guideline was initiated by the ESO. Two chairpersons (M.D.I.V. and N.E.) were selected to assemble and coordinate the Guideline Module Working Group (MWG). The initial working group consisted of 12 experts, 1 of whom withdrew during the guideline development process because of other obligations (G.C., see Acknowledgements). Later, 2 delegates were invited to join on behalf of the European Association of Neurosurgical Societies (EANS; T.R.M.) and the European Society for Minimally Invasive Neurological Therapy (ESMINT, C.A.T.). Thus, the final group contained 13 experts. The ESO Guideline Board and Executive

Committee reviewed the intellectual and financial disclosures of all MWG members and approved the composition of the group. The full details of all MWG members and their disclosures are included in the [Table S1](#). The MWG was supported by 5 non-voting members (A.R.-P., E.-O.T., N.W., L.H., S.T. [see Acknowledgements]).

Development and approval of clinical questions

This guideline was prepared according to the ESO standard operating procedures (SOP),⁵ which are based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.⁶ The MWG developed a list of topics and corresponding questions of greatest clinical interest. Questions were formatted using the PICO approach (Population, Intervention, Comparator and Outcome). We decided on 10 topics for which we formulated 15 PICO questions, which were reviewed by 2 external reviewers as well as members of the ESO Guideline board and Executive Committee.

We considered separate outcomes for the different PICOs due to the different nature of the underlying research questions. Using the Delphi method, the members of the MWG voted in a closed ballot to identify which outcomes were of highest priority, according to the GRADE methodology using a 9-point scale (7–9: critical; 4–6: important; 1–3: of limited importance). The final recommendations are based on those outcomes that have been rated as critical according to the GRADE approach. Results of the outcome ratings for each PICO question are shown in [Table S2](#).

Literature search

For each PICO question, search terms were developed by the MWG and guideline methodologist. Where a validated search strategy was available, this was used or adapted. Where there was a recent relevant systematic review on the question of interest, the corresponding search strategy and results were used and updated as necessary. Search strategies are described in [Supplementary Materials](#).

The search was performed by the ESO Guideline methodologist. The following databases were searched: PubMed, Medline, Cochrane from inception to July 2023. An update search was performed in May 2025. Reference lists of review articles, the authors' personal reference libraries and previous guidelines were also searched for additional relevant records.

Search results were loaded into the web-based Covidence platform (Health Innovation, Melbourne, Australia) for assessment by the MWG. Per PICO question, 2 MWG members formed a "PICO group." The PICO groups consisted of: PICO 1 M.D.I.V., G.C. (see Acknowledgement); PICO 2 M.K., R.H.; PICO 3 P.V., G.J.E.R.; PICO 4

E.C.-G., N.E.; PICO 5 M.-N.P., P.V.; PICO 6 M.H., E.R.G.; PICO 7 T.G., M.H.; PICO 8 R.H., T.G.; PICO 9 G.J.E.R., N.E. and PICO 10 E.R.G., M.-N.P. The MWG members were supported by 3 junior members (A.R.-P., E.-O.T., N.W.) who independently screened (2 per PICO) the titles and abstracts of publications registered in Covidence and then assessed the full text of studies to determine the potential relevance. All disagreements were resolved by discussion between the 2 reviewers and the PICO leads.

We included studies on acute aneurysmal SAH in humans, in which at least 90% of the evaluated aneurysms had to be saccular. We included studies with the following designs: (1) meta-analyses of studies mentioned under 2–6; (2) RCTs; (3) prospective observational/cohort studies; (4) prospective case-control studies; (5) prospective registry studies with external validation; (6) single-arm cohort studies including > 50 patients. We excluded the following studies: (1) studies that did not report death, functional outcome or any clinical outcome of interest to be assessed according to PICO questions; (2) registry studies based on hospital codings/health insurance systems without external validation; (3) studies reporting on aneurysms associated with arteriovenous malformations or in populations with specific diseases (such as collagen disorders, moyamoya disease or syndrome, dwarfism or autoimmune disorders); (4) studies reporting on ruptured iatrogenic aneurysms or iatrogenic rupture of aneurysms during thrombectomy; (5) studies in which patients with ruptured aneurysms could not be distinguished from those with only unruptured aneurysms.

Primary outcome

For all PICO, the primary outcome measure was poor functional outcome, which was defined as a mRS score of 3–6. In studies where a Glasgow Outcome Scale (GOS) score was reported, a GOS 1–3 was used as an equivalent measure.⁷

SAH grading

In the literature on aSAH, different scales are used for describing the clinical condition on admission, such as the Hunt&Hess scale⁸ and World Federation of Neurosurgical Societies (WFNS) scale.⁹ We used the rating scales as described in the cited manuscript. The Hunt&Hess and WFNS scales are explained in Table 1.

Data analysis

L.H. performed data extraction and analysis. In cases where relevant data were not reported in an eligible study, the corresponding author was contacted by the PICO leader. In the case of no response, one of the guideline chairs also contacted the corresponding author. If no answer was received, data were considered as missing.

Where feasible, we conducted fixed-effects meta-analyses, estimating heterogeneity using the REML method, provided no substantial heterogeneity was detected. Results are presented as effect estimates with corresponding 95% CIs. Heterogeneity was assessed using the χ^2 test and quantified with the I^2 statistic. When I^2 exceeded 50%, a random-effects model was applied. We also calculated 95% prediction intervals to account for

Table 1 Scales used to describe the clinical condition of an aSAH patient on admission.

	Hunt&Hess	WFNS	
		Glasgow Coma Scale score	Motor deficit
1	Asymptomatic or mild headache and slight neck stiffness	15	No
2	Moderate-severe headache, neck stiffness, no neurological deficit except cranial nerve palsy	13-14	No
3	Drowsiness, confusion, or mild focal neurological deficit	13-14	Yes
4	Stupor, moderate-severe hemiparesis, early decerebrate rigidity, autonomic disturbance	7-12	± Deficit
5	Deep coma, decerebrate rigidity, moribund appearance	3-6	± Deficit

Abbreviation: aSAH = aneurysmal subarachnoid haemorrhage; WFNS = World Federation of Neurosurgical Societies.

between-study variability. Results are displayed using forest plots. All analyses were performed in R using the meta package.¹⁰

Evaluation of the quality of evidence and formulation of recommendations

The risk of bias of each included randomised trial was assessed with the Cochrane RoB2 tool.¹¹ As recommended, the evidence synthesis did not use a quality “score” threshold but classified overall risk of bias at the study level and then in the aggregate.¹²

The results of data analysis were imported into the GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.). For each PICO question and each outcome, the following were considered: risk of bias based on the type of available evidence (randomised or observational studies); considerations on inconsistency of results; indirectness of evidence, imprecision of results and other possible bias. LH generated the GRADE evidence profiles/summary of findings tables, which MWG members used to prepare “Evidence-based recommendations,” based on the GRADE approach. The direction, strength and formulation of the recommendations were determined according to the GRADE evidence profiles and the ESO-SOP (Table 2).^{5,6} The phrasing of the recommendations was extensively discussed between all MWG members until consensus was reached.

Finally, expert consensus-statements were added whenever the PICO group considered that there was insufficient evidence available to provide evidence-based recommendations and where practical guidance is needed for routine clinical practice. Expert consensus statements were modified using the Delphi method until consensus was reached regarding the phrasing of the statement. The expert consensus statements were then sent to all MWG-members for anonymous voting. According to the ESO SOP for guidelines,⁵ only those consensus statements that reached a majority of votes are reported in the guideline. Importantly, these expert consensus statements should not be regarded as evidence-based recommendations, since they only reflect the opinion of the writing group.

Table 2 Formatting based on strength of recommendations.

Strength of recommendation	Balance of desirable and undesirable consequences	Recommendation formatting
Strong recommendation for intervention	The desirable consequences clearly outweigh the undesirable consequences in most settings	“We recommend”
Strong recommendation against intervention	The undesirable consequences clearly outweigh the desirable consequences in most settings	“We recommend...not”
Weak recommendation for intervention	The desirable consequences probably outweigh the undesirable consequences in most settings	“We suggest”
Weak recommendation against intervention	The undesirable consequences probably outweigh the desirable consequences in most settings or when the balance between desirable and undesirable consequences is closely balanced or uncertain	“We suggest...not”
Ungraded consensus-based statement	The desirable consequences probably outweigh the undesirable consequences in most settings, but there is little evidence	“We suggest”

Drafting of the document, revision and approval

Each PICO question was addressed in distinct sections, in line with the updated ESO SOP.⁵ First, the “Analysis of current evidence” section summarised current pathophysiological considerations followed by a summary and discussion of the results of the identified RCTs and other studies. Second, “Additional information” was added when more details on the studies referred to in the first section were needed to provide information on key subgroup analyses of the included studies, on ongoing or future RCTs, and on other studies which can provide important clinical guidance on the topic. Third, an “Expert consensus statement” paragraph was added whenever the MWG considered that insufficient evidence was available to provide evidence-based recommendations for situations in which practical guidance is needed for everyday clinical practice.

The Guideline document was reviewed by all MWG members and modified using a Delphi approach until a consensus was reached. The final submitted document was peer-reviewed by 2 external reviewers, 2 members of the ESO Guideline Board and 1 member of the Executive Committee.

Results

An overview of the risk of bias assessments of the included trials is shown in [Figure S1](#). The GRADE evidence profiles that informed the evidence-based recommendations are shown in [Tables S4–S14](#).

Topic 1. Medical (non-)invasive treatment to decrease the risk of rebleeding and poor functional outcome

PICO 1a

In adult patients with aneurysmal subarachnoid haemorrhage (aSAH), does treatment with antifibrinolytic drugs compared to no antifibrinolytic drugs decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, we recommend against routine administration of antifibrinolytic drugs prior to treatment of the ruptured aneurysm to decrease the risk of poor functional outcome.	⊕⊕⊕	↓

Analysis of current evidence

We identified 12 RCTs comparing treatment with antifibrinolytic drugs vs no antifibrinolytic drugs, and 1 recent Cochrane review.^{13–25} Eleven RCTs^{14–24} studied the effect of tranexamic acid, and 1 trial¹³ the effect of epsilon amino-caproic acid on aneurysm rebleeding or functional outcome. Ten RCTs were performed in an era during which aneurysm treatment was postponed to the post-delayed cerebral ischaemia (DCI) period. In those trials, the effect of long-term treatment with antifibrinolytic drugs was studied. The 2 most recent RCTs studied the effect of

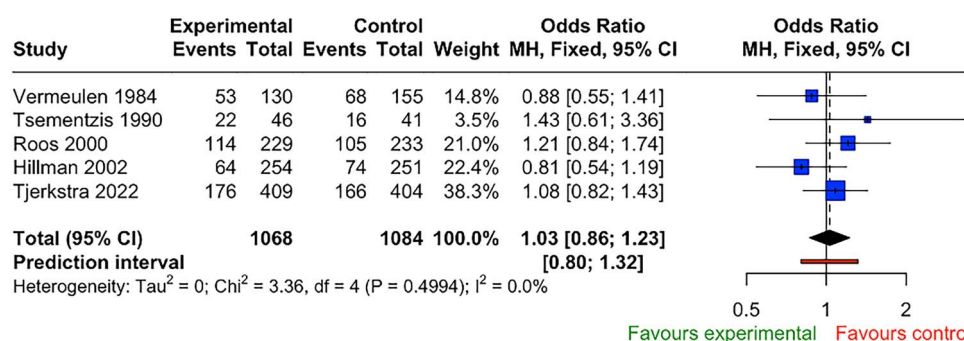


Figure 1 Effect (odds ratio) of antifibrinolytic drugs compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage.

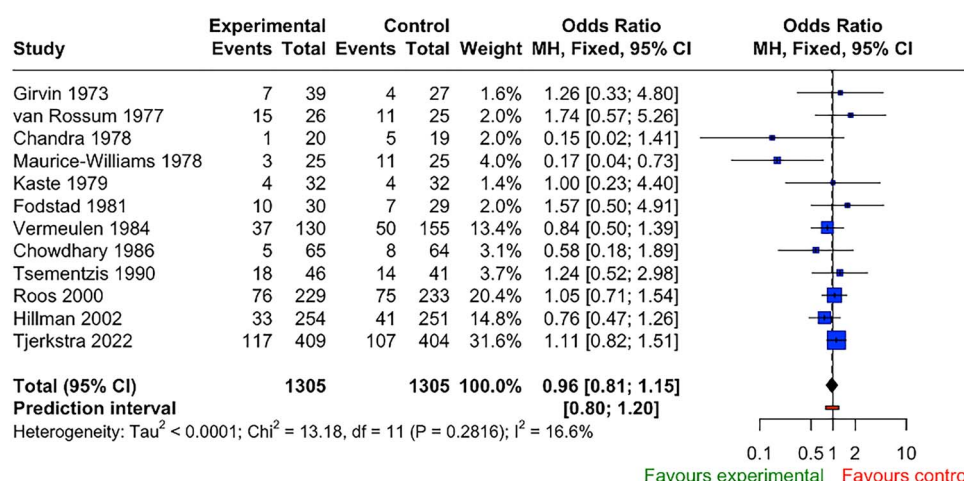


Figure 2 Effect (odds ratio) of antifibrinolytic drugs compared with control on case-fatality in adults with aneurysmal subarachnoid haemorrhage.

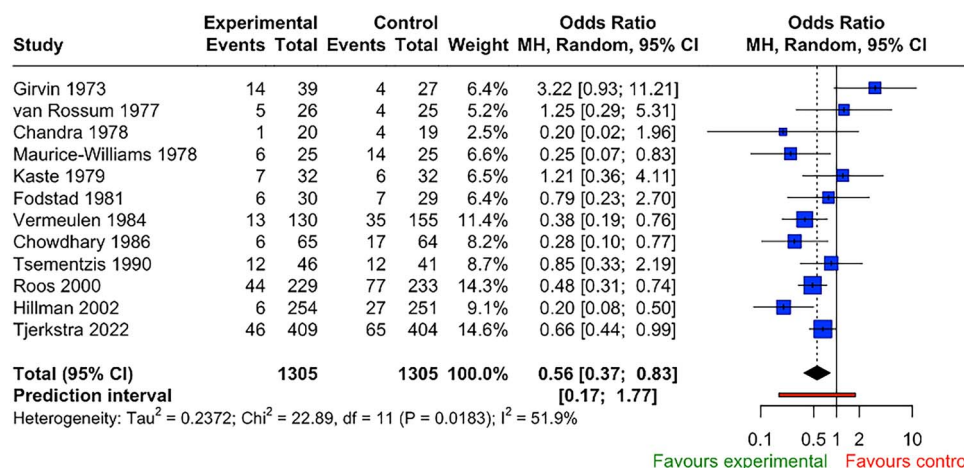


Figure 3 Effect (odds ratio) of antifibrinolytic drugs compared with control on rebleeding in adults with aneurysmal subarachnoid haemorrhage.

short-term treatment.^{20,23} The largest RCT also included patients with non-aneurysmal SAH.²³ From that trial, we extracted data on patients with aneurysmal SAH.²⁶

Pooled analyses of all available RCTs showed that treatment with antifibrinolytic drugs does not decrease the risk of poor functional outcome (odds ratio [OR]: 1.03; 95% CI, 0.86–1.23; Figure 1) or case-fatality (OR: 0.96; 95% CI, 0.81–1.15; Figure 2), despite a decreased risk of rebleeding (risk ratio [RR]: 0.56; 95% CI, 0.37–0.83; Figure 3). The discrepancy between a reduced risk of rebleeding and a neutral effect on outcome has been explained as resulting from a higher risk of ischaemic complications and

hydrocephalus in patients treated with antifibrinolytic drugs, or impeded recovery from ischaemic injury.

The 2 most recent RCTs were performed in an era that reflects current clinical practice with early aneurysm treatment and both microsurgical and endovascular aneurysm treatment options.^{20,23} Only the Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA) trial was adequately powered to detect a potential effect on clinical outcome.²³ In ULTRA, tranexamic acid was started in the initial hospital directly after head CT confirmed a diagnosis of SAH. The median time between ictus and CT diagnosis was 93 min, and the time between ictus and the start of

tranexamic acid was 185 min. Treatment of the ruptured aneurysm occurred after a median time of 14 h after CT diagnosis. In the 955 participants with SAH, tranexamic acid had no statistically significant effect on rebleeding (OR: 0.71; 95% CI, 0.48–1.04) and did not decrease the odds of poor functional outcome (OR: 1.16; 95% CI, 0.89–1.50) or case-fatality (OR: 1.15; 95% CI, 0.86–1.54) in the whole study population.

Similar results were found in the subgroup of 813 patients with aneurysmal SAH. Although a statistically significant reduction in rebleeding was observed (OR: 0.66; 95% CI, 0.44–0.99), no effect on poor functional outcome (OR: 1.08; 95% CI, 0.82–1.43) or case-fatality (OR: 1.11; 95% CI, 0.82–1.51) was found. Short-term treatment with tranexamic acid did not increase the risk of DCI (OR: 0.99; 95% CI, 0.72–1.36)²⁶ or hydrocephalus (OR: 1.23; 95% CI, 0.93–1.63). In conclusion, the ULTRA trial provided strong evidence that very early and very short-lasting antifibrinolytic therapy does not decrease the risk of poor functional outcome in patients with aSAH.

Additional information

After publication of the ULTRA trial, several studies were performed to investigate the effect of tranexamic acid in certain subgroups. Patients with a good clinical condition on admission and men treated with tranexamic acid had worse functional outcomes compared to those not treated with tranexamic acid.²⁷ No effect on outcome was observed in patients with a poor clinical condition on admission and in women. Although the start of tranexamic acid > 6 h after ictus was associated with a reduced risk of rebleeding, it did not result in better outcomes.²⁸

PICO 1b

In adult patients with aSAH, does treatment with antihypertensive drugs compared to no antihypertensive drugs decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on the administration of blood pressure lowering drugs prior to treatment of the ruptured aneurysm to decrease the risk of poor functional outcome.	⊕	–

Expert consensus statements:

- In adult patients with aSAH and systolic blood pressures higher than 160–180 mm Hg persisting after installment of analgesics, oral nimodipine and urinary catheter prior to aneurysm treatment, we suggest considering blood pressure lowering drugs to lower systolic blood pressure to around 160 mm Hg to reduce the risk of rebleeding.

Vote: 11/13

- If it is decided to give blood pressure lowering drugs, we suggest continuous infusion of short-acting drugs, e.g. labetalol, and avoiding diuretic drugs to maintain normovolemia. Care should be taken to ensure that the blood pressure reduction is gradual, with systolic blood pressure reduced cautiously over time (corresponding to no more than a 10% reduction in mean arterial pressure within the first 2 hours) to decrease the risk of DCI.

Vote: 11/13

Analysis of current evidence

We did not identify any RCTs during the last 4 decades investigating the effect of antihypertensive drugs with the primary aim of decreasing the risk of rebleeding of the ruptured aneurysm and thereby improving outcome.

Additional information

Several observational studies investigated the relationship between antihypertensive drug treatment and the risk of rebleeding.^{29–32} One study showed that blood pressure treatment may decrease the risk of rebleeding, but not poor outcome, potentially as a result of an increased risk of cerebral infarction.²⁹ A study without a control group found that the incidence of rebleeding was low (3.1%) after the implementation of a strategy of intensive systolic blood pressure reduction (target 120 ± 20 mm Hg).³⁰ Another study found that after the implementation of a blood pressure management protocol (systolic blood pressure target of 160 mm Hg), the incidence of in-hospital rebleeding declined from 6.7% to 2.8% (OR: 0.4; 95% CI, 0.10–1.63) and the incidence of DCI from 44.2% to 7.7% (OR: 0.10; 95% CI, 0.04–0.23).³¹ A recent study compared the incidence of in-hospital rebleeding between a hospital with a policy of aggressive blood pressure lowering (systolic blood pressure target before aneurysm treatment ≤ 140 mm Hg) vs a hospital with a more liberal blood pressure approach, and found a trend (adjusted HR 0.66 [95% CI, 0.23–1.92]) towards a lower incidence of rebleeding in the hospital with a more aggressive blood pressure lowering strategy. However, there were differences in risk factors for rebleeding between the 2 centres, which introduced major bias.³²

PICO 2

In adult patients with aSAH, does early aneurysm occlusion compared to no early aneurysm occlusion decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on treating the ruptured aneurysm as early as possible to decrease the risk of poor functional outcome.	⊕	–

Expert consensus statement

In adult patients with aSAH, we suggest treatment of the ruptured aneurysm within 24 hours after ictus. The timing should be optimized to ensure that the most dedicated team of experts is available when needed.

Vote: 13/13

Analysis of current evidence

We identified only one small RCT that assessed the timing of aneurysm treatment.³³ The study was conducted in the pre-coiling era and included 211 good-grade (Hunt and Hess grades I–III) aSAH patients (aged 16 to 65 years) admitted to a single hospital between 1985 and 1987. Patients with intracerebral haematomas, decreased level of consciousness or severe neurological deficits were excluded. All included patients had anterior circulation aneurysms, and patients were randomly assigned to early (0–3 days), intermediate (4–7 days) or late (8 days and later) surgical clipping. Sixteen patients never underwent aneurysm surgery due to severe deterioration or death before

the planned surgery. Delayed cerebral ischaemia and rebleeding were the main causes of preoperative deterioration. None of the patients received antifibrinolytic agents or hypertensive drug treatment, while intramuscular betamethasone 4 mg 4 times daily was routinely given. Of the 211 patients, 159 randomly received either intravenous followed by oral nimodipine or placebo treatment up to 21 days. The 3-month case-fatality rates were not different between early, intermediate and late surgery groups (case-fatality rates of 6%, 6% and 13%, respectively). Using a 3-point outcome scale (independent, dependent, death), 92% of the early surgery group patients were independent at 3 months, 79% in the intermediate group and 80% in the late surgery group. However, dependency was significantly higher in the intermediate surgery group (11 patients, 16%) in comparison to the early surgery group (2 patients, 3%). In summary, early surgery within 3 days after bleeding in comparison to delayed surgery did not lead to higher case-fatality. A comparison between early and intermediate surgery groups (late surgery group excluded) suggested that 3-month functional outcome was better for patients operated early.

During the endovascular treatment era (since the early 1990s), no randomised trial has addressed the effect of timing of aneurysm occlusion on outcome of SAH patients.

Additional information

Due to the paucity of high-quality studies, recent (published within the last 10 years) meta-analyses were reviewed as supporting information. These meta-analyses generally include lower quality studies, which have inherent selection and treatment biases. In a meta-analysis including 16 observational studies of endovascular aneurysm occlusion, treatment within 24 h reduced the odds for poor outcome in comparison to patients treated at > 1 day, but not when compared to 24–72 h.³⁴ Another meta-analysis of surgical patients included the only published randomised trial,³³ 1 prospective and 12 retrospective studies for quantitative analyses.³⁵ Early surgery, defined as surgery within 3 days,³⁵ was associated with better outcomes irrespective of the clinical condition on admission and a higher survival rate. Similarly, in a third meta-analysis published in 2017, aneurysm treatment within 48 h was compared to treatment between 48 h and 7 days, and to delayed (>7 days) treatment of poor-grade SAH patients.³⁶ The meta-analysis included all published studies (even small case series) between 1990 and 2014 that reported on surgical or endovascular treatment for poor-grade SAH patients.³⁶ A total of 26 studies with 1255 patients assessed outcomes by treatment timing.³⁶ Based on these highly miscellaneous data, the authors concluded that poor-grade SAH patients treated within 48 h had the highest rates of good neurological outcome (61% compared to 40% for treatment between 48 h and 7 days, and 37% for delayed treatment).³⁶ In another meta-analysis including also only poor-grade SAH patients (14 articles, 1111 patients), aneurysm treatment within < 24 h from symptom onset, clipping or coiling, was not associated with a decreased risk of poor functional outcome when compared to delayed (>24 h) treatment.³⁷ The results between studies were inconsistent and depended on statistical methods used.³⁷

It is estimated that treatment < 1 day results in, at most, a 0.3% reduction in the incidence of rebleeding³⁸ as the rebleeding incidence depends strongly on the admission delay; most rebleeds occur before hospital admission or at the emergency room. In terms of poor outcome, it has been estimated that emergency aneurysm occlusion (within 4 h from admission, not from ictus) can reduce poor outcome due to rebleeding only in 0.4% (95% CI, 0.2–1.1) of patients.³⁹ In other words, 250 SAH patients would have to be treated within 4 h from admission to prevent one poor outcome due to rebleeding.³⁹

Topic 3. Aneurysm treatment modality

PICO 3a

In adult patients with aSAH, does any type of endovascular aneurysm occlusion compared to neurosurgical aneurysm occlusion decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH in good clinical condition (WFNS I–III) with aneurysms of either the anterior or posterior circulation that can be treated by either regular coiling (i.e. without adjunctive devices) or neurosurgical clipping, we recommend regular coiling as the preferred strategy to decrease the risk of a poor functional outcome.	⊕⊕⊕⊕	11

Expert consensus statements

1. We suggest that all patients with aSAH are discussed in an interdisciplinary manner, with at least one neurosurgeon and one neuro-interventionalist.
Vote: 13/13
2. In adult patients with aSAH, we suggest that the team discuss which modality would result in the best clinical outcome of the specific patient, with the safest and optimal occlusion of the specific aneurysm.
Vote: 13/13
3. In adult patients with aSAH younger than 45 years of age, we suggest that the better long-term protection from clipping compared to coiling is taken into consideration for choosing the treatment modality of the aneurysm.
Vote: 12/13
4. In adult patients with aSAH admitted in a poor clinical condition (defined as GCS < 13), we suggest a multidisciplinary approach to decide on type and timing of aneurysm treatment taking into account the (presumed) cause of the poor clinical condition.
Vote: 13/13
5. In adult patients with aSAH and a poor or worsening clinical condition from a space-occupying intracerebral or subdural haematoma, we suggest immediate surgery for aneurysm clipping and haematoma removal.
Vote: 11/13

Analysis of current evidence

A Cochrane systematic review included 4 randomised clinical trials involving 2458 participants that compared neurosurgical clipping vs endovascular coiling.⁴⁰ The evidence in this Cochrane review comes mainly from the largest of these 4 trials (International Subarachnoid Haemorrhage Trial [ISAT]: 2143 participants). Most patients were in good clinical condition (WFNS I–III) and had an aneurysm on the anterior circulation. At 1 year after SAH,

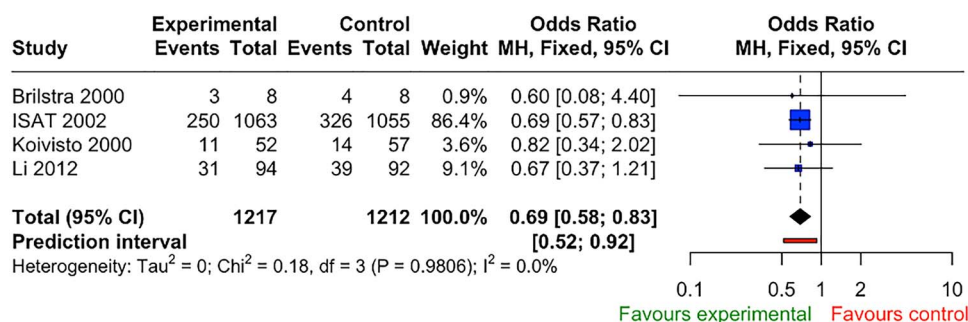


Figure 4 Effect (odds ratio) of endovascular coiling compared with neurosurgical clipping on 12-month poor functional outcome with aneurysmal subarachnoid haemorrhage.

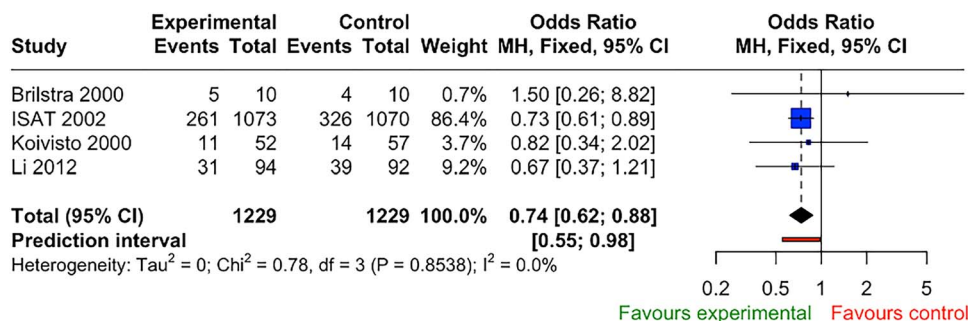


Figure 5 Effect (odds ratio) of endovascular coiling compared with neurosurgical clipping on 12-month poor functional outcome with aneurysmal subarachnoid haemorrhage (worst-case scenario).

the OR of poor outcome (death or dependency) for endovascular coiling vs neurosurgical clipping was 0.69 (95% CI, 0.58–0.83; Figure 4), with an absolute risk reduction of poor outcome of 7% (95% CI, 4%–11%). The better outcome after coiling was substantiated in the worst-case-scenario analysis in which all patients lost to follow-up after coiling were given a poor outcome and those lost to follow-up after clipping a good outcome. In this worst-case scenario, the OR for poor outcome for endovascular coiling vs neurosurgical clipping was 0.74 (95% CI, 0.62–0.88; Figure 5), and the absolute risk reduction was 6% (95% CI, 2%–10%). In the subgroup of patients with a posterior circulation aneurysm (2 trials, 69 participants), the OR for poor outcome was 0.27 (95% CI, 0.09–0.82; Figure S2) and the absolute decrease in risk of poor outcome was 27% (95% CI, 6%–48%).

The data from this review therefore show that coiling is associated with better clinical outcomes for patients in good clinical condition with ruptured aneurysms of either the anterior or posterior circulation that are suitable for both neurosurgical clipping and endovascular coiling. This review provides evidence of the benefit of regular endovascular coiling only, because no randomised trials were included on balloon- or stent-assisted coiling or for other endovascular procedures, such as intrasaccular devices or flow-diverting stents.

Patients with middle cerebral artery (MCA) aneurysms were underrepresented in this review, and for patients with aSAH in poor clinical condition, the review found no reliable randomised evidence comparing the potential harms and benefits of endovascular coiling vs neurosurgical clipping. It must also be noted that most patients admitted to the participating hospitals at time of enrolment of the randomised trial have been treated outside the

trial. The results from these trials can therefore, as for any other trial, only be extrapolated to patients fulfilling the inclusion and exclusion criteria of these trials. The overarching inclusion criterion in all these trials was equipoise for both treatment options.

Long-term follow-up was available for ISAT, but not for the other trials included in the review. At 10 years, the OR of poor outcome for endovascular coiling vs neurosurgical clipping was 0.70 (95% CI, 0.56–0.88; Figure S3).

Additional information

One other controlled trial has been performed to compare neurosurgical clipping and endovascular treatment: the Barrow Ruptured Aneurysm Trial (BRAT).⁴¹

The BRAT was a single-centre clinical trial excluded from the Cochrane review due to major methodological limitations. It was not truly randomised (patients were allocated alternately), the protocol was unpublished and the trial was unregistered. Patients without aneurysms or with aneurysms unsuitable for 1 treatment were included, and 30% did not receive their assigned treatment, causing group imbalance. Missing outcomes (10%–15%) were excluded at 1 year, no intention-to-treat analyses were done after 3 years and subgroup analyses were not prespecified, leading to a very high risk of bias.

At 1 year, patients assigned to coiling had better outcomes than those assigned to clipping. However, at 3, 6 and 10 years no outcome differences were found. At 10 years, complete obliteration occurred in 93% of clipped vs 22% of coiled aneurysms, with rebleeding in 2/83 coiled patients and none of the 175 clipped patients.

For patients in good or moderate clinical condition (WFNS I–III) with aneurysms of either the anterior or posterior circulation that can be treated by either regular coiling or neurosurgical clipping, we have good evidence that coiling is associated with better clinical outcomes. The results of the trials cannot be generalised to the whole population of patients with ruptured aneurysms and to all endovascular and microsurgical techniques available today. For patients in a poor clinical condition and for those with an aneurysm that cannot be treated by regular coiling, there is no reliable randomised evidence comparing the potential harms and benefits of endovascular coiling vs neurosurgical clipping. In the following, we list patient populations where decisions have to be made on less robust data, based on an individual, interdisciplinary decision-making process. We here provide the data underlying our expert consensus statement.

Patients in poor condition

Patients with space-occupying haematomas were not included into the listed trials. This is still a patient population where the priority for microsurgical evacuation of the haematoma is the driver for the decision to rapidly operate these patients and clip the aneurysm in the same setting.

Age

Patients of lower age might be considered differently. Although the trials included in the Cochrane review did not specify subgroups according to age, it has been argued that the advantage of coil embolisation over clip ligation cannot be assumed for patients < 40 years old. In this age range the difference in the safety of the 2 procedures is small, and the better long-term protection from aSAH afforded by clip placement may give this treatment an advantage in life expectancy for patients < 45 years of age.⁴²

Complex aneurysm morphology

Patients harbouring aneurysms of complex anatomy are under-represented in the trials. The role of the aneurysm anatomy as a driver of decision making thus remains unclear. The current evidence fails to show superiority for any treatment modality in the case of aneurysms > 10 mm, broad necked aneurysms (usually defined as neck width $\geq$ 4 mm or dome-to-neck ratio < 2), branching vessels arising from the aneurysm neck, fusiform aneurysms, blister aneurysms, etc. Similarly, the complexity of the aneurysm anatomy does not support the preferential use of endovascular implants other than coils over microsurgical clipping.

Finally, the results obtained in the trials are limited to interdisciplinary neurovascular centres where treating physicians have sufficient experience in the treatment of these patients during the whole complex course following subarachnoid haemorrhage.

PICO 3b

In adult patients with aSAH, does any type of endovascular aneurysm treatment other than coiling compared to coiling of the ruptured aneurysm decrease the risk of poor functional outcome?

Analysis of current evidence

The trials included in the Cochrane review⁴⁰ and BRAT⁴¹ compared endovascular coiling vs neurosurgical clipping. Since

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on the use of endovascular treatment options other than regular coiling for treatment of the ruptured aneurysm to decrease the risk of poor functional outcome.	⊕	-

Expert consensus statements

1. Given the limited comparative evidence available, we suggest that in adult patients with subarachnoid haemorrhage from a ruptured aneurysm which cannot be treated with regular coiling, the multidisciplinary team discusses the safety, effectiveness, and durability of microsurgical and alternative endovascular options to determine the preferred treatment strategy.

Vote: 12/13

2. In adult patients with aSAH, we suggest stent-assisted coiling in selected cases where other treatment options are not feasible.

Vote: 13/13

3. In adult patients with aSAH, we suggest to reserve flow diversion as a last-line treatment option.

Vote: 12/13

the implementation of coils, advanced endovascular devices, such as balloon-assisted coiling, stent-assisted coiling, flow diverting stents and intrasaccular devices, have been introduced with the aim to treat ruptured aneurysms not suited for regular coiling, eg, wide-neck aneurysms. These newer devices have enabled the endovascular repair of more complex aneurysms, but these devices also differ with respect to immediate and long-term occlusion rates as well as risks of complications, compared to coiling or microsurgical clipping. So far, only one trial has been initiated to test the superiority of endovascular management of patients with ruptured aneurysms, in which all endovascular means were included: The ISAT-2.⁴³

International Subarachnoid Haemorrhage Trial-2 was a randomised trial comparing any endovascular vs microsurgical treatment of ruptured intracranial aneurysms, focusing on those excluded from previous trials. The trial was stopped after 10 years because of slow recruitment when 270 of the 1896 planned patients had been enrolled. In total, 133 patients were randomised to microsurgical aneurysm treatment and 130 to endovascular treatment. Seven patients were excluded. This trial differed from the previous trials in the type of endovascular treatment, which was most often balloon-assisted coiling (83%). The other patients were treated with stents or flow-diverters. Moreover, 40% of the ruptured aneurysms were on the MCA, an anatomical location that was underrepresented in the previous Cochrane review. In the intention-to-treat analysis, poor outcome had occurred in 35 (27%) of 130 endovascular patients and in 40 (30%) of 133 surgical patients (RR: 0.90; 95% CI, 0.61–1.31). Residual aneurysms at 1 year were less frequent with microsurgery (10/118 [8%, 95% CI, 5%–15%]) than EVT (22/109 [20%, 95% CI, 14%–29%]). Because the trial was terminated prematurely, it lacked statistical power to rule in or out statistically significant results. Thus, for endovascular

procedures other than coiling, there is no reliable evidence from randomised trials comparing these treatments vs neurosurgical clipping.

Additional information

Stent-assisted coiling

Evidence supporting stent-assisted coiling for ruptured intracranial aneurysms remains limited and heterogeneous. A systematic review on 17 retrospective case series published before 2010 totalling 339 patients⁴⁴ highlighted substantial variability across published case series. The pooled results suggested higher rates of complications than with regular coiling, with clinically significant intracranial haemorrhagic complications in 8% and clinically significant thromboembolic events in 6% of patients. In a subsequent systematic review and meta-analysis⁴⁵ on 8 retrospective cohort studies with 1408 ruptured intracranial aneurysms treated before 2016, ischaemic complications occurred more often in the stent-assisted group (16.6% vs 11.0%; RR: 1.75; 95% CI, 1.3–2.36), as did haemorrhagic complications (10.3% vs 5.7%; RR: 1.6; 95% CI, 1.09–2.35), compared to regular coiling. More recent prospective multi-centre registry data provide additional insight into contemporary practice. A Chinese prospective registry study reporting on 278 patients with aneurysmal SAH from wide-neck aneurysms treated with stent-assisted coiling⁴⁶ between 2020 and 2023 found clinically relevant thromboembolic complications in 11.5% of patients and clinically relevant haemorrhagic complications in 4.7%.

In conclusion, there is no good controlled evidence on stent-assisted coiling compared to regular coiling, and the observational studies suggest a high risk of complications.

Balloon-assisted coiling

In contrast to stent-assisted coiling, balloon remodelling does not involve permanent intravascular implants and does not require antiplatelet therapy. A meta-analysis on studies published between 1997 and 2006⁴⁷ reported no statistically significant differences in procedural complications between balloon-assisted and regular-unassisted coiling. However, the meta-analysis was criticised for its methodology and the exclusion of articles reporting higher complication rates.^{48–50} A French prospective, multicentre observational study on 768 patients treated from November 2006 to September 2008 (CLARITY)⁵¹ reported a significantly higher rate of adequate angiographic occlusion with balloon-assisted coiling (94.9%), compared with regular coiling (88.7%) ($P = .017$), while overall rate of treatment-related complications, with or without clinical manifestations, was similar in both treatment groups (17.4% with coil embolisation and 16.9% with remodelling). Thus, good comparative and recent data on balloon-assisted coiling vs regular coiling are lacking. The few available data suggest that balloon remodelling has a safety profile comparable to regular coiling.

Flow diversion

Flowdiverting stents were designed for treatment of complex aneurysms, such as wide-necked sidewall aneurysms or blood blister-like aneurysms. However, they are increasingly used for other indications, eg, bifurcation aneurysms. The use of flowdiverting stents in patients with aSAH remains controversial, because they require stent deployment in the acute phase, often without adequate antiplatelet preparation, which increases the

risk of thromboembolic complications. In addition, mandatory dual antiplatelet therapy increases the risk of haemorrhagic complications during necessary neurosurgical interventions (eg, external ventricular drain [EVD] placement). Because flow diversion does not immediately exclude the aneurysm from the circulation, there is a persistent risk of early rebleeding in the acute period. A meta-analysis including 20 studies (17 retrospective) published before 2018 evaluating 223 patients with acutely ruptured intracranial aneurysms treated with flow-diverter stents found that the risk of rebleeding after treatment was 4%, all occurring within 72 h after treatment.⁵² The overall risk of treatment complications was 17.8%, with the majority being ischaemic complications.

No studies are available in which the use of flowdiverting stents are compared to regular coiling (without additional stent) or to surgical clipping in patients with ruptured aneurysms. Observational studies suggest that the use of flow diversion in recently ruptured aneurysms is associated with a high risk of ischaemic and haemorrhagic complications.

Intrasaccular devices

Although intrasaccular devices (also known as endosaccular flow disruptors) were specifically designed for treatment of wide-neck saccular aneurysms, their use has expanded to other indications. A meta-analysis⁵³ of 16 studies published before 2024 compared the Woven EndoBridge (WEB) with either stent-assisted coiling or regular coiling, and included both studies with unruptured and ruptured intracranial aneurysms. The total risk of complications was approximately 6.5% in patients treated with WEB, compared with 14% in patients treated with stent-assisted coiling and 12% in regular coiling. The rates of adequate and complete occlusion during follow-up were similar in the 3 treatment groups, although patients treated with WEB had a shorter follow-up duration. The CLARYS study was a prospective multicentre study conducted in 13 European centres that enrolled 60 patients with a ruptured aneurysm in the anterior or posterior circulation.⁵⁴ Twenty-three periprocedural complications occurred in 18 patients and resolved without sequelae in 16 patients. Two of these complications were attributed to the procedure and/or the use of the WEB, leading to a procedure/device-related intraoperative complication rate of 3.3%. WEB-related 1-month and 1-year morbidity and mortality were 0%. At 1 year, 19/46 aneurysms (41.3%) were completely occluded (Raymond-Roy grade I), 21/46 (45.7%) had a residual neck and 6/46 (13.0%) had residual aneurysm filling.⁵⁵ Six patients (13%) underwent target aneurysm re-treatment within 1 year. Currently, there are no prospective long-term (>10 years) follow-up studies available with large numbers of patients and independent core lab assessments.

PICO 4

In adult patients with aSAH, does any type of pharmacological or interventional treatment aiming to reduce the risk of DCI compared to no such treatment decrease the risk of poor functional outcome?

Analysis of current evidence

We systematically reviewed the literature for RCTs evaluating pharmacological and interventional strategies for DCI prevention.

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, we recommend prophylactic treatment with oral nimodipine to decrease the risk of poor functional outcome.	⊕⊕⊕⊕	↑↑

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, we do not recommend prophylactic treatment with either tirilazad, statins, magnesium sulfate, or endothelin receptor antagonists to decrease the risk of poor functional outcome.	⊕⊕⊕	↓↓

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on prophylactic treatment with antiplatelet drugs or lumbar drainage to decrease the risk of poor functional outcome until further data from RCTs are available.	⊕⊕	–

Only strategies investigated in at least 3 RCTs were included. In the first paragraph, we present the available evidence for calcium antagonists. Following the publication of the BRANT trial⁵⁶ and several other RCTs, oral nimodipine became the standard of care for preventing DCI in Europe, consistent with the recommendations from previous ESO guidelines.⁴ Therefore, the subsequent paragraphs on other treatment strategies analysed only those RCTs in which patients received nimodipine as a standard of care. Pharmacological and interventional strategies were categorised based on their mechanism of action, with some categories containing a single drug and others encompassing multiple drugs with similar pharmacodynamic properties.

Treatment protocols varied considerably across studies, particularly regarding dosing regimens and duration of therapy. In trials with multiple intervention arms (eg, different dosages), all intervention groups were aggregated and compared against the control group. To maintain methodological consistency, only intention-to-treat analyses from RCTs were considered.

Since the current definition of DCI was standardised in 2010,⁵⁷ earlier studies employed surrogate measures such as delayed ischaemic neurological deficits or symptomatic vasospasm. For this analysis, these outcomes were consolidated under the broader definition of DCI to enable pooling of studies.

Calcium antagonists

Calcium antagonists can induce vasodilation by inhibiting calcium influx into vascular smooth muscle. Therefore, calcium antagonists have been investigated for the prevention of DCI after aSAH. For our analysis, we included 7 RCTs comparing oral or intravenous (IV) nimodipine to placebo,^{56,58–63} as well as one trial comparing nicardipine with placebo,⁶⁴ involving a total of 2276 patients. Trials comparing different doses of nicardipine or IV nimodipine were excluded. We also reviewed 3 meta-analyses, including 1 Cochrane review,^{65–67} but no additional data were retrieved from these meta-analyses.

Overall, treatment with calcium antagonists was associated with a reduction in poor functional outcome (OR: 0.75; 95% CI, 0.61–0.93; [Figure 6](#)) and cerebral infarction (OR: 0.58; 95% CI, 0.35–0.95; [Figure S4](#)), but not of case-fatality (OR: 0.82; 95% CI, 0.66–1.02; [Figure S5](#)). The positive effect of calcium antagonists

on poor functional outcome was driven by trials investigating the effect of oral nimodipine, which showed a reduction in poor functional outcome (OR: 0.56; 95% CI, 0.40–0.76; [Figure 6](#)), but not of case-fatality (OR: 0.74; 95% CI, 0.53–1.02; [Figure S5](#)). A Cochrane review⁶⁶ similarly reported no overall association between nimodipine treatment and case-fatality, although a statistically significant reduction was observed after excluding studies of lower methodological quality (RR: 0.82; 95% CI, 0.67–0.99). Collectively, these results indicate continued uncertainty regarding nimodipine's efficacy in reducing case-fatality.

Tirilazad

Tirilazad inhibits lipid peroxidation and scavenges free radicals, thereby protecting cell membranes from oxidative damage. In experimental SAH models, tirilazad improved cerebral blood flow (CBF), reduced angiographic vasospasm and decreased infarct volume.⁶⁸

The potential protective effect of tirilazad was evaluated in patients with aSAH in 1 phase 2 trial⁶⁹ and 4 phase 3 RCTs conducted between 1995 and 1999, including almost 4000 patients.^{68,70–72} Additionally, a Cochrane review published in 2010⁷³ further analysed its efficacy and safety, but no additional data were retrieved.

Our meta-analysis showed that tirilazad does not reduce poor functional outcome (OR: 0.97; 95% CI, 0.84–1.12; [Figure 7](#)), or case-fatality (OR: 0.68; 95% CI, 0.42–1.09; [Figure S6](#)). Tirilazad reduced the incidence of DCI (OR: 0.80; 95% CI, 0.70–0.93; [Figure S7](#)), but not cerebral infarction (OR: 0.96; 95% CI, 0.58–1.58; [Figure S8](#)).

Statins

Statins not only decrease cholesterol levels but also have anti-inflammatory and antioxidant properties, improve endothelial function via increased nitric oxide (NO) production and reduce endothelin-1 (ET-1) levels.⁷⁴ Since many of these pathways are probably involved in the pathogenesis of DCI, statins have been extensively investigated in aSAH patients for DCI prevention.

We identified 10 RCTs conducted between 2005 and 2020,^{75–84} which included a total of 1575 patients. In 6 out of 10 studies, nimodipine was administered as standard care to all patients.^{75,77,78,80,82,83} Of these 6 studies, 4 investigated simvastatin,^{78,80,82,83} 1 investigated atorvastatin,⁷⁵ and 1 pravastatin.⁷⁷ Four trials were phase 2 studies^{77,78,82,83} and 3 trials had fewer than 50 participants.^{78,82,83} We also reviewed 7 meta-analyses^{85–91} to double-check whether all available RCTs were included in the current PICO, and to check whether or not additional data were presented in the existing reviews. However, no additional data were identified.

Overall, statin treatment did not reduce the incidence of poor functional outcome (OR: 1.09; 95% CI, 0.86–1.38; [Figure 8](#)), case-fatality (OR: 1.25; 95% CI, 0.85–1.83; [Figure S9](#)) or DCI (OR: 1.00; 95% CI, 0.33–3.07; [Figure S10](#)). Cerebral infarction was not analysed in the included studies.

Magnesium sulphate

Magnesium sulphate exerts pleiotropic effects, including calcium channel blockade, enhanced nitric oxide production, inhibition of NMDA receptors, reduction of inflammatory mediators and antioxidant properties. Its role as a preventive treatment for DCI has been evaluated in 13 RCTs^{92–103} conducted between 2002 and 2018, involving a total of 2944 patients. Each RCT

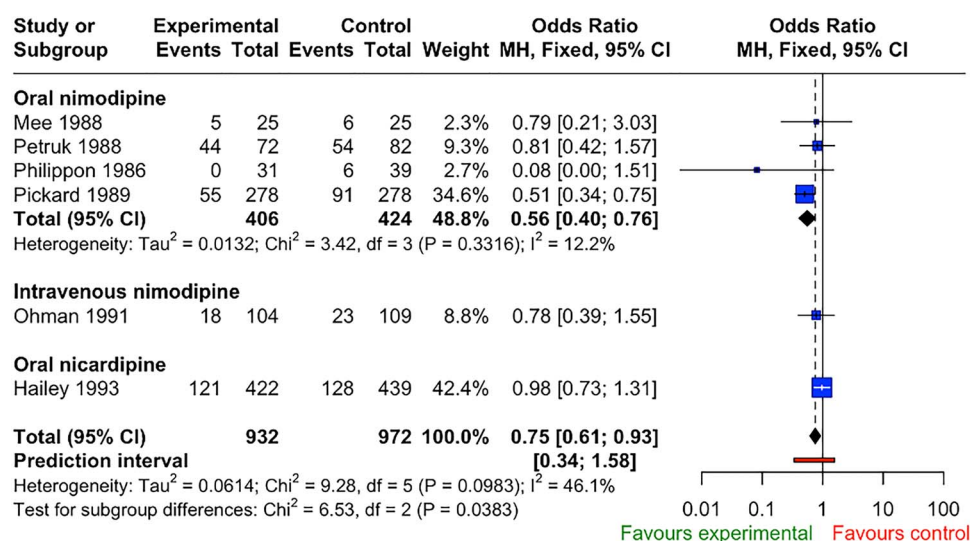


Figure 6 Effect (odds ratio) of calcium antagonists compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage.

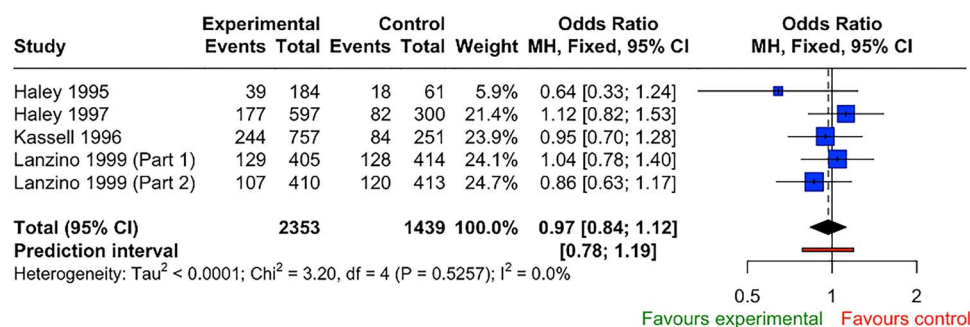


Figure 7 Effect (odds ratio) of tirilazad compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage.

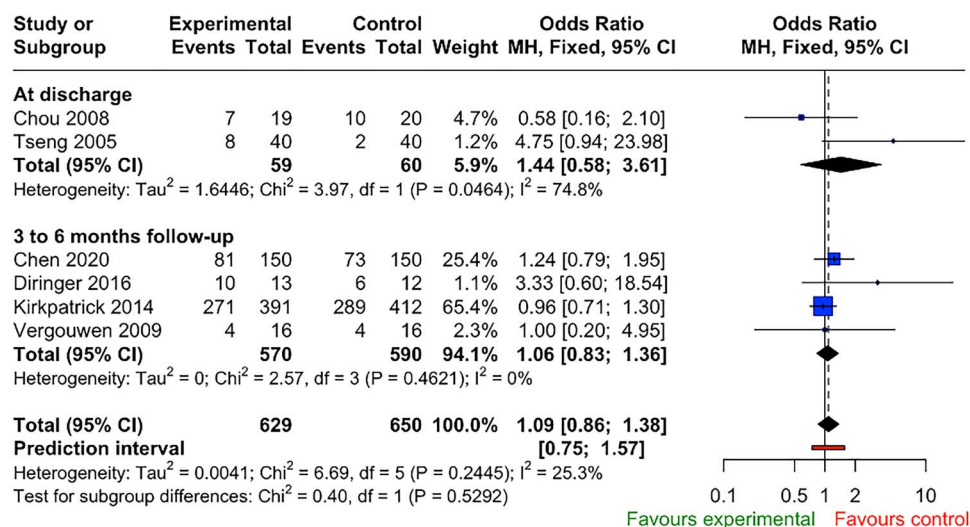


Figure 8 Effect (odds ratio) of statins on compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage.

used a different dosing regimen and treatment duration. Nine trials^{93–96,98,100–103} evaluated magnesium sulphate as an adjunct to nimodipine, comparing it with placebo plus nimodipine and therefore were included in the analysis. Seven meta-analyses were also reviewed^{104–110}; however, no additional data were identified.

Magnesium sulphate did not decrease the risk of poor functional outcome (OR: 0.94; 95% CI, 0.78–1.12; **Figure 9**) or reduce case-fatality (OR: 0.81; 95% CI, 0.42–1.57; **Figure S11**). Although it was not associated with a decreased risk of DCI (OR: 0.52; 95% CI, 0.19–1.42; **Figure S12**), magnesium sulphate was associated with a lower risk of cerebral infarction (OR: 0.30; 95% CI, 0.14–0.62;

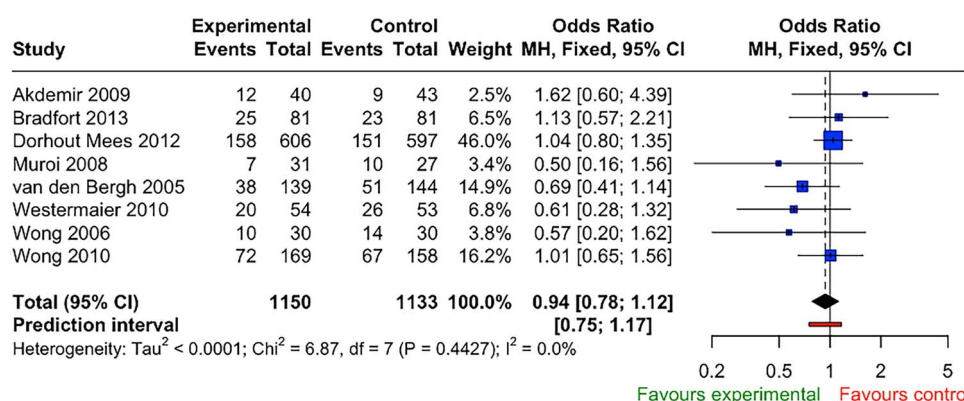


Figure 9 Effect (odds ratio) of magnesium sulphate compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage.

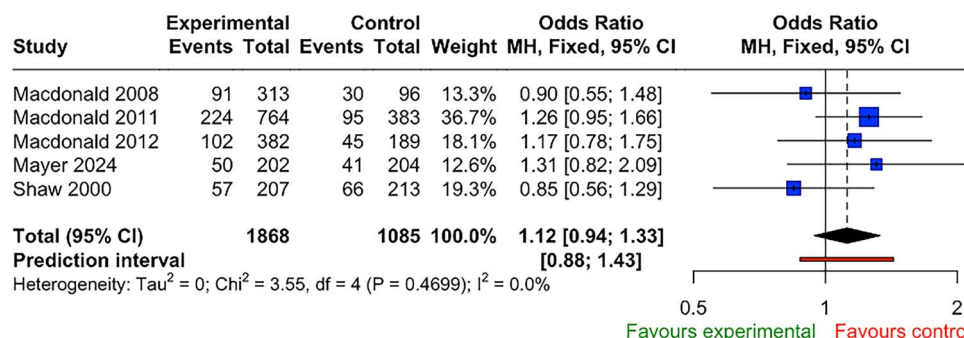


Figure 10 Effect (odds ratio) of ETRAs compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage. Abbreviation: ETRAs = endothelin receptor antagonists.

Figure S13). Of note, infarct outcomes were assessed in only 165 patients.

Endothelin receptor antagonists (ETRA)s

Endothelin receptor antagonists (ETRA)s block the effects of ET-1, which is a protein with strong vasoconstrictive properties produced by endothelial cells after subarachnoid haemorrhage.

Our search identified 8 RCTs,^{111–118} 1 Cochrane review,¹¹⁹ and 7 other meta-analyses.^{120–126} Five trials comprising 2957 patients between 2000 and 2024 included nimodipine as a standard of care^{111–113,117,118} and were thus included in our analyses. Four trials analysed the effect of clazosentan,^{111,113,117,118} which is a selective endothelin A receptor antagonist, and 1 trial the effect of TAK-044,¹¹² which is a non-selective antagonist of both endothelin A and B receptors.

ETRA)s did not reduce poor functional outcome (OR: 1.12; 95% CI, 0.94–1.33; Figure 10) or case-fatality (OR: 1.07; 95% CI, 0.69–1.65; Figure S14), although they reduced the risk of DCI (OR: 0.63; 95% CI, 0.48–0.82; Figure S15). Moreover, ETRAs did not reduce the overall risk of cerebral infarction (OR: 0.77; 95% CI, 0.49–1.20; Figure S16).

Antiplatelet drugs

It has been hypothesised that microthrombosis contributes to the pathogenesis of DCI.¹²⁷ Therefore, the effect of antiplatelet drugs has been extensively investigated in patients with aSAH. The following antiplatelet drugs were investigated: cilostazol (4 RCTs, 405 patients),^{128–131} acetylsalicylic acid (2 RCTs, 211 patients),^{132,133} dipyridamole (1 RCT, 348 patients),¹³⁴ tirofiban

(1 RCT, 30 patients),¹³⁵ E5880 (1 RCT, 68 patients),¹³⁶ catacloxt (1 RCT, 24 patients)¹³⁷ and OKY-046 (1 RCT, 256 patients).¹³⁸

Of them, only 3 trials^{132,133,135} including 241 patients used nimodipine as the standard of care and were included in the meta-analysis. Two trials^{133,135} were phase 2 and 1 trial¹³² was phase 3. Two trials investigated acetylsalicylic acid^{132,133} and 1 trial investigated tirofiban.¹³⁵ We also identified 1 Cochrane review¹³⁹ and 5 additional meta-analyses, but these did not yield further data.^{140–144}

Overall, antiplatelet therapy did not reduce the risk of poor functional outcome (OR: 0.67; 95% CI, 0.33–1.34; Figure 11) or reduce case-fatality (OR: 1.05; 95% CI, 0.42–2.59; Figure S17). Furthermore, antiplatelet treatment did not reduce the risk of DCI (OR: 0.72; 95% CI, 0.15–3.49; Figure S18) or cerebral infarction (OR: 0.50; 95% CI, 0.06–4.38; Figure S19).

Lumbar drainage

Lumbar drainage (LD) has been investigated as a potential strategy to prevent DCI by facilitating cerebrospinal fluid (CSF) removal and cisternal bloodclot wash-out downstream.¹⁴⁵ Our analysis included 3 RCTs comprising 557 patients.^{146–148} A further meta-analysis yielded no additional data.¹⁴⁹ Of the 3 RCTs, 1¹⁴⁸ reported functional outcome using means and medians of GOS scores at 1- and 3-month follow-up, instead of proportions of patients with poor outcome. The corresponding author was contacted multiple times for more information but did not respond. Therefore, that trial could not be included in the meta-analysis. Instead, the results of that trial are reported separately.

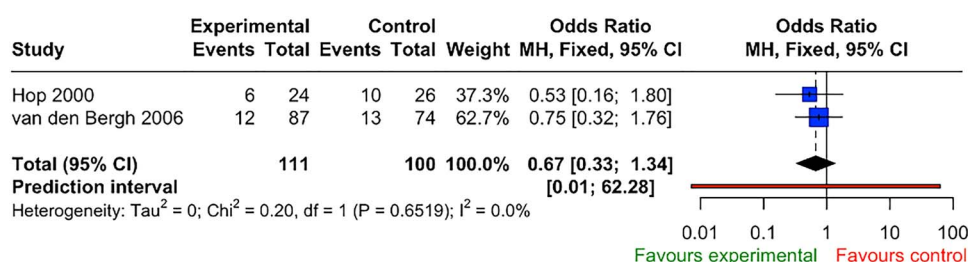


Figure 11 Effect (odds ratio) of antiplatelet drugs compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage.

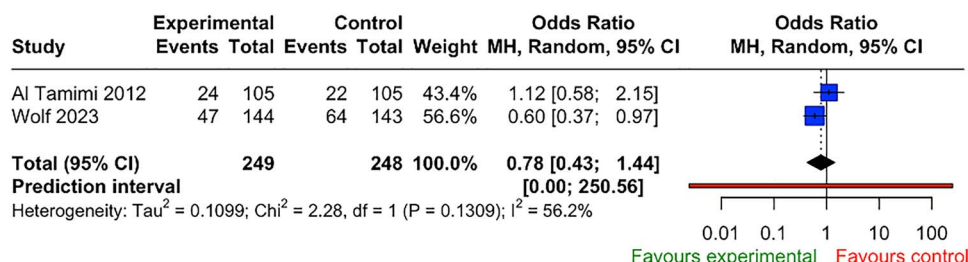


Figure 12 Effect (odds ratio) of LD compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage. Abbreviation: LD = lumbar drainage.

The methodology was similar between the 2 trials included in the pooled analysis, with lumbar CSF drained at a rate of 5–10 mL/h for an average duration of 4–5 days. The procedures were safe, with a low risk of complications, primarily minor infections or mechanical issues. Serious complications (such as infection, rebleeding or herniation) were very uncommon (<2%).^{146,147}

Lumbar drainage did not reduce the risk of poor functional outcome at 3–6 months (OR: 0.78; 95% CI, 0.43–1.44; Figure 12) or overall case-fatality (OR: 0.75; 95% CI, 0.43–1.31; Figure S20). However, it was associated with a lower risk of DCI (OR: 0.41; 95% CI, 0.24–0.70; Figure S21) and cerebral infarction (OR: 0.55; 95% CI, 0.38–0.79; Figure S22). An additional study not included in the meta-analysis¹⁴⁸ reported higher GOS scores at both 1 and 3 months in patients treated with LD compared to controls (median 5 [IQR: 1–5] vs 4 [IQR: 1–5], $P = .04$).

Based on the currently available evidence, which includes 2 RCTs with conflicting results and a third positive study the results of which could not be included in the pooled analysis, no recommendation can be made for or against the use of LD to decrease the risk of poor functional outcome after aSAH. Further research is needed to provide conclusive evidence.

Topic 5. Treatment of delayed cerebral ischaemia

PICO 5a

In adult patients with aSAH and clinical deterioration due to DCI, does hypertension induction compared to no hypertension induction decrease the risk of poor functional outcome?

Analysis of current evidence

The only randomised-controlled study performed on the effects of induced hypertension in aSAH patients with DCI showed no reduction in poor outcome (adjusted RR for poor outcome 1.0

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, no recommendation can be made on hypertension induction to decrease the risk of poor functional outcome.	⊕⊕	-

Expert consensus statement

In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, we suggest considering induced hypertension, provided that the ruptured aneurysm is treated and after standard therapy has proven insufficient. Clinical contraindications and potential complications of induced hypertension should be considered.

Vote: 11/13

[95% CI, 0.6–1.8]) and a possibly higher rate of serious adverse events in the intervention group (RR: 2.0; 95% CI, 0.9–5.0). It must be noted that the trial was prematurely stopped after 41 out of 240 patients (17%) were enrolled. Therefore, there was insufficient power to draw a final conclusion on the role of induced hypertension in aSAH patients with DCI.¹⁵⁰ Of note, although the mean arterial pressure was on average 12 mm Hg higher in patients in the hypertension induction group compared to those in the control group, no statistically significant difference in cerebral perfusion was observed.¹⁵¹

Additional information

We retrieved additional information on the effects of induced hypertension in adult patients with aSAH and clinical deterioration due to DCI. In a retrospective study conducted in 3 academic hospitals in the Netherlands between 2006 and 2015, 479 (29%) of 1647 enrolled patients had clinical deterioration due to DCI. In this cohort, hypertension induction reduced the odds to develop DCI-related cerebral infarction (adjusted hazard ratio [HR], 0.59; 95% CI, 0.35–0.99) and a strong effect of induced

hypertension was observed on the prevention of poor outcome (adjusted OR: 0.27; 95% CI, 0.14–0.55), suggesting induced hypertension might be reasonable in selected patients.¹⁵² Another retrospective study from the Netherlands, that included patients admitted between 2015 and 2019, compared 2 centres using hypertension induction in patients with DCI with 1 centre not using this strategy.¹⁵³ Two authors, blinded to the patients’ hospital and treatment given, independently evaluated whether neurological status on days 1 and 5 after DCI onset had improved, remained stable or worsened compared with the status at DCI onset, based on Glasgow Coma Scale (GCS) scores and physicians’ neurological assessments documented in the medical records. Discrepancies were resolved by a third blinded author. Although at day 1 after DCI more patients in the hypertension induction group had clinical improvement compared to those without hypertension induction (adjusted RR [aRR]: 1.63 [95% CI, 1.17–2.27]), there was no difference in clinical improvement between the groups at day 5 after DCI (aRR: 1.04 [95% CI, 0.84–1.29]) and no difference in functional outcome (RR: 1.24 [95% CI, 0.81–1.90]).

PICO 5b

In adult patients with aSAH and clinical deterioration due to DCI, does endovascular treatment of vasospasm compared to no endovascular treatment decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, no recommendation can be made on endovascular treatment of vasospasm to decrease the risk of poor functional outcome.	⊕⊕	-

Expert consensus statements
1. In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia in combination with refractory and severe vasospasm, we suggest considering intraarterial pharmacological treatment as a rescue therapy in selected patients to decrease the risk of poor functional outcome. Vote: 11/13
2. In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia in combination with refractory severe vasospasm, the current evidence is insufficient to support the routine use of mechanical vasodilatation with balloon angioplasty. In selected cases, this approach may be considered as a last-line rescue treatment after careful multidisciplinary discussion of the potential risks and uncertain benefits. Vote: 12/13
3. In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia in combination with refractory severe vasospasm, the current data are insufficient to support the use of mechanical vasodilatation with temporary deployment of retrievable stents to decrease the risk of poor functional outcome. Vote: 13/13

Analysis of current evidence

Endovascular treatment of vasospasm in aSAH—such as intra-arterial pharmacological therapy and mechanical vasodilatation using balloon angioplasty or temporary deployment of a

retrievable stent—has been explored in clinical studies as a potential strategy to treat DCI. Two RCTs on the effects of endovascular treatment of vasospasm in aSAH patients with DCI have been completed to date.^{154,155} An RCT in 3 German centres was stopped prematurely for safety reasons after a prespecified interim analysis, when 36 out of the planned 92 patients were randomised.¹⁵⁴ Eighteen patients were randomised to endovascular treatment and 18 to the control arm. Two patients in the intervention arm did not receive endovascular treatment and were not included in the analysis. Of the 16 patients who underwent endovascular treatment, 5 patients received 1 treatment, 7 patients 2 treatments, 2 patients 3 treatments, 1 patient 4 treatments and 1 patient 5 treatments. The majority of procedures (29/34) consisted of intra-arterial nimodipine and 4/34 procedures were done by balloon angioplasty. Five out of 34 (15%) endovascular treatment procedures resulted in major treatment complications (2 dissections, 3 infarctions). No effect on the primary endpoint (incidence of new infarct lesions measured on diffusion weighted MR images) was observed. Patients randomised to the control arm had a better clinical outcome at 6 months than patients randomised to endovascular treatment of vasospasm (mRS 2 ± 1.5 vs 4 ± 1.8; *P* = .004). The study did not demonstrate a clinical benefit and reported worse functional outcomes in the invasive group. Since the trial was likely underpowered due to early termination and a smaller-than-planned sample size, a potential benefit of invasive diagnostic and endovascular treatment cannot be definitively excluded. In addition, variability in vasospasm severity may have limited the generalisability of the findings. The second trial was a single-centre RCT from Thailand with 68 patients, of whom 36 patients were randomised to a single endovascular treatment session with intra-arterial nimodipine and 32 patients to the control arm.¹⁵⁵ The results showed a positive effect on motor improvement at discharge (58% in the intervention arm and 22% in the control group; *P* = .002), but no effect on functional outcome (measured with the mRS) at discharge or at 6 months. Although the trial suggested a potential short-term benefit of endovascular treatment for vasospasm, the small sample size and single-centre design limit the robustness and generalisability of the findings. These limitations reduce the certainty of the evidence derived from this study.

In a pooled analysis of the 2 trials, endovascular treatment of vasospasm in aSAH patients with DCI did not reduce the risk of poor functional outcome (OR: 2.33; 95% CI, 1.05–5.18; [Figure 13](#)) or case-fatality (OR: 2.93; 95% CI, 0.58–14.90; [Figure S23](#)).

Additional information

We identified one systematic review focussing mainly on intra-arterial pharmacological treatment and balloon angioplasty. In addition, we included data from 2 observational studies evaluating temporary stent-retriever deployment as a novel strategy for mechanical vasodilatation. A systematic review and meta-analysis¹⁵⁶ of 7 non-randomised, predominantly retrospective cohort studies (517 patients) compared endovascular therapy (intra-arterial pharmacological treatment with or without balloon angioplasty) with the standard treatment for vasospasm after aSAH. Endovascular therapy, mainly intra-arterial

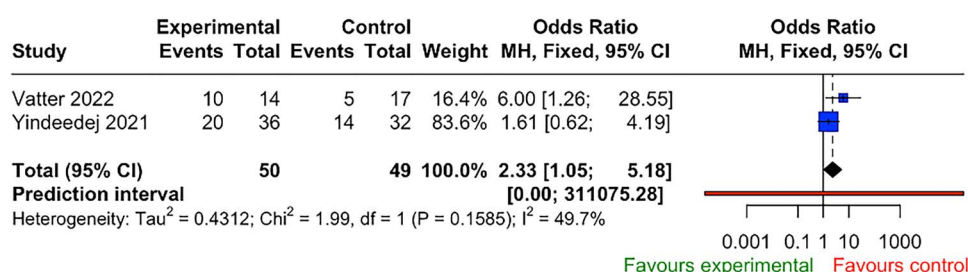


Figure 13 Effect (odds ratio) of endovascular treatment of vasospasm compared with control on poor functional outcome in adults with aneurysmal subarachnoid haemorrhage with DCI. Abbreviation: DCI = delayed cerebral ischemia.

pharmacological treatment, was associated with a decreased risk of in-hospital mortality (RR: 0.49; 95% CI [0.29–0.83]), but not of functional outcome at discharge (RR: 0.99; 95% CI [0.68–1.45]) or at follow-up (RR: 1.09; 95% CI [0.86–1.39]), or of major cerebral infarction on CT at discharge (RR: 0.79; 95% CI [0.34–1.84]), compared to standard of care.

Only limited data are available on balloon angioplasty. A multicentre retrospective cohort study from 3 US academic centres evaluated the safety and efficacy of non-compliant balloon angioplasty for vasospasm after aSAH.¹⁵⁷ Fifty-two patients were included who had new focal or global neurologic deficits resulting from DCI in combination with moderate or severe angiographic vasospasm. In total, 165 angioplasty procedures were performed. The study did not include a control group. The main outcomes were angiographic improvement of vasospasm, delayed cerebral infarction on CT or MRI and functional outcome (mRS). Angiographic improvement occurred in 97% of treated vessels, and clinical symptoms improved in 78.8% of patients. Cerebral infarction developed in 46.2% of patients, and 61.5% achieved favourable functional outcome (mRS 0–2) at follow-up. No procedure-related complications were reported. The authors concluded that non-compliant balloon angioplasty appears safe and effective in improving angiographic vasospasm in patients with medically refractory vasospasm. However, in the absence of a control group, no conclusion can be made on the effect on functional outcome. A single-centre retrospective observational study evaluated the effect of distal balloon angioplasty for vasospasm after aSAH.¹⁵⁸ The study included 392 patients treated between 2012 and 2017. Between 2012 and 2015, 160 patients received proximal balloon angioplasty, if needed followed by intra-arterial pharmacological therapy for distal vasospasm. From 2015 to 2017, 232 patients received proximal balloon angioplasty, if needed followed by distal balloon angioplasty. The primary endpoint was delayed cerebral infarction occurring in the territory of a previously treated vessel. Distal balloon angioplasty was associated with lower rates of post-angioplasty delayed cerebral infarction (2.2% vs 7.5%) and fewer repeat angioplasty procedures (8% vs 19%). However, overall delayed cerebral infarction, mortality and favourable functional outcome did not differ significantly between treatment periods. Procedure-related complications were uncommon, with angioplasty-related infarction in ~2.5% and symptomatic intracranial haemorrhage in ~0.7%–1.3%. The authors concluded that distal balloon angioplasty may reduce angiographic recurrence of vasospasm and post-angioplasty infarction but did not demonstrate a clear clinical benefit.

Finally, temporary deployment of retrievable stents has been reported in small observational series as a mechanical approach for vasospasm treatment. However, since the available studies were limited to small uncontrolled cohorts, none of the studies adhered to the inclusion criteria for this guideline.

In conclusion, the available evidence for endovascular treatment of vasospasm is predominantly observational and retrospective. Adequately powered, randomised controlled clinical trials with predefined clinical endpoints are urgently needed to answer the question whether endovascular treatment of vasospasm in patients with DCI is safe and decreases the risk of poor functional outcome after aSAH.

Topic 6. Neuroimaging and neuromonitoring

PICO 6a

In adult patients with aSAH, does any type of neuroimaging compared to regular neurological examination decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on neuroimaging to decrease the risk of poor functional outcome.	⊕	-

Expert consensus statements

- In adult patients with aSAH and clinical deterioration, we suggest plain head CT in combination with CT-Perfusion (CTP) imaging to detect the cause of deterioration.
Vote: 11/13
- In adult patients with aSAH who are neurologically not assessable but at high risk for DCI, we suggest plain head CT and CTP at least once between day 4 and 14.
Vote: 10/13
- In adult patients with aSAH, we do not suggest a routine DSA for screening of macrovascular vasospasm.
Vote: 13/13

Analysis of current evidence

The literature search yielded no randomised trials or otherwise controlled studies, but only uncontrolled observational studies, which are discussed in the additional information section.

Additional information

Angiography

Anatomical imaging of cerebral arteries with DSA provides the highest spatial resolution for brain arteries and serves as the gold standard for the assessment of macrovascular diameter.¹⁵⁹ However, due to the invasiveness and inherent procedural risks of DSA, CTA is often used as an alternative for detection of macrovascular spasm. In a meta-analysis comparing CTA with DSA,¹⁶⁰ CTA had a sensitivity of 79.6% (95% CI, 74.9%–83.8%) and specificity of 93.1% (95% CI, 91.7%–94.3%). However, although there is a strong association between macrovascular spasm and DCI,^{161,162} a causal relationship is increasingly questioned. Other hypotheses for the pathogenesis of DCI include microthrombosis, microcirculatory spasm, cortical spreading ischaemia and impaired cerebral autoregulation. In addition, clinical trials showed that treatment strategies that reduce macrovascular spasm do not decrease the risk of poor functional outcome, which questions the usefulness of detecting angiographic vasospasm.^{126,154}

Perfusion imaging

Imaging of brain perfusion may detect tissue at risk for irreversible ischaemic damage¹⁶³ and guide therapeutic interventions. Due to its practicability and favourable risk/benefit profile for aSAH patients, CTP measurement evolved as the most used perfusion imaging modality.^{164–166} CTP combines information about macro- and microvascular blood flow and may distinguish between reversible hypoperfusion and irreversible ischaemia.¹⁶³ Quantitative image analyses with calculation of CBF, cerebral blood volume, mean transit time (MTT), time to peak and time to drain have been used to investigate impaired brain perfusion in aSAH patients. Increase in MTT has repeatedly been reported to accurately predict DCI before irreversible ischaemia occurs.¹⁶⁷ In a prospective cohort of 64 aSAH patients with quantitative CTP at day 3, MTT predicted DCI with a sensitivity of 95% (95% CI, 83%–99%) and a negative predictive value of 96% (95% CI, 87%–99%) indicating very high diagnostic accuracy as screening tool for DCI.^{168,169} In a meta-analysis of 570 patients, a decrease of CBF (pooled mean difference – 11.9 mL/100 g per minute [95% CI, –15.2 to –8.6]) and an increase in MTT (pooled mean difference 1.5 s [CI, 0.9–2.2]) during the high-risk phase (days 4–14 after ictus) was associated with DCI. However, absolute values of quantitative CTP parameters vary between different CT scanners and analysis algorithms.¹⁷⁰ Therefore, measuring perfusion by CTP needs standardisation to define generalisable absolute perfusion thresholds after aSAH in future studies.

Magnetic resonance imaging (MRI)

Although MRI is a sensitive modality for the early detection of cerebral ischaemia, its feasibility in the routine management of patients with aSAH during the high-risk period for DCI is limited by both patient-related and logistical factors. Many patients with aSAH are restless or have a decreased level of consciousness and therefore unable to lie still, which makes an MRI scan impossible. Furthermore, having a patient on the respiratory machine for about 20 min and monitoring that patient in the MR suite is challenging and often undesirable. In addition, when ischaemic

lesions are detected on MRI, it is often difficult to determine whether these findings are attributable to DCI, acute ischaemic events (resulting from the acute aneurysm rupture) or procedure-related ischaemia. Collectively, these considerations limit the utility of MRI as a diagnostic tool in routine clinical practice. Emerging technologies, such as bedside ultra-low-field portable MRI systems and further reductions in acquisition time, may help to address some of these limitations in the future.

PICO 6b

In adult patients with aSAH, does any type of neuromonitoring compared to regular neurological examination decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on neuromonitoring to decrease the risk of poor functional outcome.	⊕	–

Expert consensus statements

1. In adult patients with aSAH, no suggestion can be given on the use of TCD monitoring.
Vote: 10/13
2. In adult patients with aSAH and radiological hydrocephalus who are neurologically not assessable, we suggest ICP monitoring via EVD if an EVD is in place.
Vote: 13/13
3. In adult patients with aSAH without radiological hydrocephalus who are neurologically not assessable, no suggestion can be given on ICP monitoring.
Vote: 11/13
4. In adult patients with aSAH who are neurologically not assessable, we do not suggest invasive multimodal neuromonitoring with continuous measurement of partial pressure of brain tissue oxygen (PbtO2) and/or microdialysis due to the uncertain risk/benefit ratio of these modalities.
Vote: 10/13
5. In adult patients with aSAH who are neurologically not assessable, we do not suggest the routine use of continuous EEG monitoring.
Vote: 13/13

Analysis of current evidence

The literature search yielded no randomised trials or otherwise controlled studies, but only uncontrolled observational studies, which are discussed in the additional information section.

Additional information

Transcranial Doppler TCD

Transcranial Doppler is widely used for routine monitoring of arterial blood flow velocities as an indirect measure to detect large artery vasospasm after aSAH. The non-invasive nature and bedside availability of TCD offer advantages over other imaging modalities for vasospasm monitoring. However, as discussed

above, there is ongoing debate about the clinical relevance of macrovascular spasm and elevated blood flow velocities in cerebral arteries measured by TCD.^{171,172} A meta-analysis¹⁷³ of 15 studies comparing TCD with DSA for detection of angiographic vasospasm in the middle cerebral artery reported a pooled sensitivity of 66.7% (95% CI, 55.9–75.9) and specificity of 89.5% (95% CI, 80.3–94.7). An estimated vasospasm incidence of 70% in aSAH patients results in a positive predictive value of 93.7% and negative predictive value of 53.4%. Due to even lower negative predictive values for all other cerebral arteries, TCD does not reliably exclude the presence of vasospasm. The limited diagnostic accuracy of TCD, and the fact that most patients with large artery vasospasm do not have clinical deterioration due to DCI undermines its usefulness as a reliable screening tool in the monitoring of aSAH patients.¹⁷⁴

Continuous EEG

In unconscious patients, subtle neurological changes caused by focal cerebral ischaemia are often difficult to recognise. Continuous EEG (cEEG) may partially compensate for missing functional information. cEEG can be used for monitoring seizure activity and brain function in critically ill patients with altered mental status.¹⁷⁵ In aSAH patients, seizure activity in cEEG has been reported in up to 19% of patients, which may contribute to worse clinical outcome.¹⁷⁶ In addition to seizure detection, cEEG data can be analysed to define patterns of DCI-related pathological electric activity of the brain. For example, a decreased alpha to delta ratio is associated with DCI.¹⁷⁶ In a prospective study of 227 consecutive aSAH patients, 103 were eligible for quantitative EEG analyses. In this cohort, cEEG predicted DCI with a sensitivity of 91% (95% CI, 81%–98%) and specificity of 83% (95% CI, 71%–93%) in low-risk patients, and a sensitivity of 95% (95% CI, 87%–99%) and specificity of 77% (95% CI, 36%–99%) in high-risk patients.¹⁷⁷ However, the identified EEG patterns for DCI prediction and diagnosis need further validation in independent cohorts of aSAH patients with standardised definitions. In addition, clinical trials are needed to investigate whether therapeutic interventions based on cEEG findings decrease the risk of poor functional outcome in aSAH patients, to justify the high resource requirements for around-the-clock real-time data acquisition and interpretation.¹⁷⁴

Invasive neuromonitoring probes

Parenchymal monitoring probes can be used to obtain additional physiological data in neurologically unassessable aSAH patients, eg, ICP, regional CBF and the metabolic status of the brain.¹⁷⁴ Intracranial pressure elevations are common and have been reported in up to 80% of poor grade aSAH patients.¹⁷⁸ In unconscious patients with radiographic signs of hydrocephalus, ICP can be reliably monitored via an EVD¹⁷⁹ (also see PICO 7). However, there is uncertainty about the risk/benefit profile of EVD insertion for ICP monitoring in aSAH patients without radiographic hydrocephalus.

Parenchymal ICP probes are considered less invasive and commonly used for this indication.¹⁷⁹ The SYNAPSE-ICU study was an international, prospective observational cohort study of 2395 patients with acute brain injury, of whom 521 (22%) had SAH,^{180,181} which aimed to explore practice variation in ICP monitoring variation to prioritise uncertainties in the clinical

management of critical care patients with acute brain injury and support further collaborative prospective studies. The study showed that SAH patients with ICP monitoring received more aggressive therapy treatments compared to patients without ICP monitoring. Intracranial pressure monitoring was associated with a reduction in poor functional outcome (OR: 0.14; 95% CI, 0.02–0.53) and case-fatality (HR: 0.25; 95% CI, 0.13–0.49) in SAH patients in a poor clinical condition, but not in those with 2 reactive pupils.

Combined probes allow for continuous measurement of brain tissue oxygen pressure (PtbO₂) and ICP. This, in combination with systemic blood pressure measurements, may provide information about cerebral autoregulation.¹⁸² Brain tissue oxygen pressure monitoring has been reported to be sensitive in detection of metabolic cerebral compromise even in the absence of elevated ICP.¹⁸³ In addition, microdialysis with quantification of interstitial metabolites, such as lactate and pyruvate, have been reported to detect metabolic derangements in situations without impaired PtbO₂.¹⁸³ Treatment paradigms for poor grade aSAH patients based on an extended definition of DCI integrating multimodal neuromonitoring data (ICP, PtbO₂, microdialysis) have been reported to increase 12 months favourable neurological outcome in a cohort of 55 consecutive poor grade aSAH patients.¹⁸⁴ However, due to the very limited sample size of reported neuromonitoring studies in aSAH patients, inconsistent definitions of DCI across studies, the lack of validated clinically relevant thresholds and limited therapeutic options, there is uncertainty about the risk/benefit profile of invasive monitoring methods. In addition, invasive multimodal neuromonitoring is inherently limited by providing only regional information around the site of implantation and a lack of data from clinical good grade aSAH patients.

PICO 7

In adult patients with aSAH, does treatment of hydrocephalus (either by EVD, ventriculoperitoneal [VP]-shunt or LD) compared to no treatment of hydrocephalus decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH and hydrocephalus, no recommendations can be made on CSF diversion strategies to decrease the risk of poor functional outcome.	⊕	–

Analysis of current evidence

External ventricular drain

There are no RCTs comparing the placement of an EVD with the absence of an EVD in aSAH patients with hydrocephalus. Furthermore, there are no prospective observational studies meeting the inclusion criteria.

Lumbar drain

There are 4 RCTs that meet the predefined inclusion criteria.^{146–148,185} All identified RCTs evaluate the effects of LD placement in addition to an EVD in patients with impaired consciousness, or as a standalone procedure in conscious patients without acute hydrocephalus. The primary goal of LD placement

Expert consensus statements

1. In adult patients with aSAH who present with radiological hydrocephalus and a decreased level of consciousness, we suggest CSF drainage.

Vote: 13/13

2. In adult patients with aSAH who present with obstructive hydrocephalus and a decreased level of consciousness, we suggest EVD placement.

Vote: 13/13

3. In adult patients with aSAH who present with communicating hydrocephalus and a decreased level of consciousness, we suggest LD or repeated LPs as the strategy of first choice for CSF drainage.

Vote: 11/13

4. In adult patients with aSAH who present with radiological hydrocephalus and a normal level of consciousness, we do not suggest CSF drainage.

Vote: 12/13

5. In adult patients with aSAH who come at a point at which prolonged CSF drainage (by EVD, LD or repeated LPs) carries a higher risk of severe complications than placement of a permanent CSF diversion, we suggest permanent CSF diversion.

Vote: 13/13

6. In adult patients with aSAH who present with symptomatic chronic hydrocephalus, we suggest permanent CSF diversion.

Vote: 13/13

in these studies was the prevention of DCI and thus potentially a decreased risk of poor functional outcome. Therefore, the results of these studies are presented in PICO 4, which addresses the prevention of DCI.

There are no RCTs comparing the placement of an LD and the absence of an LD in aSAH patients with hydrocephalus to decrease the risk of poor functional outcome or case-fatality. In addition, there are no prospective observational studies meeting the inclusion criteria.

Lumbar puncture

There are no RCTs comparing the effect of LP with no LP in aSAH patients with hydrocephalus. Nor are there any prospective observational studies meeting the inclusion criteria.

Internal ventricular drain

There are no RCTs comparing the placement of a VP shunt with no VP shunt in aSAH patients with chronic hydrocephalus. Nor are there any prospective observational studies meeting the inclusion criteria.

Additional information

EVD in acute hydrocephalus after aSAH

The placement of an EVD in patients with acute hydrocephalus following aSAH, whether obstructive or communicating, is common practice in nearly all centres treating aSAH patients. External

ventricular drain allows rapid control of acute hydrocephalus and ICP, and thereby is often considered a lifesaving treatment. In case of obstructive hydrocephalus or significant mass effect it is the only treatment possible, since LD or LP in these situations can lead to death by brain herniation.¹⁸⁶ However, although commonly performed, EVD also has specific risks: brain haemorrhage along the catheter tract, catheter malposition, mechanical brain injury with putative long-term effect on motor function, cognition and risk of seizures, as well as catheter-related infection.^{187,188} In addition, there is a debate regarding the indications for EVD placement, which can be clinical (decreased level of consciousness) and/or radiological (ventricular enlargement).¹⁸⁹ Therefore, the risk/benefit ratio of EVD insertion must be weighed and alternatives considered.

LD and LP in acute hydrocephalus after aSAH

In case of acute and communicating hydrocephalus, a LD or LP can also be used instead of an EVD.^{190–194} Placement of an LD or performance of an LP probably carries a lower risk of complications than the placement of an EVD. However, CSF diversion by means of a LD or LP in case of obstructive hydrocephalus or significant cerebral oedema poses a risk of tonsillar herniation and thus death, and is therefore contraindicated in these situations.

Regarding the LD, an observational study without control group reported no complications related to LD insertion (infection, brain herniation, over drainage) in 28 Fisher III aSAH patients.¹⁹⁰ In another study, 229 Fisher III aSAH patients without obstructive hydrocephalus had an LD inserted, and the rate of CSF infection was 0.4%, which may be lower than that observed with EVD.¹⁹¹ One study in aSAH patients with symptomatic hydrocephalus retrospectively compared 56 patients with an EVD and 21 patients with a LD. The decision to treat with EVD or LD depended on the surgeon on call. Overall drain complications were 32.0% in patients with EVD and 9.5% in patients with LD. External ventricular drain vs LD complications consisted of haemorrhage (1.8% vs 0%), infection (7.1 vs 0%), clogged drain (25% vs 0%), dislodgement of drain (1.8% vs 4.6%) and replacement of drain (16% vs 4.8%). No case of cerebellar tonsillar herniation occurred.

Regarding LP, in an observational study, 17 patients with symptomatic communicating hydrocephalus were treated by serial LPs. None had CSF infection or tonsillar herniation, and none required EVD insertion.¹⁹³ In a recent study, 86 patients with aSAH and acute symptomatic hydrocephalus were treated with LP as initial treatment. Seventy patients (81%) showed initial improvement after initial LP, 39 (45%) improved with LP only and 41 (48%) needed continuous drainage by LD or EVD. Thus, LD or EVD insertion could be avoided in approximately half of the patients. The rate of complications related to LP was not explicitly reported.¹⁹²

Timing of CSF drainage in acute hydrocephalus after aSAH

Cerebrospinal fluid drainage in aSAH patients before occlusion of the ruptured aneurysm may modify aneurysm transmural pressure, which may increase the risk of aneurysmal rebleeding. This question has been investigated in several observational studies.

Regarding EVD, a meta-analysis of observational studies reported rebleeding among 106/960 patients (11%) treated with EVD, vs 250/2711 patients without EVD (9.2%; OR: 1.60, 95% CI, 0.82–3.22).¹⁹⁵ However, several confounding factors limit the interpretation of these findings, particularly the

time interval between ictus, EVD placement, rebleeding and aneurysm treatment. Another study compared 3 matched patient groups: those with hydrocephalus treated with EVD, those with hydrocephalus without EVD and those without hydrocephalus ($n = 34$ per group).¹⁹⁶ The mean time from ictus to CSF drainage was 12 h, and drainage continued for an average of 6.3 days prior to aneurysm treatment. Rebleeding rates were similar across groups, occurring in 7/34 patients in both hydrocephalus groups and in 6/34 patients in the group without hydrocephalus. These findings suggest that early EVD placement with prolonged CSF drainage does not appear to increase the risk of rebleeding. Although EVD itself may not increase rebleeding risk, another study with 194 patients suggested that not EVD by itself, but rather the volume and timing of CSF drainage (60 mL of CSF drained in 6 h) may increase the risk of rebleeding.¹⁹⁷ This observation indicates that the risk may be related to both the volume and timing of CSF drainage.

Regarding LD, in a retrospective study, rebleeding occurred in 11/324 (3.4%) patients with LD and in 2/51 (3.9%) patients without LD.¹⁹⁸

Permanent CSF shunt in aSAH

There are no high-quality studies evaluating the benefit of placing a permanent shunt in chronic hydrocephalus following aSAH. Insertion of permanent shunt is proposed when the EVD or LD cannot be removed, or in case of symptomatic chronic hydrocephalus.

When an external drain has been inserted (EVD or LD), the removal of this drain usually relies on a clamping attempt with clinical and radiological assessment. The duration of external drainage that necessitates the placement of an internal shunt is unknown, as well as the number of failures of drain closure indicating the insertion of a permanent CSF shunt. Of note, the longer the EVD is inserted, the higher the risk of catheter-related infection is.¹⁹⁹

Chronic hydrocephalus after aSAH may also become clinically manifest after the removal of the external drain, several weeks after discharge.²⁰⁰ A retrospective study that included 39 patients provides controlled data. Patients presenting with gait ataxia, cognitive disturbance and urinary incontinence had enlarged ventricles and normal CSF opening pressure on LP. Patients with high CSF opening pressure were excluded. Of the remaining participants, 24 received a VP shunt and 15 did not receive a VP shunt. At 1 and 6 months, Barthel index scores (39 vs 47) and Mini Mental Status (18 vs 19) were improved in the VP shunt group.²⁰¹

PICO 8

In adult patients with aSAH, does treatment on a dedicated neuro-ICU or high care unit compared to a general ICU or high care unit decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on admission to a dedicated neuro-ICU or high care unit to decrease the risk of poor functional outcome.	⊕	-

Expert consensus statement

In adult patients with aSAH, we suggest admission and management in a dedicated neuro-ICU or high care unit to decrease the risk of poor functional outcome.

Vote: 13/13

Analysis of current evidence

No RCTs directly compare the effects of dedicated neuro-ICU or high care units with general ICU or high care units on outcomes in patients with aSAH.

Additional information

Dedicated neuro-ICU or high care unit vs general-ICU or high care unit

Several observational studies have compared outcomes between aSAH patients managed in a neuro-ICU vs a historical cohort in a general ICU.^{202–208} There are 5 studies suggesting a benefit of dedicated neuro-ICU on functional outcomes in aSAH patients.^{202–206} A Japanese retrospective study compared 83 aSAH patients admitted to an intensive care unit (ICU) managed by general intensivists between 2001 and 2006 (historical control group) to 151 aSAH patients admitted to an ICU managed by neurointensivists between 2007 and 2014.²⁰² Patients admitted to the unit led by neurointensivists had better outcomes at hospital discharge in univariate analysis (discharge mRS 0–2; 58.3% vs 41.0%; $P = .01$). Of note, an independent effect on outcomes (mRS 0–2) was only seen in a subgroup of good-grade aSAH patients (Hunt and Kosnik grades I and II) (OR: 4.54 [95% CI, 1.08–22.17]; $P = .045$), but not in patients with a poor clinical condition on admission.²⁰² A single-centre North American study found that implementation of a neurointensivist-led team was associated with a higher chance of being discharged home (141/386 [36.5%] vs 80/317 [25.2%]; $P < .001$), and a lower chance of being discharged to a rehabilitation facility (25.2% vs 36.5%) without a difference in mortality (25.4% vs 26.8%) and discharge to nursing care (5.7% vs 5.4%).²⁰³ The cohort of the ICU managed by a neurointensivist team consisted of 386 SAH patients admitted between 1998 and 2002 and were compared to a historical control group of 317 aSAH patients admitted between 1995 and 1998. Improved discharge disposition was seen in subgroups of patients with admission Hunt and Hess grades I and II and grade III, but not for aSAH admission grades IV and V. In a single centre retrospective North American study the implementation of a neurointensivist co-management approach in a neurosurgical ICU (296 aSAH patients admitted between 2005 and 2007 compared to a historical control group of 216 aSAH patients admitted between 2003 and 2005) did not show an effect on hospital mortality (18.2% after vs 13.4% before [$P = .14$]), although there was a statistically significant decrease of mean length of ICU stay (from 12.4 days to 10.9 days, $P = .02$) and of the need for VP shunts (23.0% vs 11.5% [$P = .001$]).²⁰⁴

In a single-centre North-American study including 363 SAH patients among a mixed cohort of 2096 stroke patients, availability of a neurocritical care specialist, but not a specialised neurocritical care units was associated with improved discharge

disposition, lower in-hospital mortality (48/259 [18.5%] vs 33/104 [31.7%]; $P = .006$), or withdrawal of care, and lower mortality at 3 months (52/259 [20.1%] vs 33/104 [31.7%]; $P = .018$) and 12 months (54/259 [20.8%] vs 35/104 [33.7%]; $P = .01$) specifically in aSAH patients.²⁰⁵ When the trained neurointensivist left the unit and was not replaced, a greater rate of in-hospital mortality or discharge to hospice (OR: 2.206 [95% CI, 1.062–4.584]; $P = .034$), overall worsened discharge disposition (OR: 2.455 [95% CI, 1.165–5.177]; $P = .018$) and shorter ICU LOS (OR: 0.459 [95% CI, 0.229–0.917]; $P = .028$) was observed.

In a European study, the effect of the implementation of a neurocritical care protocol was studied among microsurgically clipped aSAH patients ($n = 198$, admitted between 1999 and 2003) compared to historical controls ($n = 150$, 1993–1994). The latter group included a significantly higher percentage of severe aSAH patients (WFNS grades IV and V) compared to the historical group (47.0% vs 15.3%, $P < .0001$) and WFNS grade V patients were not treated in the historical control group.²⁰⁶ While overall outcomes were similar, the study showed significant improvement for the most severe cases. In the historical group, all patients with WFNS grade V died or survived in a vegetative state, as they were not treated with aneurysm surgery. In contrast, 35.1% of WFNS grade V patients in the latter group (20 out of 57 patients) achieved a good functional outcome. The authors concluded that specialised neurocritical care is particularly beneficial for patients with high-grade aSAH.

Contrarily, a German study included 755 aSAH patients (456 in a neurosurgical ICU, 2005–2013 vs 299 in a general ICU, 1990–2005), found that the type of ICU was neither associated with discharge GOS nor 6-month GOS (OR: 1.45 [95% CI, 0.53–3.95]) for long-term outcome.²⁰⁷ In a North-American study the implementation of a neurointensivist team ($n = 108$ aSAH patients admitted between 1998 and 2000) was neither associated with NICU mortality (HR 1.39 [95% CI, 0.67–2.88]) nor in-hospital mortality (HR 1.48 [95% CI, 0.65–3.34]). However, NICU and hospital length of stay were significantly reduced (HR 1.60 [95% CI, 1.13–2.26] and HR 1.43 [95% CI, 1.01–2.03]).²⁰⁸

Due to limitations in study design—primarily retrospective observational studies with historical control groups—along with changes in clinical care over time, variations in pre-hospital management and differences in the timing of aneurysm treatment, the impact of specialised neurocritical care on patient outcomes is likely multifactorial.^{202–208} Higher levels of evidence can only be achieved through prospective randomised trials.

Topic 9. Centre volume and number/volume of neurosurgeon and neurointerventionalist

PICO 9a

In adult patients with aSAH, does treatment in a high-volume centre compared to a low-volume centre decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on admission/transfer to a high-volume centre to decrease the risk of poor functional outcome.	⊕	-

Expert consensus statement

We suggest that all patients with spontaneous SAH are admitted or immediately transferred to centres that treat at least 70 patients with aSAH per year, or at least 35 patients with aSAH per year in remote areas where access is limited.

Vote: 12/13

Analysis of current evidence

The literature search found no randomised or otherwise controlled trials, but only retrospective or registry-based studies, which are discussed in the additional information section.

Additional information

We found 2 systematic reviews analysing studies on the relationship between hospital case volume and in-hospital mortality.

The first review included studies published up to 2012 assessing the relationship between hospital caseload and in-hospital mortality for patients undergoing treatment after aneurysmal subarachnoid haemorrhage.²⁰⁹ This review included 4 studies, describing 36,600 patients. The quality of studies was graded as low in 3 and very low in 1. A meta-analysis using a random effects model showed a decrease in hospital mortality (OR: 0.77 [95% CI, 0.60–0.97]) in high-volume hospitals treating SAH patients. Removal of the study with very low quality increased the effect size (OR: 0.68 [95% CI, 0.56–0.84]). The definition of hospital volume differed among studies. In one study, low volume was defined as 9 or fewer patients per year, whereas in another, it was defined as fewer than 30 patients per year. Similarly, one study defined high volume as more than 20 patients annually, and another defined it as more than 50 patients a year. Apart from the non-uniform cut-off values for low- or high-volume centres, there was also uncertainty about the case-mix between centres, and no adjustment for baseline characteristics was not performed.

The second systematic review included studies that reported in-hospital mortality in SAH patients and provided an adjusted OR or core data on baseline characteristics, such as age, sex and co-morbidities, to calculate an adjusted OR.²¹⁰ The 5 included studies were published between 2002 and 2019; 4 were of high methodological quality according to the Newcastle–Ottawa Scale, and the fifth had a moderate quality. Three studies came from Asia, and 2 from Europe and the United States. In total, the 5 studies enrolled 46,186 patients. Crude in-hospital mortality ranged from 7.0% to 40%. High hospital case volume was associated with reduced in-hospital mortality (OR: 0.53; 95% CI, 0.42–0.68). This association was found in each included study separately, and was consistent in subgroups divided according to geographical region, treatment modality (surgical vs endovascular), proportion of surgical patients, sample size and annualised case volume grouping.

Studies dichotomised the annualised case volumes, or divided these into tertiles or quartiles, with the highest categories starting at 19, 30, 70 or 100 patients per year. For one study, the cut-offs were not reported.

We also found one study that did not use in-hospital data for outcome assessment, but mortality at 1 year after SAH. This study was based on registries of Denmark, Norway and Sweden, and included 5773 SAH patients and 1807 patients with unruptured aneurysms admitted between 2002 and 2010 in 15 neurosurgical centres.²¹¹ It used population-based death registries for outcome assessment in patients with SAH and unruptured intracranial aneurysms. For case volume load, the centres were divided into 3 tertiles (with < 36 patients per year in the lowest tertile and > 63 in the highest tertile). One-year mortality in patients with aSAH was slightly higher with increasing case load (HR per 10-patient increase, 1.04; 95% CI, 1.00–1.07) after adjusting for several baseline factors, but not SAH severity. One of the potential explanations for these discrepant results that the authors provide is that, in these Scandinavian countries, all treatments of intracranial aneurysms are performed at academic hospitals by specialised cerebrovascular surgeons and interventional neuro-radiologists. In contrast to the somewhat worse outcome after SAH in high volume centres, however, there was a trend towards better outcome for treatment of unruptured aneurysms in high volume centres in this study, which is not in line with this potential explanation. Others have argued that the worse outcome in high-volume centres is explained by selection bias, with high-volume centres accepting patients in poor clinical condition more often, and thus at higher risk of poor outcome.²¹²

In conclusion, there is high consistency between studies regarding a positive relationship between hospital caseload and in-hospital outcomes. Also, throughout the range of criteria for high-volume centres, there is consistency regarding high case volume and in-hospital favourable outcomes. This relation remains even if the cut-off for high volume is based on high caseloads, such as 70 or even 100 patients per year.

In the absence of RCTs and given the improbability that such trials will be conducted on this topic, there is an urgent need for prospective comparative effectiveness studies to evaluate whether patients admitted to high-volume centres experience better outcomes than those treated at low-volume centres. In addition, these studies should aim to determine the optimal volume threshold for defining a centre as high-volume.

PICO 9b

In adult patients with aSAH, does aneurysm treatment by a high-volume neurosurgeon or neurointerventionalist, compared to a low-volume neurosurgeon or neurointerventionalist, decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on case-volume per neurosurgeon and neurointerventionalist to decrease the risk of poor functional outcome.	⊕	-

Expert consensus statement

In adult patients with aSAH, we suggest that aneurysms are repaired by neurosurgeons or neurointerventionalists who perform the treatment of choice in more than 30 patients with aneurysms (ruptured and unruptured) per year.

Vote: 12/13

Analysis of current evidence

The literature search found no controlled studies.

Additional information

For several common procedures, such as carotid endarterectomy, coronary artery bypass grafting, valve replacement and abdominal aortic aneurysm repair, surgeon specialisation is an important predictor of operative mortality independent of volume in that specific procedure.²¹³ The literature search revealed no such data on intracranial aneurysm repair.

We found one study that investigated the association between the neurosurgeon's scientific productivity and clinical outcomes following microsurgical clipping of ruptured aneurysms.²¹⁴ The study was a post-hoc analysis of 3307 patients from 162 centres in 21 countries, who had undergone clipping of ruptured intracranial aneurysms by 147 neurosurgeons and who had participated in drug trials between 1990 and 1997. In this single study, patients under the care of neurosurgeons with higher H-indices had better functional outcomes ($P = 0.01$) compared to neurosurgeons with lower H-indices, without any statistically significant difference in mortality. Neither the total number of publications nor possession of a graduate degree had an impact on outcomes.

In the ESO guidelines on unruptured intracranial aneurysms it was suggested to repair unruptured intracranial aneurysms only in centres performing the proposed treatment in > 30 patients with (ruptured or unruptured) aneurysms per year per neurosurgeon or neurointerventionalist.²¹⁵

PICO 10

In adult patients with aSAH, does radiological follow-up beyond 6 months after aneurysm treatment, compared to a maximum radiological follow-up duration of 6 months, decrease the risk of poor functional outcome?

Evidence-based Recommendations	Quality of evidence	Strength
In adult patients with aSAH, no recommendation can be made on radiological follow-up beyond 6 months after microsurgical or endovascular aneurysm treatment to decrease the risk of poor functional outcome.	⊕	-

Analysis of current evidence

There are no completed RCTs or prospective cohort studies investigating whether radiological follow-up beyond 6 months in adult patients with aSAH decreases the risk of poor functional

Expert consensus statements:

1. In adult patients with aSAH who are treated with coils and adequate occlusion within 6 months, we suggest at least one additional radiological follow-up at or beyond 12 months after aneurysm repair to investigate potential aneurysm recanalization, as long as a potential re-treatment remains an option.

Vote: 13/13

2. In adult patients with aSAH who are treated with microsurgical clipping and adequate occlusion within 6 months, we do not suggest further radiological follow-up to investigate potential aneurysm recanalization.

Vote: 11/13

3. In adult patients with aSAH who have neck remnants or partially occluded aneurysms (irrespective of type of aneurysm treatment), we suggest radiological follow-up beyond 6 months after aneurysm treatment as long as a potential re-treatment remains an option.

Vote: 13/13

4. In adult patients with aSAH who are treated with endovascular devices other than coils, we suggest radiological follow-up at least five years after treatment, regardless of the degree of occlusion, to ensure adequate long-term occlusion and as long as a potential re-treatment remains an option.

Vote: 11/13

5. In adult patients with aSAH, we suggest radiological follow-up beyond 6 months after aneurysm treatment in order to evaluate for de novo aneurysms at 5-year intervals as long as a potential treatment remains an option, in those with a high-risk profile (such as young age, positive family history for aSAH, autosomal dominant polycystic kidney disease).

Vote: 12/13

outcome, compared to radiological follow-up only until 6 months after aneurysm treatment.

Additional information

In the current literature, relevant studies are limited to the assessment of radiological follow-up beyond 6 months after aneurysm treatment in adult patients with aSAH. There are no studies available addressing radiological follow-up within 6 months after aneurysm treatment for comparison.

Recanalisation

Recanalisation of a treated aneurysm can occur at different stages with everything beyond 6 months being labelled as late recanalisation. Data on late recanalisation stem from non-randomised, uncontrolled studies, which show high heterogeneity in follow-up duration, follow-up modality, definition of recanalisation and rupture status of the aneurysm, limiting the generalisability of the studies.

A study enrolling 435 aSAH survivors after clipping, with a total follow-up time of 5681 patient-years found a probability of 0.7% of re-occurrence within 10 years for patients without a residual neck immediately after treatment, compared to 13.9% in patients with a neck remnant.²¹⁶ These results were confirmed by a recent meta-analysis including 1167 patients (463 with ruptured aneurysms) treated first line with the smart coil device, which showed a late recanalisation rate of 10% (95% CI, 6%–17%).²¹⁷ For the WEB device, late recanalisation rates of 11% and 11.5% were reported,^{218,219} while for flow-diverters, rates of adequate occlusion were higher at 12 months compared to 6 months and ranged between 77% and 92%.^{220–222} A WEB database study evaluating 763 patients, of whom 230 had treatment of a ruptured intracranial aneurysm, found an occlusion rate of 65.1% during a

mean follow-up duration of 17.7 months, with 7.3% of the patients requiring re-treatment.²²³ On multivariate analysis, independent factors negatively correlated with complete aneurysm occlusion at the last follow-up were being a former smoker (OR: 0.5; 95% CI, 0.3–0.8), maximal aneurysm diameter (OR: 0.8; 95% CI, 0.7–0.8) and the presence of an aneurysm wall branch (OR: 0.4; 95% CI, 0.28–0.73).

Recurrent SAH

The best available evidence on long-term risk of recurrent aSAH (either from the target aneurysm, another aneurysm at baseline or from a de novo aneurysm after aSAH) comes from the ISAT trial which followed the UK cohort for 18 years. In this cohort, the risk of recurrent aSAH between 30 days and 1 year was 0.6% in the coiling group and 0.4% in the clipping group; between 1 and 5 years, it was 0.021% and 0.006% and after 5 years, it was 0.5% and 0.3%, respectively. For the target aneurysm, the risk of recurrent aSAH was 1.6% in the coiling group and 0.5% in the clipping group suggesting a very limited clinical impact of prolonged surveillance.²²⁴ It may be that these numbers are an underestimation, since re-treatment may have prevented recurrent aSAH. In the long-term follow-up study, no data on follow-up imaging and re-treatment were available. On the other hand, in the era that ISAT was performed, re-treatment was rarely conducted.

We retrieved additional data from uncontrolled cohort studies. One study reported on 1001 patients with aSAH treated with coil or clip in 9 high-volume centres in the United States from 1996 to 1998.²²⁵ During a mean follow-up of 4 years, 19 post-procedural re-ruptures occurred. This study suggests a strong correlation of re-rupture risk and initial occlusion rate with higher rate of re-rupture in initially incompletely occluded aneurysms (overall risk: 1.1% for complete occlusion, 2.9% for 91%–99% occlusion, 5.9% for 70%–90%, 17.6% for < 70%; $P < .0001$ in univariate and multivariable analysis). In addition, long-term follow-up data (mean 73.7 months) from a single-centre study including 570 patients with coil embolisation after aSAH suggests a rate of late re-rupture (defined as > 30 days after treatment) of 1.6%, which is in line with the ISAT data.²²⁶

De novo aneurysm formation

De novo aneurysm formation is a second reason for extended follow-up. Studies on this topic are limited by incomplete follow-up, varying imaging modalities and a lack of standardisation in timing of imaging. This limits our understanding of the true rates of recurrence and/or re-rupture, particularly with the use of newer endovascular devices. A meta-analysis from 2018 including patients with and without SAH reported the overall incidence of de novo aneurysm formation of 2% (95% CI, 2%–3%) over a mean follow-up time of 8.3 years. If a de novo aneurysm was found, 11.2% were detected in the first 5 years, and the majority (88.8%) after more than 5 years.²²⁷ This study did not find a statistically significant difference in rates of de novo aneurysm formation between patients who had ruptured aneurysms and those with unruptured aneurysms. A recent meta-analysis including 9351 patients from 19 cohort studies published between 1993 and 2021 found that during a follow-up period of 2.5–18.5 years, 304 (3.25%) patients developed a de novo aneurysm.²²⁸ Main risk factors were age < 60 years (RR: 1.41; 95% CI, 1.25–1.58), female sex (RR: 1.63; 95% CI, 1.27–2.08), smoking history (RR: 1.37; 95% CI, 1.07–1.80), family history of IAs (RR: 2.30; 95% CI,

1.32–4.00) and multiple IAs at initial diagnosis (RR: 1.69; 95% CI, 1.11–2.58). In this paper a prediction model from those studies was developed. This prediction model showed an increasing risk for de novo aneurysms with an increasing risk score resulting in a 25% risk at scores of 16–23. Another study supported these risk factors and found that stage 3 or greater chronic kidney disease in patients with autosomal dominant polycystic kidney disease as an additional risk factor for de novo aneurysms.²²⁹

Different follow-up modalities must be used for microsurgical or endovascular therapy. As clips result in severe artefacts on MRI, only DSA or CTA are suitable for detecting recanalisation or a growing aneurysm remnant at the treated location. MRA is only useful for the detection of new aneurysms at other locations not affected by clip-related artefacts.

In conclusion, these data indicate that (progressive) recanalisation and recurrent SAH of a treated aneurysm or de novo aneurysm may occur beyond 6 months after aneurysm treatment. However, a beneficial effect of radiological follow-up beyond 6 months after aneurysm treatment on outcome has not been established. Most aneurysms with recanalisation will not rupture during a patient's lifetime, while re-treatment carries a risk of complications that may affect outcome. It remains unclear whether the beneficial effect on prevention of recurrent aSAH outweighs the risk of complications from re-treatment.

Discussion

We used the GRADE methodology to develop evidence-based recommendations and formulated expert consensus statements in areas of uncertainty to assist physicians in decision-making regarding patients with aSAH. All 15 evidence-based recommendations and 37 expert consensus statements are summarised in Table 3. Full consensus among the voting MWG members was obtained on 16 expert consensus statements, and a majority agreed on the other 21 statements. This ESO/EANS/ESMINT guideline on aSAH expands upon previous guidelines from the European Stroke Organisation (2013),⁴ American Heart Association/American Stroke Association (2023),²³⁰ and Neurocritical Care Society (2023).²³¹ The 2013 ESO guideline addressed the management of both unruptured intracranial aneurysms and subarachnoid haemorrhage. In 2022, the ESO guideline was updated for unruptured intracranial aneurysms.²¹⁵

Only a few evidence-based recommendations in this guideline are supported by high-level evidence. These include the use of oral nimodipine (PICO 4) and treatment of the ruptured aneurysm by regular coiling when both regular coiling and microsurgical clipping are equally suitable in patients who are in a good clinical condition (PICO 3). In addition, there were evidence-based recommendations with a moderate level of evidence *against* giving antifibrinolytic drugs (PICO 1), tirilazad, statins, magnesium sulphate, or ETRAs (all PICO 4). There was a low level of evidence for the routine use of lumbar drains (PICO 4). Although 3 RCTs were performed investigating the effect of LD, we could only include data from 2 RCTs in a pooled analysis on functional outcome and concluded that no recommendation could be made on the routine use of lumbar drains until more RCT data become available. Also for PICO 5, there was a low-level of evidence. This is particularly noteworthy given the widespread clinical use of rescue therapy (induced hypertension or endovascular treatment of vasospasm) in patients who develop DCI. Similarly, there was a

very low-level of evidence for the use of endovascular techniques and devices other than regular coiling for the treatment of the ruptured aneurysm, despite their widespread use. In areas where more guidance was needed, expert consensus statements were developed to support clinical decision-making in routine practice.

One of the major differences from the previous ESO guideline is that we now address the use of balloon-assisted coiling, intrasaccular devices, stent-assisted coiling and flow-diverting stents for the treatment of the ruptured aneurysm. Although the ISAT trial²³² demonstrated that regular coiling is superior to microsurgical clipping for (small neck) ruptured aneurysms that are equally suitable for both approaches, it is often assumed that advanced endovascular techniques offer a similar advantage over microsurgical clipping. However, this assumption has not been confirmed in an RCT. Studies in unruptured intracranial aneurysms show that stent-assisted coiling and flowdiverting stents are associated with a higher risk of treatment complications compared to regular coiling.²³³ The ISAT-2 trial compared any endovascular treatment (>80% treated by balloon-assisted coiling) with microsurgical treatment of the ruptured intracranial aneurysm, but the trial was prematurely terminated because of poor enrolment and was therefore underpowered to draw strong conclusions.

The literature on endovascular treatment options for intracranial aneurysms primarily consists of case series or registries, most of which are retrospective or sponsored by industry, and the few comparative studies mostly have a non-randomised design. The only randomised comparison was severely underpowered because it was stopped prematurely when only 14% of the patients needed were included. The available studies also have other methodological flaws. In a systematic review of 1356 studies with 410,993 patients, key outcomes were rarely clearly defined and were often incompletely reported.²³⁴ A definition for safety was provided in only 2% of studies, and only 0.1% specified a complication, mortality or morbidity rate below which a procedure would qualify as safe. Definitions of effectiveness were similarly uncommon: only 2% addressed this outcome at the aneurysm level, and none defined a threshold for ineffectiveness. Another review evaluating flow-diverting stents for unruptured intracranial aneurysms reported industry involvement or conflicts of interest in 7 of 13 studies, highlighting the potential for bias in the published outcomes.²³⁵ We recommend investigator-initiated RCTs in which the safety, efficacy and durability of new devices are compared with existing treatment options, with predefined outcomes that are assessed by independent outcome assessors without industry involvement.

In the absence of high-level evidence for the use of advanced endovascular treatments in situations where regular coiling of the ruptured aneurysm is not possible, we formulated expert consensus statements in which it was suggested to have an interdisciplinary discussion on the safety, effectiveness and durability of the microsurgical and endovascular options other than regular coiling to decide upon the preferred strategy. If regular coiling is not possible, we suggest that the multidisciplinary team discusses the safety, effectiveness and durability of microsurgical and alternative endovascular options to determine the preferred treatment strategy, given the limited comparative evidence available. Stent-assisted coiling has a less favourable safety profile in patients with a ruptured aneurysm, so we suggest that this treatment is only performed if other treatment options are not feasible. Flow diversion also has a less favourable safety profile and often does not result in

Table 3 Synoptic table of all recommendations and expert consensus statements.

Recommendation	Expert consensus statement
PICO 1a: In adult patients with aSAH, does treatment with antifibrinolytic drugs compared to no antifibrinolytic drugs decrease the risk of poor functional outcome?	
In adult patients with aSAH, we recommend against routine administration of antifibrinolytic drugs prior to treatment of the ruptured aneurysm to decrease the risk of poor functional outcome. Quality of evidence: Moderate ⊕⊕⊕ Strength of recommendation: Strong against intervention ↓↓	
PICO 1b: In adult patients with aSAH, does treatment with antihypertensive drugs compared to no antihypertensive drugs decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on the administration of blood pressure lowering drugs prior to treatment of the ruptured aneurysm to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation:-	1. In adult patients with aSAH and systolic blood pressures higher than 160-180 mm Hg persisting after installment of analgesics, oral nimodipine and urinary catheter prior to aneurysm treatment, we suggest considering blood pressure lowering drugs to lower systolic blood pressure to around 160 mm Hg to reduce the risk of rebleeding. 2. If it is decided to give blood pressure lowering drugs, we suggest continuous infusion of short-acting drugs, e.g. labetalol, and avoiding diuretic drugs to maintain normovolemia. Care should be taken to ensure that the blood pressure reduction is gradual, with systolic blood pressure reduced cautiously over time (corresponding to no more than a 10% reduction in mean arterial pressure within the first 2 hours) to decrease the risk of DCI.
PICO 2: In adult patients with aSAH, does early aneurysm occlusion compared to no early aneurysm occlusion decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on treating the ruptured aneurysm as early as possible to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	In adult patients with aSAH, we suggest treatment of the ruptured aneurysm within 24 hours after ictus. The timing should be optimized to ensure that the most dedicated team of experts is available when needed.

Table 3 Continued.

PICO 3a: In adult patients with aSAH, does any type of endovascular aneurysm occlusion compared to neurosurgical aneurysm occlusion decrease the risk of poor functional outcome?	
In adult patients with aSAH in good clinical condition (WFNS I-III) with aneurysms of either the anterior or posterior circulation that can be treated by either regular coiling (i.e. without adjunctive devices) or neurosurgical clipping, we recommend regular coiling as the preferred strategy to decrease the risk of poor functional outcome. Quality of evidence: High ⊕⊕⊕⊕ Strength of recommendation: Strong for intervention ↑↑	1. We suggest that all patients with aSAH are discussed in an interdisciplinary manner, with at least one neurosurgeon and one neuro-interventionalist. 2. In adult patients with aSAH, we suggest the team discuss which modality would result in the best clinical outcome of the specific patient, with the safest and optimal occlusion of the specific aneurysm. 3. In adult patients with aSAH younger than 45 years of age, we suggest that the better long-term protection from clipping compared to coiling is taken into consideration for choosing the treatment modality of the aneurysm. 4. In adult patients with aSAH admitted in a poor clinical condition (defined as GCS < 13), we suggest a multidisciplinary approach to decide on type and timing of aneurysm treatment taking into account the (presumed) cause of the poor clinical condition. 5. In adult patients with aSAH and a poor or worsening clinical condition from a space-occupying intracerebral or subdural haematoma, we suggest immediate surgery for aneurysm clipping and haematoma removal.
PICO 3b: In adult patients with aSAH, does any type of endovascular aneurysm treatment other than coiling compared to coiling of the ruptured aneurysm decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on the use of endovascular treatment options other than regular coiling for treatment of the ruptured aneurysm to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	1. Given the limited comparative evidence available, we suggest that in adult patients with subarachnoid haemorrhage from a ruptured aneurysm which cannot be treated with regular coiling, the multidisciplinary team safety, effectiveness, and durability of microsurgical and alternative endovascular options to determine the preferred treatment strategy. 2. In adult patients with aSAH, we suggest stent-assisted coiling in selected cases where other treatment options are not feasible. 3. In adult patients with aSAH, we suggest to reserve flow diversion as a last-line treatment option.

Table 3 Continued.

PICO 4: In adult patients with aSAH, does any type of medical treatment aiming to reduce the risk of delayed cerebral ischaemia (DCI) compared to no such treatment decrease the risk of poor functional outcome?	
In adult patients with aSAH, we recommend prophylactic treatment with oral nimodipine to decrease the risk of poor functional outcome. Quality of evidence: High ⊕⊕⊕⊕ Strength of recommendation: Strong for intervention ↑↑ In adult patients with aSAH, we do not recommend prophylactic treatment with either tirilazad, statins, magnesium sulfate, or endothelin receptor antagonists to decrease the risk of poor functional outcome. Quality of evidence: Moderate ⊕⊕⊕ Strength of recommendation: Strong against intervention ↓↓ In adult patients with aSAH, no recommendation can be made on prophylactic treatment with antiplatelet drugs or lumbar drainage to decrease the risk of poor functional outcome until further data from RCT are available. Quality of evidence: Low ⊕⊕ Strength of recommendation: -	
PICO 5a: In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, does hypertension induction compared to no hypertension induction decrease the risk of poor functional outcome?	
In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, no recommendation can be made on hypertension induction to decrease the risk of poor functional outcome. Quality of evidence: Low ⊕⊕ Strength of recommendation: -	In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, we suggest considering induced hypertension, provided that the ruptured aneurysm is treated and after standard therapy has proven insufficient. Clinical contraindications and potential complications of induced hypertension should be considered.

Table 3 Continued.

PICO 5b: In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, does endovascular treatment of vasospasm compared to no endovascular treatment decrease the risk of poor functional outcome?	
In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia, no recommendation can be made on endovascular treatment of vasospasm to decrease the risk of poor functional outcome. Quality of evidence: Low ⊕⊕ Strength of recommendation -	1. In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia in combination with refractory and severe vasospasm, we suggest considering intra-arterial pharmacological treatment as a rescue therapy in selected patients to decrease the risk of poor functional outcome. 2. In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia in combination with refractory severe vasospasm, the current evidence is insufficient to support the routine use of mechanical vasodilatation with balloon angioplasty. In selected cases, this approach may be considered as a last-line rescue treatment after careful multidisciplinary discussion of the potential risks and uncertain benefits. 3. In adult patients with aSAH and clinical deterioration due to delayed cerebral ischaemia in combination with refractory severe vasospasm, the current data are insufficient to support the use of mechanical vasodilatation with temporary deployment of retrievable stents to of poor functional outcome.
PICO 6a: In adult patients with aSAH, does any type of neuroimaging compared to regular neurological examination decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on neuroimaging to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	1. In adult patients with aSAH and clinical deterioration, we suggest plain head CT in combination with CT-Perfusion (CTP) imaging to detect the cause of deterioration. 2. In adult patients with aSAH who are neurologically not assessable but at high risk for DCI, we suggest plain head CT and CTP at least once between day 4 and 14. 3. In adult patients with aSAH, we do not suggest a routine DSA for screening of macrovascular vasospasm.

Table 3 Continued.

PICO 6b: In adult patients with aSAH, does any type of neuromonitoring compared to regular neurological examination decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on neuromonitoring to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	1. In adult patients with aSAH, no suggestion can be given on the use of TCD monitoring. 2. In adult patients with aSAH and radiological hydrocephalus who are neurologically not assessable, we suggest ICP monitoring via EVD if an EVD is in place. 3. In adult patients with aSAH without radiological hydrocephalus who are neurologically not assessable, no suggestion can be given on ICP monitoring. 4. In adult patients with aSAH who are neurologically not assessable, we do not suggest invasive multimodal neuromonitoring with continuous measurement of partial pressure of brain tissue oxygen (PbtO₂) and/or microdialysis due to the uncertain risk/benefit ratio of these modalities. 5. In adult patients with aSAH who are neurologically not assessable, we do not suggest the routine use of continuous EEG monitoring.
PICO 7: In adult patients with aSAH, does treatment of hydrocephalus (either by EVD, VP-shunt or lumbar drainage) compared to no treatment of hydrocephalus decrease the risk of poor functional outcome?	
In adult patients with aSAH and hydrocephalus, no recommendation can be made on CSF diversion strategies to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	1. In adult patients with aSAH who present with radiological hydrocephalus and a decreased level of consciousness, we suggest CSF drainage. 2. In adult patients with aSAH who present with obstructive hydrocephalus and a decreased level of consciousness, we suggest EVD placement. 3. In adult patients with aSAH who present with communicating hydrocephalus and a decreased level of consciousness, we suggest LD or repeated LPs as the strategy of first choice for CSF drainage.

Table 3 Continued.

	4. In adult patients with aSAH who present with radiological hydrocephalus and a normal level of consciousness, we do not suggest CSF drainage. 5. In adult patients with aSAH who come at a point at which prolonged CSF drainage (by EVD, LD or repeated LPs) carries a higher risk of severe complications than placement of a permanent CSF diversion, we suggest permanent CSF diversion. 6. In adult patients with aSAH who present with symptomatic chronic hydrocephalus, we suggest permanent CSF diversion.
PICO 8: In adult patients with aSAH, does treatment on a dedicated neuro-ICU or high care unit compared to a general ICU or high care unit decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on admission to a dedicated neuro-ICU or high care unit to decrease the risk of poor Quality of evidence: Very low ⊕ Strength of recommendation: -	In adult patients with aSAH, we suggest admission and management in a dedicated neuro-ICU or high care unit to decrease the risk of poor functional outcome.
PICO 9a: In adult patients with aSAH, does treatment in a high-volume centre compared to a low-volume centre decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on admission/transfer to a high-volume centre to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	We suggest that all patients with spontaneous SAH are admitted or immediately transferred to centres that treat at least 70 patients with aSAH per year, or at least 35 patients with aSAH per year in remote areas where access is limited.
PICO 9b: In adult patients with aSAH, does aneurysm treatment by a high-volume neurosurgeon or neurointerventionalist compared to a low-volume neurosurgeon or neurointerventionalist decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on case-volume per neurosurgeon and neurointerventionalist to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	In adult patients with aSAH, we suggest that aneurysms are repaired by neurosurgeons or neurointerventionalists who perform the treatment of choice in more than 30 patients with aneurysms (ruptured and unruptured) per year.

Table 3 Continued.

PICO 10: In adult patients with aSAH, does a radiological follow-up beyond 6 months after aneurysm treatment compared to a maximum radiological follow-up duration of 6 months decrease the risk of poor functional outcome?	
In adult patients with aSAH, no recommendation can be made on radiological follow-up beyond 6 months after microsurgical or endovascular aneurysm treatment to decrease the risk of poor functional outcome. Quality of evidence: Very low ⊕ Strength of recommendation: -	1. In adult patients with aSAH who are treated with coils and adequate occlusion within 6 months, we suggest at least one additional radiological follow-up at or beyond 12 months after aneurysm repair to investigate potential aneurysm recanalization, as long as a potential re-treatment remains an option. 2. In adult patients with aSAH who were treated with clip reconstruction and adequate occlusion within 6 months, we do not suggest further radiological follow-up to investigate potential aneurysm recanalization. 3. In adult patients with aSAH who have neck remnants or partially occluded aneurysms (irrespective of type of aneurysm treatment), we suggest radiological follow-up beyond 6 months after aneurysm treatment as long as a potential re-treatment remains an option. 4. In adult patients with aSAH who are treated with endovascular devices other than coils, we suggest radiological follow-up at least five years after treatment, regardless of the degree of occlusion, to ensure adequate long-term occlusion and as long as a potential re-treatment remains an option. 5. In adult patients with aSAH, we suggest radiological follow-up beyond 6 months after aneurysm treatment in order to evaluate for de novo aneurysms at 5-year intervals as long as a potential treatment remains an option, in those with a high-risk profile (such as young age, positive family history for aSAH, autosomal dominant polycystic kidney disease).

Abbreviations: aSAH = aneurysmal subarachnoid haemorrhage; CSF = cerebrospinal fluid; CTP = CT perfusion; DCI = delayed cerebral ischaemia; DSA = digital subtraction angiography; EEG = electroencephalogram; EVD = external ventricular drain; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ICU = intensive care unit; LD = lumbar drainage; LP = lumbar puncture; MAP = mean arterial pressure; PbtO₂ = partial pressure of brain tissue oxygen; PICO = population, intervention, comparator and outcome; TCD = transcranial Doppler; VP-shunt = ventriculoperitoneal shunt; WFNS = World Federation of Neurosurgical Societies.

immediate aneurysm occlusion, which may lead to rebleeding of the ruptured aneurysm in the first few days. Therefore, we suggest to reserve flow diversion as a last-line treatment option.

Another important difference to the 2013 ESO guideline⁴ is the expert consensus statement on the timing of aneurysm treatment. The 2013 guideline suggested treating the ruptured aneurysm “as early as logistically and technically possible to reduce the risk of rebleeding; if possible, it should be aimed to intervene at least within 72 h after onset of first symptoms.” This was based on a small randomised trial,³³ which showed a trend towards better outcomes in patients operated within 3 days after the bleeding. The current ESO/EANS/ESMINT guideline suggests “treatment of the ruptured aneurysm within 24 hours after ictus; the timing should be optimised to ensure that the most dedicated team of experts is available when needed.” Nevertheless, the timing of aneurysm treatment remains a topic

of debate. Although ultra-early aneurysm treatment within 24 h or even emergency aneurysm treatment within 6 h after ictus may reduce the risk of rebleeding, it may be that such early aneurysm treatment, or related general anaesthesia, increases the extent of early brain injury and the risk of DCI, thereby offsetting the beneficial effect on rebleeding.²³⁶ However, the current literature on aneurysm treatment within 24 h after ictus only consists of low-quality observational studies. A randomised trial is required to determine the optimal timing of aneurysm treatment within the 72-h window, if deemed ethically acceptable.

Also, since the publication of the 2013 ESO guidelines, the results of 3 randomised trials on rescue therapy in patients with DCI have been published.^{150,154,155} The RCTs on hypertension induction and intra-arterial nimodipine showed no effect on functional outcome, while the other RCT on endovascular treatment of vasospasm showed worse outcomes in those treated

endovascularly compared with those receiving hypertension induction. However, each of these trials included less than 70 patients and were thus underpowered to draw strong conclusions and to formulate evidence-based recommendations. Although some people may feel that it is unethical to include patients with DCI in an RCT to investigate the effect of rescue therapy, and thus withhold rescue therapy in the control arm of the trial, the results of the 3 available RCTs show that new trials on this topic are urgently needed. This ESO/EANS/ESMINT guideline committee on aSAH endorses the conduct of future RCTs to definitively assess the effects of hypertension induction or endovascular treatment of vasospasm in patients with aSAH who develop DCI.

We also need to address certain limitations. First, for most PICO, no data from RCTs were available to develop evidence-based recommendations based on high-level evidence. For the expert consensus statements, we often used data from observational studies, which were at high risk of bias. Second, the proposed minimum volumes for centres (70 aSAH patients per year, or 35 per year for centres in remote areas) and for interventionalists (30 procedures per year, in either ruptured or unruptured aneurysms) may appear high. However, they are consistent with the growing body of evidence demonstrating improved outcomes with higher aneurysm treatment volumes.^{237–239} The majority (12/13 votes) of the MWG agreed that centralised and specialised care is necessary for improving patient outcomes.

In conclusion, this guideline offers up-to-date, evidence-based recommendations and expert consensus statements for the management of patients with aSAH. Given that the majority of PICOs are supported by low-level, very low-level or no evidence, we strongly encourage the conduct of RCTs or well-designed prospective comparative studies focusing on clinically relevant outcomes related to the diagnosis, prevention and treatment of complications following aSAH.

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Author contributions

All PICO leaders and the guideline chairs were involved in writing the first draft of the manuscript. L.H. conducted the statistical analyses. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Supplemental material

Supplementary material is available at *European Stroke Journal* online.

Conflicts of interest

All authors have completed a declaration of competing interests and details are available in [Table S1](#).

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