# RECOMMENDATIONS FOR THE MANAGEMENT OF MEDICAL COMPLICATIONS IN PATIENTS FOLLOWING ANEURYSMAL SUBARACHNOID HEMORRHAGE

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SUMMARY – These are evidence based guidelines for the management of medical complications in patients following aneurysmal subarachnoid hemorrhage, developed and endorsed by the Croatian Society of Neurovascular Disorders, Croatian Society of Neurology including Section for Neurocritical Care, Croatian Neurosurgical Society, Croatian Society for Difficult Airway Management and Croatian Medical Association. They consist of recommendations for best monitoring, medical treatment and interventions based on the literature, evaluation of the results of large international clinical trials, and collective experience of the authors.

Key words: *Subarachnoid hemorrhage; Aneurysm; Complications; Medical treatment; Practice guideline*

Subarachnoid hemorrhage (SAH) is a relevant health problem and a significant cause of morbidity and mortality throughout the world. The annual incidence of aneurysmal SAH (aSAH), which varies widely among populations, perhaps because of genetic differences, competing burden of disease and issues of case ascertainment, is generally accepted to be 9.1 *per* 100 000 *per* year worldwide[1]. Because death resulting from aSAH often occurs before hospital admission, the true incidence of aSAH might be even higher[2]. The data also show that the incidence of aSAH increases with age, with a typical average age at onset

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in adults ≥50 years[1,3], increases as children get older[1,4], is higher in women than in men[5], with a higher incidence reported in younger men (24-45 years of age), in women between 55 and 85 years and men >85 years of age, and also differs according to race and ethnicity[6,7].

The prognosis of aSAH is influenced by multiple non-modifiable factors and by factors that can be influenced by therapeutic interventions and management procedures. The most reliable data on the natural history of ruptured saccular intracranial aneurysms are obtained from the study by Pakarinen *et al.*[8]. Cumulative case fatality rates over time after aSAH are as follows: day 1: 25%-30%; week 1: 40%-45%; first month: 50%-60%; sixth month: 55%-60%; year 1: 65%; and year 5 after SAH: 65%-70%. It is estimated that approximately 12% of patients die before reaching medical attention[9]. If those patients who die before medical attention are included, 43% of all SAH patients die without recovering from the initial bleeding; of those, 74% die within the first 24 hours, 7% within 2-3 days, 12% within 4-7 days, 5% within week 2, 1% within week 3, and 1% later than 3 weeks after the initial SAH[8]. If a ruptured aneurysm is left untreated, about one-third of patients who recover from the initial hemorrhage die because of recurrent bleeding within 6 months after SAH[10]. The cumulative risk of rebleeding by 6 months after SAH is 50%, the annual risk of rebleeding decreases to 3% during the next 10 years, while in two-thirds of these late, recurrent bleedings cause death[11-13]. Despite improvements in surgical and medical treatment, rupture of an aneurysm is still associated with high rates of case fatality (roughly one-third) and severe disability (one-sixth)[14,15]. However, between 1973 and 2002, the case fatality rate decreased by approximately 17%[16] and the possibility to recover an independent state has increased by 1.5% *per* year[14]. Case fatality and functional outcome after SAH are determined by the severity of the initial bleeding[14,17], age[17,18], aneurysm site[18] and size[17,18], history of hypertension[17,18], high systolic blood pressure[17], heavy alcohol consumption[19] and cigarette smoking, that has also been reported to increase the risk of delayed cerebral ischemia (DCI)[20].

After aneurysm rupture, the possibility of poor outcome rises and is probably determined by multiple independent factors including disease-associated events, treatment-associated factors and complications associated with prolonged bed rest. As described above, aSAH can have devastating effects on the central nervous system as well as a profound impact on several other organs. The course of the disease can be prolonged and additionally complicated by systemic manifestations affecting cardiovascular, pulmonary and renal function. Due to profound effects of the hemorrhage itself and accompanying complications, aSAH patients are routinely admitted to an intensive care unit (ICU) and are cared for by a multidisciplinary team including neurologists-neurointensivists, neurosurgeons, anesthesiologists and interventional neuroradiologists. The ICU course of aSAH patients ranges from a few days to a few weeks and is frequently accompanied by multiple medical complications[21], including the following: hydrocephalus, rebleeding, delayed cerebral ischemia from vasospasm, seizures, cardiopulmonary complications and hyponatremia.

There have been few guidelines published for aSAH management[22-24], emphasizing mostly risk factors, prevention, natural history and prevention of rebleeding, and recommendations discussing the critical care issues involved in the care of aSAH patients[21]. Since the complex multiorgan pathophysiology of aSAH presents a multitude of clinical challenges which demand attention[21], the purpose of these Recommendations is to offer an overview and practice guidelines for the management of medical complications in patients following aSAH, being responsible for the outcome and health-related quality of life in patients after aSAH. Recommendations are in accordance with the Recommendations of the Neurocritical Care Society's Multidisciplinary Consensus Conference[21], Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage for Healthcare Professionals of the American Heart Association/American Stroke Association[22], and European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage[23]. Recommendations have been developed based on the literature, evaluation of the results of large international randomized controlled trials and the collective experience of the authors. These Recommendations have been assessed and endorsed by the Croatian Society of Neurovascular Disorders, Croatian Society of Neurology – Section of Neurocritical Care, Croatian Society of Neurosurgery, and Croatian Society for Difficult Airway Management.

These Recommendations are assessing the complications of aSAH. Because of the multiplicity of different complications and low incidence of each, not being high enough to conduct a prospective clinical trial, the superiority of certain procedure over the other was not possible to assess. Most of the complications are managed according to the expert opinion. Therefore, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was preferred for the evaluation of evidence and recommended treatment.

As specified, the quality of the data was assessed and recommendations have been developed using the GRADE system[25]. The quality of evidence was graded as:

- High = Further research is very unlikely to change our confidence in the estimate effects.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low = Any estimate of effect is very uncertain.

The GRADE system classifies recommendations as strong or weak, according to the balance among benefits, risks, burden and cost, and the quality of evidence. An advantage of GRADE system is that it allows for strong recommendations in the setting of lower quality evidence and thus it is well suited to this situation[25]. Recommendations were either strong or weak and based primarily on the quality of evidence and translation of the evidence into practice in a specific setting.

## Hydrocephalus

Aneurysmal SAH can cause hydrocephalus, defined as a bicaudate index on the computed tomography (CT) scan exceeding the 95$^{th}$ percentile for age, by two mechanisms: obstruction of cerebrospinal fluid (CSF) pathways (i.e. acute, obstructive, noncommunicating type) and blockage of arachnoid granulations by scarring (i.e. chronic, delayed, nonobstructive, communicating type)[26]. Acute hydrocephalus occurs in 15% to 87% of patients with aSAH[27,28]. Chronic shunt-dependent hydrocephalus occurs in 8.9% to 48% of patients with aSAH[29-31].

Acute hydrocephalus may be caused by obstruction of the CSF circulation pathways by interfering with CSF outflow through the sylvian aqueduct, fourth ventricular outlet, basal cisterns and subarachnoid space. CSF production and absorption rates are unaltered[32]. Intraventricular blood is the strongest determinant for the development of acute hydrocephalus. Other risk factors include bilateral ambient cisternal blood, increased age, vasospasm, use of antifibrinolytic drugs, left ventricular systolic dysfunction, subdural hematoma and seizures[33]. Acute hydrocephalus associated with SAH is usually managed by external ventricular drainage or lumbar drainage. External ventricular drainage for patients with aSAH is generally associated with neurological improvement[34]. About one-third of patients with acute hydrocephalus are asymptomatic and half of the patients with initial hydrocephalus and impairment of consciousness improve spontaneously within 24 hours[35]. Patients with acute hydrocephalus may be in poor neurological condition immediately after aSAH and have dilated ventricles on CT scan. Such acute hydrocephalus is related to the amount of intraventricular hemorrhage rather than aneurysmal bleeding itself[36]. Some neurosurgeons prefer not to use ventricular drain in these patients immediately, as half of them will improve spontaneously and there is a risk of rebleeding and infection. The risk of aneurysm rebleeding with external ventricular drainage has been studied in 3 retrospective case series, and the risk of rebleeding was found to be high in one study[37], whereas the other 2 studies found no increased risk[38,39]. Although ventriculostomy increases the risk of rebleeding and meningitis/ventriculitis[40], the recommended approach is to start immediate external ventricular drainage keeping intracranial pressure between 10 and 20 mm Hg in all of these patients, if there is no other obvious explanation for a reduced level of consciousness, such as massive intracerebral hemorrhage (ICH)[41]. Lumbar drainage as a consecutive treatment of external ventricular drainage before shunting for the treatment of aSAH associated hydrocephalus has been reported to be safe in terms of no increase in the risk of rebleeding, particularly in patients with spontaneous ICH when the third and fourth ventricles are free of blood, i.e. communicating hydrocephalus. This approach may be considered as an alternative approach to reduce the frequency of permanent shunts, but it is important to pay attention to downward herniation in case of supratentorial swelling and the development of hygroma[42,43]. The theoretical risk of tissue shift after placement of lumbar drain in patients with severe intracranial hypertension should be considered when deciding which method of cerebrospinal fluid diversion to use, particularly in patients with associated intraparenchymal hematomas. When obstructive hydrocephalus is suspected, an external ventricular drainage should be preferred. Furthermore, preliminary data have also suggested that lumbar drainage is associated with a reduced incidence of vasospasm[44,45]. Serial lumbar punctures to manage acute aSAH associated hydrocephalus have also been described as safe, but this strategy has only been assessed in small retrospective series[38,46].

Only a proportion of patients with aSAH associated acute hydrocephalus develop shunt-dependent chronic hydrocephalus. A number of retrospective series have attempted to identify factors predictive of its development[29,30,47,48]. A meta-analysis of 5 nonrandomized studies with 1718 pooled patients (1336 having undergone clipping and 382 having undergone coiling) found a lower risk of shunt dependency in the clipping group (relative risk 0.74; 95% confidence interval, 0.58-0.94) than in the coiling group ($p<0.01$)[48]. However, only 1 out of 5 studies showed an independent significant difference[49]. Three other nonrandomized series not included in the meta-analysis showed no significant difference between clipping and coiling in shunt-dependent chronic hydrocephalus[31,50,51]. Fenestration of lamina terminalis has been suggested to reduce the incidence of shunt-dependent chronic hydrocephalus, yet a meta-analysis of 11 randomized studies with 1973 pooled patients found no significant difference between patients who had and had not undergone fenestration of the lamina terminalis[52]. A nonrandomized study not included in the meta-analysis and not reporting statistical significance compared 95 patients who had undergone aneurysmal clipping, cisternal blood evacuation and lamina terminalis fenestration with 28 comparable, non-blood-cleansed, endovascular therapy-treated patients and found that shunt-dependent hydrocephalus occurred in 17% of surgical patients *versus* 33% of patients treated with endovascular therapy[50].

***Recommendations for the management of hydrocephalus associated with aSAH***

- Aneurysmal SAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (external ventricular drainage or lumbar drainage, depending on the clinical scenario) (Moderate Quality Evidence; Strong Recommendation).
- Aneurysmal SAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion (Low Quality of Evidence; Strong Recommendation).
- Weaning external ventricular drainage over >24 hours does not appear to be effective in reducing the need for ventricular shunting (Moderate Quality of Evidence; Weak Recommendation).
- Routine fenestration of the lamina terminalis is not useful for reducing the rate of shunt-dependent hydrocephalus and therefore should not be routinely performed (Moderate Quality of Evidence; Weak Recommendation).

## Rebleeding

Rebleeding following aSAH is a common event and is associated with very high mortality and poor prognosis for functional recovery in survivors. The risk of rebleeding is maximal in the first 2 to 12 hours, more than one-third of rebleeds occur within 3 hours, and nearly half within 6 hours of symptom onset[53], with reported rates of occurrence between 4% and 13.6% within the first 24 hours (that is, during transportation or before the treatment team is able to occlude the aneurysm)[54], and 5%-10% in the first 72 hours[55]. Early rebleeding is associated with worse outcome than later rebleeding[56]. Patients surviving the first day after the initial aSAH have a cumulative risk of 35%-40% to suffer rebleeding of the aneurysm, with a mortality rate of about 40%. After 4 weeks, the risk of rebleeding decreases to about 3%/year[57]. Factors associated with aneurysm rebleeding include longer time to aneurysm treatment, worse neurological status on admission, initial loss of consciousness, previous sentinel headaches, larger aneurysm size and possible systolic blood pressure >160 mm Hg[58-60]. Genetic factors, although related to the occurrence of intracranial aneurysms, do not appear to be related to an increased incidence of rebleeding[61].

The primary goal of the treatment of aneurysmal SAH is immediate repair of the ruptured aneurysm, in order to close the bleeding source and prevent rebleeding. Some patients either have too high Hunt and Hess Scale (HHS) score for immediate repair or require transport to a center where repair can be performed by experienced team, in order to minimize the serious procedural side effects of repair. Those facts can lead to further delay in repair and increased risk of rebleeding. Among the patients who present in a delayed manner and during the vasospasm window, delayed obliteration of aneurysm is associated with a higher risk of rebleeding[62]. Three interventions are considered that might modulate the risk of rebleeding: blood pressure control, antifibrinolytic therapy, and catheter *versus* CT.

### *Blood pressure control*

There is a general agreement that acute hypertension should be controlled after aSAH and until aneurysm obliteration, but parameters for blood pressure control have not been defined and there are no systematic data that address blood pressure levels in patients with unsecured aneurysms in relation to the risk of rebleeding. Data from observational studies suggest that aggressive treatment of blood pressure may decrease the risk of rebleeding, but at the cost of an increased risk of secondary ischemia[63]. Recent series do not report rebleeding at systolic blood pressure in the range of 160-200 mm Hg[63]. It seems reasonable, but without good evidence, to stop any antihypertensive medication that the patients were using and not to treat hypertension unless the blood pressure is extreme. It is not possible to give limits for 'extreme' blood pressure because it differs in different patients according to their age, previous blood pressure, cardiac history, and other factors and limits should be set on an individual basis. The clear consensus is that modest blood pressure elevation (mean arterial pressure <110 mm Hg; systolic blood pressure <160 mm Hg) is not associated with rebleeding and does not require therapy; extreme hypertension, i.e. if the systolic blood pressure exceeds 180 mm Hg, in patients with an unsecured, recently ruptured aneurysm, should be treated aiming to a modest (e.g., 25%) decrease in the mean arterial pressure; pre-morbid baseline blood pressures should be used to refine targets and hypotension should be avoided[21].

A variety of titratable medications are available. Nicardipine may give smoother blood pressure control than labetalol[64] and sodium-nitroprusside[65], although data showing different clinical outcomes are lacking. Although lowering cerebral perfusion pressure may lead to cerebral ischemia[63], a cohort study of neurologically critically ill patients did not find an association between the use of nicardipine and reduced brain oxygen tension[66]. To conclude, between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure.

### *Antifibrinolytic therapy*

Because of the increased risk of intracranial bleeding from thromboprophylaxis by means of low-molecular weight heparins, more often intracranial bleeding complications and no overall influence on outcome or appearance of post-aSAH cerebral infarction[67,68], the use of stockings and/or pneumatic devices seems more appropriate in aSAH patients before occlusion of the aneurysm[23]. In case that deep vein thrombosis prevention is indicated, low-molecular-weight heparin should be applied not earlier than 12 h after surgical occlusion of the aneurysm and immediately after coiling[23].

Antifibrinolytic therapy has been shown to reduce the incidence of aneurysm rebleeding when there is a delay in aneurysm obliteration. In a Cochrane review including 9 randomized trials of antifibrinolytic drugs in aSAH, antifibrinolytic treatment reduced the risk of rebleeding but did not influence death from all causes or a poor outcome[69]. One referral center instituted a policy of short-term use of aminocaproic acid to prevent rebleeding during patient transfer. It led to a decreased incidence of rebleeding, without increasing the risk of delayed cerebral ischemia and increased risk of deep venous thrombosis but no pulmonary embolism, with no effect on 3-month clinical outcomes[70]. A Swedish trial tested a strategy where tranexamic acid was given as soon as aSAH had been diagnosed in the local hospital (before the patients were transported) and continued until aneurysm occlusion, which was typically performed within 72 hours. It showed again the overall outcome that did not appreciably improve in patients treated with tranexamic acid, despite an impressive reduction in rebleeding[71]. If this trial is pooled with the 9 other trials included in the Cochrane review, there is still no effect on overall outcome[72].

Antifibrinolytic therapy is relatively contraindicated in patients with risk factors for thromboembolic complications (Moderate Quality Evidence; Strong Recommendation) and consequently, patients treated with antifibrinolytic therapy should have close screening for deep venous thrombosis (Moderate Quality Evidence; Strong Recommendation)[21]. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding and no compelling medication contraindications, short term (<72 hours) therapy with tranexamic acid or aminocaproic acid to reduce the risk of early aneurysm rebleeding is reasonable[22] (Moderate Quality Evidence; Moderate Recommendation). In accordance with the above, an early, short course of antifibrinolytic therapy prior to early aneurysm repair (begun at diagnosis, continued up to the point at which the aneurysm is secured or at 72 hours post-ictus, whichever is shorter) should be considered[21] (Low Quality Evidence; Weak Recommendation). Furthermore, delayed (>48 hours after the ictus) or prolonged (>3 days) antifibrinolytic therapy exposes patients to side effects of therapy when the risk of rebleeding is sharply reduced and should be avoided[21] (High Quality Evidence; Strong Recommendation) and it should be discontinued 2 hours before planned endovascular ablation of the aneurysm[21] (Very Low Quality Evidence; Weak Recommendation).

Neither aminocaproic acid nor tranexamic acid is approved by the United States Food and Drug Administration (US FDA) or by European Medical Agency (EMA) for the use in European Union, for prevention of aneurysm rebleeding[22]. There is currently no medical treatment that improves outcome by reducing rebleeding[23] (High Quality Evidence; Strong Recommendation). Although theoretically recombinant factor VIIa might prevent rebleeding, at this moment there is no evidence to support the use of recombinant factor VIIa outside study protocols in patients with aSAH[23]. Further definitive evidence of benefit from antifibrinolytic agents will require additional trials before this therapy can be implemented in clinical practice.

### *Catheter* versus *CT angiography*

Several individual case reports or case series with poorly defined total number of patients have reported aneurysmal rebleeding with rates as high as 20%-38.5% when digital subtraction angiography (DSA) is undertaken very early (less than 3-6 hours) following aSAH[73-76]. The results showed that the figures were much lower (~5%) where a clear denominator was provided to assess the incidence of rebleeding[74]; furthermore, it is unclear whether these instances of rebleeding with DSA actually reflect the risk of the procedure or are simply a manifestation of the high rebleeding rates, known to occur after initial aneurysm rupture; and, finally, there is no satisfactory direct comparison of rebleeding with and without DSA or CT angiography (CTA) within the first 6 hours post aSAH[21]. Given all the above, as well as the fact that CTA is now well established and it seems unlikely that a large study comparing DSA and CTA will ever materialize, it seems unreasonable to conclude that this is a specific risk attributed to ultra early DSA. Based on epidemiological data, choosing CTA over DSA for ultra-early angiography is a reasonable option where both options are available, the technical quality of CTA is good, and an endovascular intervention is not planned at the time of angiography[21]. However, there is no case for delaying investigation, either CTA or DSA, in the setting of aSAH, where the overwhelming aim is to detect and secure a culprit aneurysm[21].

### *Recommendations for medical measures to prevent rebleeding after aSAH*

- Early aneurysm repair should be undertaken, when possible and reasonable, to prevent rebleeding[21] (High Quality Evidence; Strong Recommendation).

- If possible, it should be aimed to intervene at least within 72 hours after onset of first symptoms[23] (High Quality Evidence; Strong Recommendation).
- This decision should depend on grading since, according to our experience, patients with worse clinical presentation (HH IV and V) should be individually evaluated and treated as soon as they become medically stable. Otherwise, the risk of treatment outweighs the risk of rerupture.
- Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding and maintenance of cerebral perfusion pressure[22] (High Quality Evidence; Strong Recommendation).
- The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mm Hg is reasonable (Moderate Quality Evidence; Strong Recommendation).
- Modest elevation in blood pressure (mean blood pressure <110 mm Hg) does not require therapy. Pre-morbid baseline blood pressures should be used to refine targets; hypotension should be avoided[21] (Low Quality Evidence; Strong Recommendation).
- An early, short course of antifibrinolytic therapy prior to early aneurysm repair (begun at diagnosis; continued up to the point at which the aneurysm is secured or at 72 hours post-ictus, whichever is shorter) should be considered[21] (Low Quality of Evidence; Weak Recommendation).
- Delayed (>48 hours after the ictus) or prolonged (>3 days) antifibrinolytic therapy exposes patients to side effects of therapy when the risk of rebleeding is sharply reduced and should be avoided[21] (High Quality Evidence; Strong Recommendation).
- Antifibrinolytic therapy is relatively contraindicated in patients with risk factors for thromboembolic complications[21] (Moderate Quality Evidence; Strong Recommendation).
- Patients treated with antifibrinolytic therapy should have close screening for deep venous thrombosis[21] (Moderate Quality Evidence; Strong Recommendation).
- When CTA and DSA are both available and CTA is of high technical quality, CTA should be performed preferentially if endovascular intervention is not planned at the time of angiography[21] (Very Low Quality Evidence; Weak Recommendation).
- There is currently no medical antifibrinolytic treatment that improves outcome by reducing rebleeding[23] (High Quality Evidence; Strong Recommendation).

**Delayed Cerebral Ischemia from Vasospasm**

Delayed cerebral ischemia from vasospasm is one of the most common causes of death, disability and delayed neurological deterioration following aSAH[76]. Notwithstanding, the definitions used to describe vasospasm and DCI are numerous and not standardized, which makes it difficult to compare results between treatment or intervention trials, and interferes with the development of evidence based guidelines. One of the major contributors to this problem is the inappropriate tendency to combine radiographic evidence of vascular narrowing and clinical findings into a single definition. It is a general agreement that inconsistencies in the use of the terms vasospasm and DCI should be avoided and that standardized definitions are needed[21].

Vasospasm is a term applied to arterial narrowing after SAH demonstrated by radiographic images or sonography. It is generally accepted that it should only be used as a term describing the findings on diagnostic studies. It is believed to be induced in the areas of thick subarachnoid clot[78]. The putative agent responsible for vasospasm is oxyhemoglobin, but its true etiology and pathogenesis remain to be elucidated[79]. According to current knowledge, the cascade of events culminating in arterial narrowing is initiated when oxyhemoglobin comes in contact with the albuminal side of the vessel events[80]. Most often, the terminal internal carotid artery or the proximal portions of the anterior and middle cerebral arteries are involved. The arterial territory involved, however, is not related to the location of the ruptured aneurysm[81]. While changes in vasospasm are commonly observed in the large caliber conveyance arteries, effects on the smaller vessels of the microcirculation, including alterations in blood brain barrier permeability, may be equally important in determining clinical impact.

Such factors may account for the higher incidence of vasospasm as defined by imaging criteria ('radiographic vasospasm') than the rates of neurological dysfunction ('clinical vasospasm')[82]. Vasospasm can result in decreased cerebral blood flow and oxygen delivery, which may produce DCI, a term applied to any neurological deterioration (e.g., hemiparesis, aphasia, altered consciousness) presumed to be related to ischemia, which persists for more than an hour and cannot be explained by other physical abnormalities noted on standard radiographic, electrophysiological or laboratory findings[78]. Neurological deterioration in the context of SAH encompasses clinically detectable neurological deterioration in a SAH patient following initial stabilization, but excludes further SAH due to new bleeding from the ruptured aneurysm. It is also generally agreed that "clinical deterioration due to DCI" should only be used to describe a clinical finding[78]. DCI may occur but neurological deterioration may not be recognized due to poor clinical condition of the patient and/or administration of sedatives. Furthermore, although DCI and vasospasm are often used as surrogate markers of each other and they can both be associated with clinical deterioration and worse outcomes, either one may also be asymptomatic and they can also occur independently[21]. Since recent studies provided evidence that cerebral infarction on neuroimaging had the strongest association with functional outcomes[83-85], it has been recommended recently by a multidisciplinary research group that SAH clinical trials should only use cerebral infarction and functional outcome as the primary outcome measures, whereas clinical deterioration due to DCI and vasospasm on angiography or TCD should only be secondary outcome measures[21].

### *Monitoring strategies for delayed neurological deterioration, delayed cerebral ischemia and vasospasm*

Knowing that DCI is one of the most common causes of delayed neurological deterioration and the major cause of secondary morbidity that is potentially treatable and reversible, early detection of impaired cerebral perfusion and early intervention to detect and reverse ischemia before the occurrence of permanent infarction is the goal of monitoring for DCI after aSAH. Furthermore, it is considered a high-priority topic because the choice of monitoring strongly influences the specific triggers used for further hemodynamic or endovascular intervention to treat vasospasm and DCI. The highest risk period for DCI occurs 3-14 days after aSAH and higher risk patients are those with larger amounts of SAH and poorer clinical grade[21].

Monitoring strategies and tools for DCI in SAH are divided into three basic categories: clinical, radiographic and physiological[21], the last two being commonly used to identify arterial narrowing and perfusion abnormalities or reduced brain oxygenation. These different tools have advantages and disadvantages.

Clinical monitoring for DCI consists of repeated neurological assessments to identify new neurological deficits that are attributable to ischemia or infarction. Two studies found that CT scans identified asymptomatic infarction in 10%-20% of patients with clinically unrecognized infarcts, more common in patients in coma[86,87]. A study using magnetic resonance imaging (MRI) found clinically unrecognized infarcts in 23% of patients[88]. The results of the studies clearly showed that not all ischemic events are detected on clinical examinations and it is generally thought that the utility of clinical examination in detecting reversible ischemia is good in good-grade patients and less reliable in poor-grade patients who are obtunded or comatose. Notwithstanding, there is a strong consensus that clinical examination is an important first assessment point in patients with aSAH; that triggers for further monitoring and intervention may differ depending on the clinical status of the patient; and that clinical examination alone is an insufficient monitoring paradigm for detection of DCI, especially in poor-grade patients[21]. Furthermore, there is a general consensus that additional radiographic and/or physiological monitoring should be routinely employed in the monitoring of aSAH patients for DCI and should be performed during the DCI at risk period, even in the absence of clinical evidence of DCI or prior to its occurrence[21].

Radiographic monitoring modalities include conventional digital subtraction angiography (DSA), CT (CT angiography, CTA and CT perfusion imaging, CTP) and MRI. DSA is considered gold standard for detection of arterial narrowing and thus is a commonly used radiographic method to define vasospasm, with a limitation of not being able to assess the adequacy of perfusion to meet metabolic demands of the tissue. On the other hand, CTA is found to be highly correlated with DSA findings of large artery narrowing, 87%-95% specific for angiographic vasospasm compared with DSA and with high specificity and negative predictive value (NPV) of 95%-99%, suggesting that it could be used as a screening tool to limit the use of DSA, but at the same time tends to overestimate the degree of stenosis[89,90]. CTP does provide some measure of tissue perfusion, which may enhance the predictive value of multi-modality CT for DCI monitoring. Its finding of delayed mean transit time >6.4 s in conjunction with arterial narrowing on CTA is found to be more accurate in predicting the need of endovascular intervention for vasospasm[91,92], but it does not currently evaluate the posterior fossa well. Considering MRI as a possible DCI monitoring tool at this time, it would require further trials for adequate and satisfactory data. Overall, according to radiographic monitoring strategy for DCI in aSAH, concerning the emerging concerns regarding radiation toxicity, an institutional protocol that balances DCI detection with attempts to minimize radiation exposure is encouraged.

Physiological monitoring modalities are the third basic category among the monitoring strategies and tools for DCI in aSAH, which include transcranial Doppler ultrasonography (TCD), electroencephalography (EEG), brain tissue oxygen monitoring, cerebral microdialysis, thermal diffusion cerebral blood flow (TD-CBF) monitoring and near-infrared spectroscopy.

Transcranial Doppler ultrasonography has long been used for monitoring patients with aSAH and has been more extensively studied in comparison with DSA. Although studies of TCD diagnostic accuracy for detection of vasospasm and DCI vary widely with regard to sensitivity and specificity[93,94], it is generally considered that TCD has a fairly high specificity but only moderate sensitivity compared with DSA[93,94]. Differentiation of elevated TCD velocities secondary to vasospasm *versus* other causes in monitoring patients with aSAH is crucial. It can be accomplished by measuring velocities in the cervical internal carotid artery (ICA) in addition to the intracerebral vessels, creating ratios for clinical use that aim to overcome the confounding effects of systemic hemodynamic factors, such as changes in cardiac output or blood pressure. TCD velocities have been used to create several clinically relevant predictive indices, including the Lindegaard ratio (ratio of middle cerebral artery (MCA) TCD velocity to ipsilateral internal carotid artery (ICA) TCD velocity), that is especially useful for vasospasm diagnosis. A $V_{MCA}/V_{ICA}$ ratio >3 is suggestive of cerebral vasospasm[95]. A similar velocity ratio profile between the basilar and extracranial vertebral arteries can be used to assess for basilar vasospasm[96]. A 2001 meta-analysis reported that, for MCA vasospasm, overall TCD specificity was 99% and sensitivity 67%, with a positive predictive value (PPV) of 97% and NPV of 78%. For the anterior cerebral artery (ACA), ICA, posterior circulation and examinations of the distal cerebral microvasculature, TCD values were significantly less sensitive and specific[97]. A consensus statement in 2004 underscored these results, supporting the conclusion that TCD is a reliable predictor for the absence of angiographic vasospasm (high NPV) at flow velocities <120 cm/s and for the presence of angiographic vasospasm (high PPV) at flow velocities >200 cm/s in the MCA territory. According to the mentioned consensus, flow velocities below 120 cm/s (absence), >200 cm/s (presence), MCA/ICA ratio >6 (presence) or rapidly increasing velocities over several days (high risk) are commonly considered thresholds[94,98]. Velocity measurements between 120 cm/s and 200 cm/s may require further technical maneuvers (manual carotid compression)[99] or additional clinical information to improve diagnostic accuracy. Moreover, intermediate TCD values generally do not reliably correlate with angiographic vasospasm[100]. Clinically, trends in TCD values or interval changes from prior readings are often more informative than absolute values[82]. Daily monitoring of changes in TCD values can speak in favor of development of vasospasm[100]. Therefore, TCD on days 2-5 can detect the development of vasospasm days before it can become clinically apparent, and this information can be used by intensivists to step up with hemodynamic management of these patients. On days 5-12, TCD can detect progression to the severe phase of spasm when development of the delayed ischemic deficit due to perfusion failure through the residual lumen is the greatest. This information can help planning interventions (angiography, nicardipine infusion). On days 12 to the end of ICU stay, TCD can document spasm resolution after treatment or intervention, sustainability of vessel potency, and infrequent cases of late or rebound vasospasm development at the end of the second or into the third week after aSAH. In conclusion, due to the absence of radiation risk, relatively low cost and ease/rapidity of bedside administration, TCD measurements are practical for serially monitoring the progression of cerebral vasospasm. The technique is limited by the lack of high-resolution anatomic detail, and its accuracy and utility are highly operator-dependent and patient movement-dependent. In addition, aberrant vessel course, aneurysm clip artifacts and suboptimal insonation windows can inhibit the detection of pathological velocities[82,101].

Brain tissue oxygen (PbtO2) monitoring and cerebral microdialysis (CMD) are directly measuring tissue oxygen delivery and metabolism, providing, rather than direct correlation, information complementary to that from radiographic studies. Their role in measuring these physiological parameters in monitoring patients with aSAH has been described in several observational studies[102,103]. However, no studies examined the effectiveness of interventions based on these monitoring tools in preventing or reversing DCI. Regarding the role of EEG in monitoring patients with SAH, findings of reduced alpha variability have been indicative of DCI, but no interventional trials examined EEG-directed DCI treatment[104]. Altogether, EEG, PbtO2 monitoring and CMD may all be useful physiological monitors for DCI detection, but the relative value of these monitors individually *versus* as part of a multi-modality monitoring strategy is not known (Low Quality Evidence; Weak Recommendation)[21].

To conclude, there is a strong consensus that clinical examination is an important first assessment point in patients with aSAH, while triggers for further monitoring and intervention may differ depending on the clinical status of the patient. Furthermore, there is also great concern that clinical examination alone was an insufficient monitoring paradigm for detection of DCI, especially in poor-grade patients, leading to a consensus that additional radiographic and/or physiological monitoring should be routinely employed in the monitoring of aSAH patients, performed during the DCI at risk time period, even in the absence of clinical evidence of DCI or prior to its occurrence[21]. Based on the past knowledge and clinical experience, the following can be recommended:

a) Low Risk Good-Grade aSAH Patients – the primary monitoring tool is repeated clinical evaluation, supplemented by monitoring with regular daily TCD. In case of the development of a new focal deficit, a change in the level of consciousness not clearly attributable to another cause, or an increase in TCD velocities/Lindegaard ratio should prompt additional investigations (CTA or DSA) that seek to detect or monitor the evolution of arterial narrowing and document the presence of perfusion deficits (CTP) that results from such narrowing. Where the selected investigation cannot be obtained emergently, within 1-2 hours, depending on the clinical situation, medical therapy for DCI should be initiated while awaiting imaging[21].

b) Good-Grade SAH Patients at High Risk of Vasospasm and/or DCI – patients with a high Fisher grade and/or arterial narrowing demonstrated with DSA/CTA at the time of initial presentation may benefit from monitoring with these techniques in the absence of detectable clinical consequences. The development of new deficits and/or changes in sensorium will often directly trigger therapeutic interventions. In case of substantial clinical uncertainty whether the change in clinical status is actually due to DCI; an endovascular intervention is being considered; and/or the risks of therapy are particularly high (e.g., blood pressure elevation in a patient with significant ischemic heart disease), repeating CTA+CTP should be performed. Regarding the radiation burden and renal impairment, in case of screening for vasospasm or DCI the risk/benefit ratio is considered more favorable[21].

c) Sedated or Poor-Grade SAH Patients – clinical examination may be less useful as a monitoring tool in this setting but should still be regularly undertaken, since a change from baseline provides an indication for further investigation or treatment. A clinical suspicion of vasospasm or DCI in these SAH patients will be triggered by a change in TCD parameters, EEG, invasive cerebral monitoring, or by the detection of vasospasm or perfusion deficits on routine screening CTA/CTP or DSA. Where the clinical suspicion of DCI is based on a non-imaging tool, it is prudent to confirm the diagnosis using CTA+CTP or DSA. It is reasonable to initiate therapy without further investigation in patients where screening using CTA or DSA has already established vasospasm and the clinical picture is consistent and in poor-grade patients where a perfusion deficit has been demonstrated on screening CTP, unless the deficit coincides with an established infarction[21].

Considering thresholds for cessation of therapy for DCI, in good-grade patients clinical assessment combined with cautious staged de-escalation of therapy provides the best basis for management decisions, whereas in poor-grade patients, this approach may need to be supplemented by investigations that include TCD trends of vasospasm, continuous EEG monitoring, PbtO2, and/or microdialysis. In case when DCI has resulted in established infarction, it may be appropriate to withdraw therapy because it has been unsuccessful. It is important to emphasize that it is unwise to base treatment decisions (initiation, titration or withdrawal) on an individual measurement provided by any single monitoring modality or monitoring device (technical artifact, inter-center variability), especially knowing that while some physiological thresholds may be associated with outcome, there is no clear evidence that correction of the monitored variable actually improves outcome. It is prudent to integrate data from all available sources with the clinical picture to help make management decisions. In case of the development of new neurological deficit with a strong likelihood of being due to ischemia and other potential causes were unlikely or had been excluded, most centers would initiate therapy. The threshold values from TCD and other monitoring devices provide additional information that underpins initiation of therapy. Some therapies, including hypertension and optimization of hemoglobin levels, may be initiated while awaiting confirmatory investigations. On the other hand, other interventions used in DCI, such as endovascular therapy, require angiography for initiation and in these instances confirmation of the diagnosis of vasospasm as a cause of DCI will automatically precede therapy[21]. Because of all the above mentioned challenges in monitoring aSAH patients, there is, however, a strong consensus that monitoring for neurological deterioration and specifically DCI should take place in an environment with substantial multidisciplinary expertise in the management of aSAH (hospital and intensive care unit), with adequate expertise to implement and interpret monitoring tools, where additional monitoring and treatment can be rapidly implemented when needed[21,105] (Very Low Quality Evidence; Strong recommendation).

## Management of Cerebral Vasospasm and DCI after aSAH

Although the pathways leading to arterial narrowing have been in focus of extensive basic research, no effective preventive therapy has been developed to date. Probably, the reason for this stems in part from the fact that the vasospasm occurs at multiple levels in the arterial and arteriolar circulation. It is known that large artery narrowing seen in angiographically visible vessels only results in ischemic neurological symptoms in 50% of patients. Although there is a correlation between the severity of large artery spasm and symptomatic ischemia, there are patients with severe large artery spasm who never become symptomatic and other with modest spasm who not only develop symptoms but go on to develop infarction[78]. Probably many factors contribute to the development of ischemia and infarction, including but not limited to distal microcirculatory failure, poor collateral anatomy, and genetic or physiological variations in cellular ischemic tolerance[106,107].

The management of aSAH-induced vasospasm is complex. Currently, the strongest evidence supports the use of prophylactic oral nimodipine and maintenance of euvolemia and initiation of hemodynamic augmentation therapy (triple-H therapy) for patients with cerebral vasospasm and/or endovascular therapy with vasodilators and angioplasty balloons[108].

As for nimodipine, the results of a recent comprehensive meta-analysis have confirmed improved neurological outcomes by preventing processes other than large-vessels narrowing and should be administered to all patients with aSAH (High Quality Evidence; Strong Recommendation)[109]. It should be noted that nimodipine has been shown to improve neurological outcomes by decreasing the incidence of cerebral ischemia[110], but not cerebral vasospasm. It has been postulated that the nimodipine beneficial role may be the result of a more complex neuroprotective mechanism of action than that of its vasodilatory effect[111]. Although the risk reduction for 'poor outcome' is statistically robust, it depends mainly on a single large trial[112] and therefore the benefits of nimodipine cannot be regarded as being beyond all reasonable doubt[23]. The practical implication is that the regimen in the dominant nimodipine trial (60 mg orally every 4 h for 3 weeks) is currently regarded as the standard treatment in patients with aSAH. If the patient is unable to swallow, the nimodipine tablets should be coarse-grained crushed and washed down a nasogastric tube with normal saline within minutes[23]. Intravenous administration of calcium antagonists is advocated by the manufacturer, but besides the fact that it is more expensive, there is no evidence to support this and cannot be recommended for routine practice on the basis of current evidence[113]. The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain[22].

With regard to blood volume, maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI (High Quality Evidence; Strong Recommendation)[21]. When DCI is diagnosed, the initial treatment is the induction of hemodynamic augmentation to improve cerebral perfusion. Traditionally, hemodynamic augmentation has consisted of hemodilution, hypervolemia and hypertensive therapy (triple-H therapy). Although no randomized trial of this intervention has been performed, the rapid improvement of many patients with this therapy and their worsening when it is stopped prematurely are a convincing proof of efficacy. The exact mechanism of benefit is unclear[22]. In some patients, increased mean arterial pressures may increase cerebral blood flow in the setting of autoregulatory dysfunction, whereas in others, there may be some direct transluminal pressure effect that leads to arterial dilation[110]. However, the existent literature provides only level B evidence regarding the utilization of triple-H therapy in the management of patients suffering from aSAH[114]. Recently, MacDonald *et al.* have reported their experience from employing continuous milrinone infusion instead of triple-H therapy. They found that milrinone regimen required less invasive monitoring and resources than triple-H therapy, while its hemodynamic effect was comparable to that of the triple-H therapy[115]. Further large-scale clinical trials are necessary for validating their observations. Accumulating literature has shifted the focus from this triple-H therapy to the maintenance of euvolemia and induced hypertension[116]. Induction of hypertension is recommended for DCI unless blood pressure is elevated at baseline or cardiac status precludes it[23] (High Quality Evidence; Strong Recommendation). The data show that both prophylactic angioplasty of the basal cerebral arteries and antiplatelet prophylaxis are ineffective in reducing morbidity[117-119]. Consequently, prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended[23] (Moderate Quality Evidence; Strong Recommendation); cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (Moderate Quality Evidence; Strong recommendation)[22].

With regard to the value of the lumbar drainage after SAH, the data from one case-control study showed a markedly reduced risk of clinically evident vasospasm and its sequels, shortened hospital stay and improved outcome. The beneficial effect is probably mediated through the removal of spasmogens that exist in the CSF, but a randomized clinical trial is warranted and ongoing phase III trial has been designed to test its influence on outcome[120]. The data from a meta-analysis of 5 randomized, controlled trials suggested a benefit from intrathecal thrombolytic infusions following aSAH but further standardization of techniques and evaluation in a larger, more rigorous randomized controlled trial is required[121]. The effect of intraventricular fibrinolysis on clinical outcome and mortality of aSAH patients is currently being investigated in a large-scale phase III clinical trial[122].

The administration of the endothelin-1 antagonist, clazosentan, has been shown to be associated with a dose-dependent reduction in the incidence of angiographic vasospasm in a phase II b trial[123], but proven to cause no significant improvement in the clinical outcome of patients with aSAH[116].

Significant interest has been arisen by the employment of magnesium as a vasodilatory agent for preventing and/or reversing cerebral vasospasm. Certainly, the use of magnesium has potential benefits in the setting of aSAH, with the minimal risk of severe adverse or side effects such as hypotension, hypocalcemia or bradycardia. Magnesium reduced the frequency of DCI in a dose-dependant fashion[124]. Results of the Mash-2 (Magnesium for Aneurysmal Subarachnoid Hemorrhage) trial revealed that treatment with magnesium did not improve outcome and was not superior to placebo in reducing poor outcome in SAH patients[125]. The potential role of magnesium in relieving persistent SAH-associated headache needs to be explored in the future. Based on the currently published data, the systemic administration of magnesium cannot be generally recommended. Magnesium sulfate is a promising agent but more evidence is needed before definitive conclusions can be drawn[126].

In regard to the employment of statins in the management of vasospasm, the currently available data have shown that in the majority of cases there is a definite vasodilatory effect on the cerebral vasculature[127-131]. Results of the STASH (SimvasTatin in Aneurysmal Subarachnoid Hemorrhage) trial are expected to clarify the exact effect of statins on the clinical outcome of patients with aSAH.

It has been postulated that other pathophysiological mechanisms than vasospasm may contribute to post-aSAH morbidity and mortality. Inflammatory mechanisms, endothelial apoptosis, cortical spreading depolarization, microthrombosis and lipid peroxidation have been implicated in the pathogenesis of delayed ischemic events[132-135]. Other agents with a potential benefit in preventing and/or treating post-aSAH vasospasm and DCI include nitric oxide promoters, free radical scavengers, thromboxane inhibitors, thrombolysis, anti-inflammatory agents and neuroprotectants. Although promising data begin to emerge for several treatments, few prospective randomized clinical trials are presently available. Additionally, future investigational efforts will need to resolve discrepant definitions and outcome measures for cerebral vasospasm in order to permit adequate study comparisons. Until then, definitive recommendations cannot be made regarding the safety and efficacy of each of these therapeutic strategies and medical management practices will continue to be implemented in a wide-ranging manner[108].

***Recommendations for prevention of delayed ischemic deficit***

- Monitoring for neurological deterioration and specifically DCI should take place in an environment with substantial multidisciplinary expertise in the management of aSAH[21] (Moderate Quality Evidence; Strong Recommendation). Patients at a high risk of DCI should be closely monitored throughout the at risk period, which is best accomplished in an ICU setting where additional monitoring and treatment can be rapidly implemented[21] (Very Low Quality Evidence; Strong Recommendation).
- Nimodipine should be administered orally (60 mg/4 h) to all patients with aSAH for a period of 21 days to prevent delayed ischemic events[21-23] (High Quality Evidence; Strong Recommendation).
- Maintenance of euvolemia and normal circulating blood volume is recommended to prevent delayed cerebral ischemia[22] (Moderate Quality Evidence; Strong Recommendation).
- Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended[22] (Moderate Quality Evidence; Strong Recommendation).
- Imaging of vascular anatomy and/or perfusion can be used to confirm the diagnosis of DCI in monitored good-grade patients who show a change in neurological examination or TCD variables[21] (High Quality Evidence; Strong Recommendation).
- A strategy for detection and confirmation of DCI should be employed. This should first and foremost involve frequent repeat neurological assessment by qualified providers. Intermittent screening or more continuous monitoring methods may additionally be used[21].
- TCD is reasonable to monitor for the development of arterial vasospasm (Moderate Quality Evidence; Strong Recommendation)[21-23]. Thresholds of mean blood flow velocities <120 cm/s for absence and >200 cm/s and/or MCA/ICA ratio >6 for presence are reasonable[21] (Moderate Quality Evidence; Strong Recommendation).

- DSA is gold standard for detection of large artery vasospasm[21] (High Quality Evidence; Strong Recommendation).
- High quality CTA can be used on screening for vasospasm and due to its high specificity may reduce the need of DSA studies[21] (Low Quality Evidence; Weak Recommendation)[21].
- Perfusion imaging with CT or MRI can be useful to identify regions of potential brain ischemia[22] (Moderate Quality Evidence; Strong Recommendation).
- In high risk patients who have a clinical picture strongly suggestive of DCI and in whom elective screening CTA or DSA has already demonstrated vasospasm/DCI, it is reasonable to initiate medical therapy without further investigation[21] (Moderate Quality Evidence; Strong Recommendation).
- In patients with clinical uncertainty regarding the cause of neurological deterioration, DSA is indicated if an endovascular intervention is planned[21] (Moderate Quality Evidence; Strong Recommendation).
- In sedated or poor-grade patients, clinical deterioration may be difficult to assess, and TCD, continuous EEG, PbtO2 monitoring and/or CMD are options for monitoring for vasospasm and DCI[21] (Low Quality Evidence; Weak Recommendation).
- Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it[22] (Moderate Quality Evidence; Strong Recommendation).
- The choice of vasopressor should be based on other pharmacological properties of the agents[21] (e.g., inotropy, tachycardia) (Moderate Quality Evidence; Strong Recommendation).
- Blood pressure augmentation should progress in a stepwise fashion with assessment of neurological function at each mean arterial pressure (MAP) level to determine if a higher blood pressure target is appropriate[21] (Poor Quality Evidence; Strong Recommendation).
- If nimodipine administration results in hypotension, then dosing intervals should be changed to more frequent lower doses. If hypotension continues to occur, then nimodipine may be discontinued[21] (Low Quality Evidence; Strong Recommendation).
- If patients with DCI do not improve with blood pressure augmentation, a trial of inotropic therapy may be considered[21] (Low Quality Evidence; Strong Recommendation). Inotropes with prominent β-2 agonist properties (e.g., dobutamine) may lower MAP and require increases in vasopressor dosage[21] (High Quality Evidence; Strong Recommendation).
- Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy[22] (Moderate Quality Evidence; Strong Recommendation).
- Hemodilution in an attempt to improve rheology should not be undertaken except for cases of erythrocythemia[21] (Moderate Quality Evidence; Strong Recommendation).
- If the aneurysm thought to have ruptured is unsecured when the patient develops DCI, cautious blood pressure elevation to improve perfusion might be attempted, weighing the potential risks and benefits[21] (Weak Quality Evidence; Strong Recommendation).
- Unsecured aneurysms which are not thought to be responsible for the acute SAH should not influence hemodynamic management[21] (Moderate Quality Evidence; Strong Recommendation).
- Magnesium sulfate is not recommended for the prevention of DCI[23] (High Quality Evidence; Strong Recommendation).
- Statins are under study[23].

## Seizures

Retrospective studies have identified several risk factors for the development of early seizures associated with aSAH, including aneurysm in the MCA[136], thickness of a aSAH clot[137], associated intracerebral hematoma[138-140], rebleeding[137], infarction[141], poor neurological grade[137], history of hypertension[142] and surgical aneurysm repair in patients >65 years of age[137]. Abnormal movements that may appear seizure-like are common at the onset of aSAH (as many as 26%) but it is usually unclear whether this is a true seizure or represents posturing at the time of aneurysm rupture[138,143]. The incidence, future implications and management of seizures associated with aSAH are controversial. Clinical seizures are uncommon after the initial aneurysm rupture, occurring in 1%-7% of patients, and when they occur in patients with an unsecured aneurysm, they are often the manifestation of aneurysmal re-rupture[144,145]. At present, no randomized, controlled trials are available to guide decisions on prophylaxis or treatment of seizures. The mode of treatment for patients with ruptured aneurysms also appears to influence the subsequent development of seizures[22]. Results of the studies have demonstrated that patients treated by endovascular coiling showed a significantly lower incidence of seizures[144,146]. Although high-quality evidence for routine anticonvulsant use in aSAH patients without seizures is lacking, short-term prophylactic antiepileptic therapy is still commonly used in patients with aSAH[137,143], based on the argument that seizures in acutely ill patients with aSAH could lead to additional injury or rebleeding from an unsecured aneurysm. Recent studies have suggested that prophylactic anticonvulsant therapy with phenytoin may worsen outcome[147], whereas the impact of other anticonvulsant medication is less clear[148]. Also, in patients with no history of seizure, a short course (72 h) of anticonvulsant prophylaxis seems as effective as a more prolonged course in preventing seizures[149]. On the other hand, the results from one large single-institution study in which anticonvulsants were used routinely showed adverse drug effects in 23% of patients[137], whereas another single-center retrospective study found the use of prophylactic phenytoin to be independently associated with worse cognitive outcome at 3 months after aSAH[147]. Furthermore, data pooled from the trials of the impact of other therapies also suggest worse outcome in those treated with anticonvulsants. The use of anticonvulsants was also associated with vasospasm, DCI and fever, which suggests that there may have been a bias in those who were treated with antiepileptic drugs[148]. Likewise, although hampered by limitations such as a small number of patients and anticonvulsant levels not routinely monitored, retrospective studies failed to demonstrate benefit from the use of prophylactic anticonvulsant after aSAH[150,151]. Inclusive, it is recommended that any purported benefit of routine anticonvulsant use in aSAH must be tempered by a consideration of the potential risks of use[22]. However, in case of a certain subgroup of patients, such as elderly patients undergoing craniotomy that have a higher seizure risk, a short course (3-7 days) of anticonvulsant prophylaxis might still be considered in some situations, especially if an agent other than phenytoin is used[21,152]. There is also agreement that patients who suffer clear clinical seizure after the period of aneurysmal rupture should be treated with anticonvulsants, but that if seizures do not recur, these anticonvulsants should be discontinued after 3-6 months. Contrary, there is no agreement whether an EEG should be performed at that time and, if so, whether seizure-free patients with an epileptic focus should be continued on anticonvulsants[21].

The association between seizures and functional outcome still remains unclear. Some studies have reported no impact on outcome[137,143], whereas others found seizures to be independently associated with worse outcome[153]. Nonconvulsive status epilepticus has been found to be a strong predictor of a poor outcome[154,155]. Concerning the treatment of nonconvulsive seizures that may be detected on continuous EEG in 10%-20% of comatose aSAH patients that are proved to have worse outcome, the impact of successful treatment as well as the influence of anticonvulsant prophylaxis on the occurrence of nonconvulsive seizures have not been studied. There is a consensus that continuous EEG is underutilized in poor-grade aSAH patients, but it is not clear whether nonconvulsive seizures represent a marker of disease severity or a target for treatment. There is general agreement that one or perhaps two anticonvulsants should be used to attempt to treat nonconvulsive seizures identified on continuous EEG, but there is disagreement whether or not to pursue more aggressive means such as benzodiazepine or barbiturate infusions if initial measures were unsuccessful[21].

### *Recommendations for medical management of seizures associated with aSAH*

- There is no evidence that supports the prophylactic use of antiepileptic drugs (Very Low Quality Evidence; Weak Recommendation).

- Antiepileptic treatment should be administered in patients with clinically apparent seizures[23].
- In patients who suffer a seizure after presentation, anticonvulsants should be introduced and discontinued after two-year seizure-free period, as defined by local practice[21] (Low Quality Evidence; Weak Recommendation).
- Continuous EEG monitoring should be considered in patients with poor-grade aSAH who fail to improve or who have neurological deterioration of undetermined etiology; in patients who presented with seizure as the initial symptom of SAH; in patients with a prolonged post-ictal disturbance of consciousness; and in patients with suspicion of nonconvulsive status epilepticus[21] (Low Quality Evidence; Strong Recommendation).
- The routine long-term use of anticonvulsants is not recommended (Moderate Quality Evidence; Weak Recommendation), but may be considered for patients with known risk factors for delayed seizure disorder, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction or aneurysm at the middle cerebral artery, and for patients with severe epileptiform changes as shown during control EEG monitoring[22] (Moderate Quality Evidence; Weak Recommendation).

**Cardiopulmonary Complications**

Cardiac dysfunction occurs in a significant number of aSAH patients. Neurogenic sympathetic hyperactivity, as well as increased levels of systemic catecholamines, has been implicated in aSAH-associated cardiac dysfunction. Cardiac dysfunction after aSAH is often referred to as 'neurogenic stress cardiomyopathy'[156] and has been attributed to the clinical syndrome of chest pain, dyspnea, hypoxemia and cardiogenic shock with pulmonary edema and elevated cardiac markers occurring within hours of SAH. This syndrome has a wide spectrum of severity and it may contribute to sudden death in 12% of patients. The manifestations are usually transient, lasting for 1-3 days, after which myocardial function returns to normal. The management should be focused on supportive care that balances cardiac needs with the neurological goals[157].

Arrhythmias occur in as many as 90% of patients and are most prevalent in the first 48 hours following aSAH. They most commonly include premature ventricular complexes, bradyarrhythmias and supraventricular tachycardia. Serious cardiac arrhythmias, most often atrial fibrillation or flutter, have been described in approximately 5% of patients[158]. Clinically significant arrhythmias after aSAH are associated with a high mortality rate and serious cardiac and neurological comorbidity[159].

Electrocardiographic changes occur during the acute stage in 50% to 100% of aSAH patients[160,161]. The most common abnormalities are nonspecific ST deviations, T-wave inversion and prolonged QT interval. These ECG changes have no clinical or prognostic consequence. Elevated troponin is found in approximately 20% of aSAH cases and is associated with an increased risk of hypotension, pulmonary edema, left ventricular dysfunction and DCI[162-164]. Patients with an abnormal ECG on admission should undergo close cardiac monitoring. The presence of rhythm disturbances should prompt aggressive measures to treat myocardial infarction, maintain normal cardiac rhythm, and minimize the presence of autonomic stress[159]. The cardiac injury that is found in up to 15% of aSAH patients is probably caused by the massive release of catecholamines[165].

Transient left ventricular dysfunction with an akinetic or dyskinetic apex has also been described in aSAH patients without significant coronary heart disease[166,167]. This phenomenon known as *Takotsubo cardiomyopathy* or transient left ventricular apical ballooning[168] is caused by severe physical (e.g., SAH) or emotional stress. More than 95% of patients that experienced this stress-induced cardiomyopathy are female[169]. Plasma catecholamine concentrations in these patients are remarkably higher than in patients presenting with myocardial infarction. A possible explanation of this cardiomyopathy is ischemia caused by coronary spasm[169].

Symptomatic pulmonary complications that are associated with worse clinical grade aSAH and higher mortality occur in over 20% of patients after aSAH[170,171]. Aneurysmal SAH patients may develop cardiac or neurogenic pulmonary edema[172], acute lung injury or acute respiratory distress syndrome. The excessive release of catecholamines (epinephrine/nor-epinephrine) or cardiac failure has been suggested as the principal cause of pulmonary complications[172,173]. It is also suggested that patients who experience pulmonary complications after aSAH have a higher incidence of symptomatic vasospasm than do patients without pulmonary complications. This most likely reflects a failure to maintain aggressive hypervolemic and hyperdynamic therapy in patients with compromised pulmonary function, as well as the possible precipitation of congestive heart failure by hypervolemic therapy in patients with preexisting delayed ischemic neurological deficit[174].

Pulmonary complications challenge medical management of patients who have sustained aSAH. Cardiopulmonary issues are worsened in the event of hypervolemia, thus the goal of therapy should be euvolemia. In general, cardiopulmonary abnormalities are more common in patients who later develop DCI and have worse outcomes[175]. They frequently complicate management by increasing procedural risk and exarcerbate brain oxygen delivery by lowering perfusion pressure and arterial oxygenation saturation. The management of these complications is heterogeneous, may vary based on the patient's clinical status, and in the setting of vasospasm and interventions should reflect current best medical practice[21].

### *Recommendations for monitoring and medical treatment of cardiopulmonary complications in aSAH patients*

- Baseline cardiac assessment with serial enzymes, electrocardiography and echocardiography is recommended, especially in patients with evidence for myocardial dysfunction[21] (Low Quality Evidence; Strong Recommendation).
- Monitoring of cardiac output may be useful in patients with evidence of hemodynamic instability or myocardial infarction[21] (Low Quality Evidence; Strong Recommendation).
- In case of pulmonary edema or evidence of lung injury, the goal of therapy should include avoiding excessive fluid intake and judicious use of diuretics targeting euvolemia[21] (Moderate Quality Evidence; Strong Recommendation).
- Standard management of heart failure is indicated with the exception that cerebral perfusion pressure/mean arterial pressure (CPP/MAP) should be maintained as appropriate for the neurological condition[21] (Moderate Quality Evidence; Strong Recommendation).
- Vigilant fluid balance management should be the foundation for monitoring intravascular volume status. While both noninvasive and invasive monitoring technologies are available, no specific modality can be recommended over clinical assessment[21,23] (Moderate Quality Evidence; Weak Recommendation).
- Central venous lines should not be placed solely to obtain central venous pressure (CVP) measures and fluid management based solely on CVP measurements is not recommended[21] (Moderate Quality Evidence; Strong Recommendation).
- Intravascular volume management should target euvolemia and avoid prophylactic hypervolemic therapy. In contrast, there is evidence for harm from aggressive administration of fluid aimed at achieving hypervolemia[21] (High Quality Evidence; Strong Recommendation)[21].
- Isotonic crystalloid is the preferred agent for volume replacement[21,23] (Moderate Quality Evidence; Weak Recommendation).
- In patients with a persistent negative fluid balance, use of fludrocortisone or hydrocortisone may be considered[21] (Moderate Quality Evidence; Weak Recommendation).

## Hyponatremia

Hyponatremia following aSAH is the most common electrolyte imbalance and has prevalence rates of approximately 30%-55%[176-178]. Elevated levels of atrial natriuretic factor (ANF) and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) have been implicated. Whether caused by SIADH or cerebral salt waste syndrome (CSW), hyponatremia in patients with aSAH has a clear association with increased morbidity, including cerebrovascular spasm[176,179]. More recent work emphasizes that the diagnosis of CSW requires hypovolemia, whereas SIADH usually results in euvolemia or modest hypervolemia[180-184]. It appears that in aSAH, both entities may coexist in the same patient being manifested by excessive urine output with simultaneous excessive free water retention[180,181]. Generally the trigger used for treatment is a sodium concentration of <135 mEq/L or if neurological deterioration is attributed to falling sodium concentration[21]. According to recently published results of a retrospective, single-institution study, the etiology and treatment of hyponatremia vary in the presence of hypervolemia/euvolemia or hypovolemia. While treating these patients, differentiating between SIADH and CSW is essential[185]. Controlled studies have been performed on the use of the corticosteroids fludrocortisone[186,187] and hydrocortisone[188,189] to prevent hyponatremia. Both corticosteroids were consistently effective in limiting excessive natriuresis and hyponatremia when started early after aSAH onset, but at the same time were associated with an increased incidence of treatable hyperglycemia and hypokalemia. Administration of isotonic fluid can prevent volume contraction but not hyponatremia. Use of slightly hypertonic sodium chloride (1.5% sodium chloride) at rates above maintenance requirements usually is efficacious for aSAH-induced hyponatremia. Data suggest that 3% saline may be safe but are too scant to assess its value in the management of hyponatremia[190].

Concerning the management of hyponatremia, it can be recommended according to current practice and general agreements that fluid restriction should not be used to treat hyponatremia; early treatment with hydrocortisone or fludrocortisone may be used to limit natriuresis and hyponatremia; mild hypertonic saline solutions can be used to correct hyponatremia; and free water intake *via* intravenous and enteral routes should be limited[21]. Furthermore, it should be emphasized that when hyponatremia in aSAH patients is treated promptly and appropriately, the patients' sodium levels return to normal without detrimental effects. Thus, it is strongly recommended to anticipate hyponatremia in patients with aSAH, timely detect and appropriately treat it to improve outcome[191].

### *Recommendations for medical treatment of hyponatremia after aSAH*

- Fluid restriction should not be used to treat hyponatremia[21] (Weak Quality Evidence; Strong Recommendation).
- The use of fludrocortisone or hydrocortisone and hypertonic saline solution is reasonable for preventing and correcting hyponatremia[22] (Moderate Quality Evidence; Strong Recommendation). Early treatment with fludrocortisone or hydrocortisone may be used to limit natriuresis and hyponatremia[21] (Moderate Quality Evidence; Weak Recommendation).
- Mild hypertonic saline solutions can be used to correct hyponatremia[21] (Very Low Quality Evidence; Strong Recommendation).
- Extreme caution to avoid hypovolemia is needed if vasopressin-receptor antagonists are used for treatment of hyponatremia[21] (Weak Quality Evidence; Strong Recommendation).
- Free water intake *via* intravenous and enteral routes should be limited[21] (Very Low Quality Evidence; Strong Recommendation).

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Sažetak

## PREPORUKE ZA LIJEČENJE KOMPLIKACIJA U BOLESNIKA NAKON ANEURIZMATSKOG SUBARAHNOIDNOG KRVARENJA

Predstavljamo smjernice za liječenje komplikacija u bolesnika nakon aneurizmatskog subarahnoidnog krvarenja temeljene na dokazima, a prihvaćene od strane Hrvatskoga društva za neurovaskularne poremećaje, Hrvatskoga društva za neurologiju uključivo i Sekciju za intenzivnu neurologiju, Hrvatskoga društva za neurokirurgiju, Hrvatskoga društva za zbrinjavanje otežanog dišnog puta i Hrvatskoga liječničkog zbora. Sastoje se od preporuka za zbrinjavanje, praćenje i liječenje bolesnika nakon aneurizmatskog subarahnoidnog krvarenja, temeljenih na dostupnoj literaturi, rezultatima velikih međunarodnih kliničkih ispitivanja i kolektivnog iskustva autora.

Ključne riječi: *Subarahnoidno krvarenje; Aneurizma; Komplikacije; Terapija lijekovima; Praktična smjernica*

# GENERAL RECOMMENDATIONS FOR THE MANAGEMENT OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

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SUMMARY – Subarachnoid hemorrhage is a neurologic emergency and a detrimental cerebrovascular event with a high rate of death and complications. Recommendations have been developed and based on literature search, evaluation of the results of large international clinical trials, collective experience of the authors, and endorsed by the Croatian Society of Neurovascular Disorders, Croatian Society of Neurology including Section for Neurocritical Care, Croatian Neurosurgical Society, Croatian Society for Difficult Airway Management and Croatian Medical Association. The aim of these guidelines is to provide current and comprehensive recommendations and to assist physicians in making appropriate decisions in the management of subarachnoid hemorrhage. Evidence based information on the epidemiology, risk factors and prognosis, as well as recommendations on diagnostic work up, monitoring and management are provided, with regard to treatment possibilities in Croatia.

Key words: *Subarachnoid hemorrhage – diagnosis; Aneurysm – diagnosis; Subarachnoid hemorrhage – therapy; Aneurysm – therapy; Practice guideline*

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Subarachnoid hemorrhage (SAH) is a neurologic emergency and a cerebrovascular event with frequent devastating effects on the central nervous system, possible secondary brain injury due to delayed cerebral ischemia and common systemic manifestations affecting cardiovascular, renal and pulmonary function. SAH is a significant cause of morbidity and mortality throughout the world, which makes it a relevant health problem. It occurs with an incidence of 2 to 20 cases *per* 100,000 individuals. It varies from region to region and the aggregate worldwide incidence is about 10 cases *per* 100,000[1]. It accounts for 2 to 5 percent of all new strokes. The prognosis is influenced by multiple non-modifiable factors and by factors that can be influenced by therapeutic interventions and management procedures. Current developments in neurocritical care have improved the level of care and clinical outcome, however, the lack of high quality data has led to numerous approaches to management and limited guidance on choosing among them. Recent international guidelines are available in the United States of America from the Neurocritical Care Society[2] and American Heart Association/American Stroke Association[3], and in the European Union from the European Stroke Organisation[4]. Due to some differences in the epidemiology and technical diagnostic and management specificities, it turned out pragmatically to publish recommendations from the Croatian standpoint.

## Definitions of Classes and Levels of Evidence Used in Recommendations

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|---|---|
| Class I | Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective. |
| Class II | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. |
| Class IIa | The weight of evidence or opinion is in favor of the procedure or treatment. |
| Class IIb | Usefulness/efficacy is less well established by evidence or opinion. |
| Class III | Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful. |

***Therapeutic recommendations***

| | |
|---|---|
| Level of Evidence A | Data derived from multiple randomized clinical trials or meta-analyses. |
| Level of Evidence B | Data derived from a single randomized trial or nonrandomized studies. |
| Level of Evidence C | Consensus opinion of experts, case studies, or standard of care. |

***Diagnostic recommendations***

| | |
|---|---|
| Level of Evidence A | Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator. |
| Level of Evidence B | Data derived from a single grade A study, or ≥1 case-control studies, or studies using a reference standard applied by an unmasked evaluator. |
| Level of Evidence C | Consensus opinion of experts. |

## Risk Factors

Risk factors can be divided into risk factors for SAH (non-modifiable risk factors: sex, age, size of aneurysm and family history, and modifiable: cigarette smoking, hypertension and excessive alcohol intake), risk factors for aneurysm formation (female sex, current cigarette smoking, hypertension, age at diagnosis and family history) and risk factors for aneurysm growth (current cigarette smoking).

The incidence in women is 1.24 times higher than in men[5]. Evidence of a sex-age effect on SAH incidence has emerged from pooled study data, with a higher incidence reported in younger men (25-45 years of age), women between 55 and 85 years of age, and men >85 years of age[5,6].

An important but non-modifiable risk factor is familial predisposition to SAH. Between 5% and 20% of patients with SAH have a positive family history[7]. First-degree relatives of patients with SAH have a 3- to 7-fold increased risk of being struck by the same disease[8-13]. In second-degree relatives, the incidence of SAH is similar to that found in the general population[8]. Also, many studies show that around 10% of patients with SAH have a family history. The chance of finding an aneurysm at screening is around 10% if two or more first-degree relatives are affected[8-10]. Two large observational studies of familial aneurysms suggest that screening these patients may also be cost-effective in preventing aneurysmal SAH (aSAH) and improving the quality of life[14,15].

The occurrence of SAH is also associated with specific heritable disorders of connective tissue, but these patients account for only a minority of all patients with SAH. Even though autosomal dominant polycystic kidney disease (ADPKD) is the most common heritable disorder associated with SAH, it is found in only 2% of all patients with SAH[16,17]. Other genetically determined disorders that have been associated with SAH are Ehlers-Danlos disease type IV and neurofibromatosis type 1, but these associations are weaker than between ADPKD and aneurysms and these syndromes are seldom found in patients with SAH[17-19].

The major identified modifiable risk factors include cigarette smoking, hypertension, alcohol abuse and use of sympathomimetic drugs (e.g., cocaine)[3]. Cigarette smoking is an independent and the most important risk factor for SAH, aneurysm formation, growth and rupture[4]. In developed countries of western hemisphere, the prevalence of smoking in SAH patients is 45%-75% (in general adult population 20%-35%), in addition 40% of all SAH patients can be attributed to cigarette smoking[20-25]. The prevalence of hypertension among SAH patients (20%-45%) is somewhat higher than in the general population. Even though the data regarding the relationship between hypertension and SAH are somewhat conflicting, hypertension can be considered to be an important risk factor for SAH and possibly for aneurysm formation and fatal aneurysm rupture[20-24]. Alcohol abuse and particularly sudden intake of high quantities is a risk factor for aneurysm rupture and should be desisted[20-25]. However, despite marked improvements in the treatment of hypertension and hyperlipidemia and the decrease in the rates of smoking over time, the incidence of SAH has not changed appreciably in the last 30 years[26]. Further on, greater vegetable consumption is associated with a lower risk of stroke and SAH[27]. Higher coffee and tea consumption[28] and higher magnesium consumption[29] were associated with a reduced risk of stroke overall, but did not change the risk of SAH.

The risk of growth and aneurysm rupture remains disputable, quite depending on the size and location of the aneurysm[30,31]. According to an international study of unruptured intracranial aneurysms[30], in patients with no history of SAH, the five-year cumulative rate of rupture of aneurysms located in the internal carotid artery, anterior communicating artery, anterior cerebral artery, or middle cerebral artery is zero for aneurysms under 7 mm, 2.6% for 7 to 12 mm, 14.5% for 13 to 24 mm, and 40% for 25 mm or more. This rate is in contrast to rupture rates of 2.5%, 14.5%, 18.4% and 50%, respectively, for the same sizes of aneurysms in the posterior circulating and posterior communicating artery[32]. In addition, when followed up on magnetic resonance imaging (MRI), aneurysms ≥8 mm tended to grow more over time[33], which implies a higher risk of rupture. Several characteristics of aneurysm morphology such as a bottleneck shape[34] and the aneurysm size to parent vessel ratio[35,36] have been associated with rupture status, but how these might be applied to individual patients to predict future aneurysmal rupture is still unclear. In addition to the mentioned international study of unruptured intracranial aneurysms[30], new findings suggest that the risk of first episodes of rupture of aneurysms under 7 mm in anterior cerebral circulation does exist, although slightly lower than 1%[37].

Patients with adequately obliterated aneurysms after aSAH have a low risk of recurrent aSAH for at least 5 years[38], although some coiled aneurysms require retreatment[39].

### *Risk factor recommendations*

1. High blood pressure is an important risk factor, so hypertension treatment may reduce the risk of aSAH (Class I; Level of Evidence B).
2. Cigarette smoking and alcohol abuse should be ceased in order to reduce the risk of aSAH[3] (Class I; Level of Evidence B).
3. The risk of aneurysm rupture might be evaluated considering its size, location and morphological and hemodynamic characteristics, together with the patient's age and health status[3] (Class IIb; Level of Evidence B).
4. Noninvasive screening is reasonable to be considered when two or more first-degree relatives are affected (Class IIb; Level of Evidence B).

## Clinical Presentation and Diagnosis

Although headache is a common presenting chief complaint in the emergency department, and aSAH accounts for only 1% of all headaches evaluated in the emergency department, it should always be suspected in patients with a typical presentation, one of the most pathognomonic pictures in all of clinical medicine[40].

The central feature of classic aSAH is sudden onset of severe headache, approximately 80% of patients describe the pain as "the worst headache of my life"[41]. Any patient's first or worst headache should suggest aSAH and prompt ordering of head computed tomography (CT) scan. In more than 20% of patients, less severe hemorrhages may cause headache of moderate intensity, neck pain, and nonspecific symptoms. Headache is often accompanied with nausea, vomiting, neck stiffness and back pain, photophobia, loss of consciousness, seizures or focal neurological deficits (including cranial nerve palsies).

Despite the classic presentation, aSAH is misdiagnosed in approximately 12% of cases. The common incorrect diagnoses are migraine and tension-type headaches. The most common diagnostic error is failure to obtain a noncontrast head CT scan[42,43].

Prodromal events in the form of sentinel or warning leaks, with minor loss of blood from the aneurysm before a major rupture, are reported to occur in 30%-50% of aSAH and precede overt aSAH by 2 to 8 weeks[44,45]. Sentinel leaks produce sudden focal or generalized head pain that may be severe. In addition to headaches, sentinel leaks may produce nausea, vomiting, photophobia or, less commonly, neck pain. These symptoms may be ignored by the physician. Therefore, a high index of suspicion is necessary because diagnosis of the warning leak or sentinel hemorrhage before a catastrophic rupture may be lifesaving[46]. Sentinel leaks usually do not generate symptoms suggestive of elevated intracranial pressure (ICP) or meningeal irritation and they usually do not occur in patients with arteriovenous malformations. Prodromal presentations occasionally are also caused by the mass effect of an expanding aneurysm and have characteristic features based on aneurysm location.

The clinical condition upon admission of a patient is most commonly rated with the Glasgow Coma Scale (GCS)[47], Hunt and Hess Scale (HHS)[48] or the World Federation of Neurological Surgeons Scale (WFNS)[49]. Obtaining a score with either HHS or WFNS on admission is recommended, as this is the single most useful predictor of long-term outcome[3].

Since subarachnoid blood is almost always detectable on CT scans on the first day of aSAH, with its typical distribution in the subarachnoid space/basal cisterns, noncontrast CT remains the single most important test for the diagnosis of aSAH[3]. Therefore, if aSAH is clinically suspected, cranial CT should be performed to confirm the diagnosis[4]. In the first 24 hours, the sensitivity of CT for SAH is 92%-95%[50-55]. With the newer generation of CT scanners, the sensitivity reaches 97%-100% within the first 6 h and 87% at 6 h or more after symptom onset[53]. The sensitivity to detect blood on head CT declines to 57%-85% on days 5 and 6 and declines to 50% after 1 week[52,56]. Fisher scale is a radiological scale based on the amount and distribution of blood on CT. The score corresponds to the likelihood of delayed cerebral ischemia (DCI) to occur[57].

Advances in MRI of the brain[58-60] can often allow the diagnosis of aSAH to be made when head CT scan is negative and there is clinical suspicion of aSAH, possibly avoiding the need of lumbar puncture.

However, in case of history or clinically suspected SAH, despite negative/inconspicuous CT and/or MRI scans, lumbar puncture should be performed[3,4].

The usefulness of MRI and MR angiography (MRA) in the acute setting is often limited by logistics, the need of acute resuscitation and critical care management of the patient and motion artifacts[3]. Computed tomographic angiography (CTA) is more readily obtainable and faster than MRA. This imaging modality carries a sensitivity of 77%-100% for all aneurysms and 95%-100% for aneurysms ≥5 mm. However, aneurysms <3 mm in size continue to be unreliably demonstrated on CTA[61,62]. In cases of perimesencephalic SAH, the role of CTA is still controversial; it remains unclear whether a negative CTA result is sufficient to rule out aneurysmal hemorrhage and that cerebral angiography is not required[63,64].

Digital subtraction angiography (DSA) was indicated if there was a diffuse aneurysmal pattern of aSAH, and repeat delayed DSA was required if the initial DSA findings were negative, which led to the detection of a small aneurysm in 14% of cases. So, despite the presence of less invasive methods (MRA and CTA), cerebral panangiography (DSA) continues to be the gold standard for detection, demonstration and localization of ruptured aneurysms[4]. The rate of complications associated with this invasive diagnostic procedure is below 0.5% in experienced centers[65].

*Clinical presentation and diagnosis recommendations*

1. aSAH is a medical emergency typically presented with sudden onset of severe headache, however, frequently misdiagnosed[3] (Class I; Level of Evidence B).
2. As the most useful indicator of outcome after aSAH, the simple validated scales (e.g., Hunt and Hess, World Federation of Neurological Surgeons) should be used for rapid determination of the initial clinical severity of aSAH[3] (Class I; Level of Evidence B).
3. The risk of early aneurysm rebleeding is high, and rebleeding is associated with very poor outcomes. Therefore, urgent evaluation and treatment of patients with suspected aSAH is recommended[3] (Class I; Level of Evidence B).
4. Acute diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture[3] *(Class I; Level of Evidence B)*.
5. CT/CTA and multisequential MRI/MRA are equally suitable for the diagnosis of SAH within 24 h and may confirm the underlying cause[4] (Class II; Level of Evidence B).
6. CTA may be considered in the workup of aSAH. If an aneurysm is detected by CTA, this study may help guide the decision on the type of aneurysm repair, but if CTA is inconclusive, DSA is still recommended (except possibly in the instance of classic perimesencephalic aSAH)[3] (Class IIb; Level of Evidence C).
7. MRI (fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences) may be reasonable for the diagnosis of aSAH in patients with a nondiagnostic CT scan, although a negative result does not obviate the need of cerebrospinal fluid analysis[3] (Class IIb; Level of Evidence C).
8. DSA is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by noninvasive angiogram) and for planning treatment (to determine whether the aneurysm is suitable to coiling or to expedite microsurgery)[3] (Class I; Level of Evidence B).
9. If no aneurysm was found, in patients with non-perimesencephalic SAH (with typical pattern of SAH) CTA or DSA should be repeated not earlier than 3 weeks after the initial bleeding, if there are no other therapeutic indications to perform imaging studies earlier[4] (Class II; Level of Evidence C).

## Treatment

All patients with aSAH should be evaluated and treated on an emergency basis with maintenance of airway and cardiovascular function.

After initial stabilization, patients should be transferred to centers with neurovascular expertise and preferably with a dedicated neurological critical care unit to optimize care[66,67]. The patients diagnosed with aSAH should be treated at high volume centers (>35 cases *per* year) with appropriate specialty neurointensive care units (NICUs), neurointensivists, vascular neurosurgeons and interventional neuroradiologists[68-70].

Once in the (neuro)critical care setting, the main goal of treatment is primarily aneurysm repair together with the prevention of rebleeding, prevention and management of vasospasm, and treatment of other medical and neurological complications.

Staff in this unit should have ample experience in assessing swallowing function to prevent pneumonia, a frequent complication after SAH and an independent risk factor for poor outcome[71].

Electrocardiography (ECG), level of consciousness (GCS), pupils, focal deficits and temperature should be monitored frequently for at least the first 7 days after aSAH, or longer as required depending on the patient's clinical condition[4].

Elevated ICP is often associated with aSAH. It can be caused by hydrocephalus, space-occupying intracerebral hemorrhage (ICH), and global and focal cerebral edema. Hydrocephalus occurs in 20%-30% of patients after SAH[72-74]. The treatment of choice is insertion of an extraventricular drain (EVD)[3], which may result in prompt clinical response such as improvement of consciousness[75]. The risk of infection ranges from 2.2% to 21.9%, depending on the number of manipulations and sterile techniques used. If there is no improvement after 36-48 h and the ICP is low, a poor neurological state is likely due to primary brain injury related to the acute effects of hemorrhage. Weaning of the EVD should begin after ICP has been controlled for 48 h, either by trials of intermittent clamping or raising the EVD level with ICP monitoring. Craniotomy and surgical decompression is reasonable in space-occupying intraparenchymal hemorrhages. Decompressive craniectomy can be beneficial in patients with life-threatening cerebral edema with and without intracerebral hemorrhage, due to infarction or recurrent hemorrhage, and should be performed rapidly to avoid herniation[76].

In the intensive care unit, blood pressure (BP) is monitored continuously *via* an arterial line. Treatment of hypertension remains controversial. Data from observational studies suggest that aggressive treatment of BP may decrease the risk of rebleeding but at the cost of an increased risk of secondary ischemia[77]. It seems reasonable, but without good evidence not to treat hypertension unless the BP is extreme. Limits for extreme BP should be set on individual basis, taking into account age of the patient, pre-SAH BP and cardiac history. Systolic BP should be kept below 160 mm Hg (for example, by means of esmolol or labetolol), only until coiling or clipping of ruptured aneurysm, to reduce the risk for rebleeding[3,4].

Regarding fluids and electrolytes, intravenous line is mandatory. A calculated fluid balance every 6 h during the initial week is advised in all patients, as well as urinary catheter. Normovolemia should be aimed[4].

Headache pain should be treated initially with paracetamol (500 mg every 3-4 h). Salicylates are best avoided because their antihemostatic effect is unwanted in patients who may have to undergo external ventricular drainage and interferes with the possibly pending neurosurgical interventions. For severe pain, use of codeine and tramadol are reasonable, while synthetic opiate like piritramide might be considered only as the last resort[4].

To avoid situations that increase ICP, the patient should be kept in bed and the application of antiemetic drugs, laxatives and analgesics should be considered before occlusion of the aneurysm[4].

Hyperglycemia develops in one-third of SAH patients. Hyperglycemia is associated with poor clinical condition on admission, and is independently associated with poor outcome[78-81].

Regarding thromboprophylaxis, in a placebo-controlled trial of enoxaparin (a low-molecular-weight heparin, LMWH) administered subcutaneously 40 mg once a day after surgical aneurysm occlusion, intracranial bleeding complications occurred somewhat more often in the enoxaparin group, while there was no overall influence on outcome or occurrence of post-SAH cerebral infarction[82,83]. Enoxaparin also increased the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors[84]. Because of this increased risk of intracranial bleeding from thromboprophylaxis by means of LMWH, the use of stockings or pneumatic devices seems more appropriate in SAH patients. A study with nonrandomized controls has suggested that deep vein thrombosis can be successfully prevented by the use of pneumatic devices[85]. A Cochrane review on the use of graduated compression stockings or intermittent pneumatic compression in patients with stroke did not find support for the use of either method[86]. In a randomized trial in patients with ICH, the combination of stockings and intermittent pneumatic compression resulted in a smaller risk of deep venous thrombosis than prevention by stockings alone[87]. This combination may be the preferred strategy because there is no reason to suppose that this effect would be any different in patients with SAH, but it needs further study.

Seizures at onset occur in around 7% of patients, but their impact on prognosis is uncertain[88]. Another 10% develop seizures in the first few weeks[89], and convulsive status epilepticus occurs in 0.2%[90]. In patients who are comatose, nonconvulsive status epilepticus has been detected in 8% of patients[91], but the proportion in this study might be an overestimation due to selection of electroencephalography (EEG) by indication. Whether continuous EEG monitoring should be performed in all SAH patients or in the subset of comatose patients is an unresolved issue. An observational study performed in 3,552 patients participating in 4 prospective, randomized, double-blind, placebo-controlled trials suggested that the outcome was worse in 65% of patients receiving prophylactic antiepileptic drugs than in the other 35% of patients who did not receive prophylactic antiepileptic medication[92]. Given the lack of evidence in favor of prophylactic treatment with antiepileptic drugs and the possible disadvantage of serious adverse drug reactions, current advice should be not to start antiepileptic drugs as prophylactic treatment.

The use of hydrocortisone in patients with SAH does not improve clinical outcome but it doubles the risk of hyperglycemia[4].

Patients in a good clinical condition in whom the aneurysm has been secured can be transferred to a regular care bed in the stroke unit[4].

*Treatment recommendations*

1. To avoid situations that increase ICP, the patient should be kept in bed and the application of antiemetic drugs, laxatives and analgesics should be considered before occlusion of the aneurysm[4] (Class IIa; Level of Evidence C).
2. Hyperglycemia over 10 mmol/L should be treated[4] (Class IIa; Level of Evidence C).
3. Increased temperature should be treated medically and physically[4] (Class IIa; Level of Evidence C).
4. Until coiling or clipping, systolic BP should be kept below 160 mm Hg[3] (Class IIa; Level of Evidence C). If systolic pressure remains high despite these treatments, further lowering of BP should be considered[4] (Class III; Level of Evidence C). If BP is lowered, the mean arterial pressure should be kept at least above 90 mm Hg[4] (Class IIa; Level of Evidence C).
5. Patients with SAH may be given thromboprophylaxis with pneumatic devices and/or compression stockings before occlusion of the aneurysm. In case deep vein thrombosis prevention is indicated, LMWH should be applied not earlier than 12 h after surgical occlusion of the aneurysm and immediately after coiling[4] (Class II; Level of Evidence B).
6. Antiepileptic treatment should be administered in patients with clinically apparent seizures[4] (Class IIa; Level of Evidence C). There is no evidence that supports the prophylactic use of antiepileptic drugs[4] (Class III; Level of Evidence C).
7. There is no proof that steroids are effective in patients with SAH[4] (Class III; Level of Evidence C).

## Aneurysm Repair

Currently, the two main therapeutic options for securing a ruptured aneurysm are microvascular neurosurgical clipping and endovascular coiling. Historically, microsurgical clipping has been the preferred method of treatment. Although the timing of surgery has been debated, most neurovascular surgeons recommend early operation. Evidence from clinical trials suggest that patients undergoing early surgery have a lower rate of rebleeding and tend to fare better than those treated later[93]. Securing the ruptured aneurysm will also facilitate the treatment of complications such as cerebral vasospasm. Although many neurovascular surgeons use mild hypothermia during microsurgical clipping of aneurysms, it has not proved to be beneficial in patients with lower grades of SAH[94].

In the early beginnings of cerebral aneurysm treatment, surgery was the only approach in aneurysm repair. Since the development of aneurysm clips, the risk of rebleeding has significantly decreased. With the establishment of microsurgery, surgical approaches have become smaller and less traumatizing. Furthermore, intraoperative indocyanine green angiography and Doppler sonography lead to extra intraoperative quality control.

After the invention of detectable platinum coils by G. Guglielmi in 1990, an alternative to surgical clipping has been developed[95]. Endovascular treatment of aneurysms has been available as an alternative to surgical therapy for more than 20 years now. Coils are made of platinum and are attached to a delivery wire. Once proper position within the aneurysm is achieved, coils are detached from the wire. Multiple coils of various length and diameter are often packed into the aneurysm to exclude it from the circulation. The International Subarachnoid Aneurysm Trial (ISAT) was a landmark study that validated the technique of endovascular coiling[96,97].

With advancements in both microsurgical and endovascular approaches, algorithms to determine the proper patient population and aneurysmal characteristics for each treatment are continually undergoing refinement.

*Timing of aneurysm repair*

Up to 15% of patients rebleed during the first few hours after the initial hemorrhage, that is, during transportation or before the treatment team is able to occlude the aneurysm. Patients surviving the first day after the initial aSAH have a cumulative risk of 35%-40% to suffer rebleeding of the aneurysm with a mortality rate of about 40%. After 4 weeks, the risk of rebleeding decreases to about 3%/year[98]. The primary goal of aSAH treatment is occlusion of the ruptured aneurysm, i.e. to close the bleeding source preventing rebleeding. As mentioned, two major treatment options are available: neurosurgical clipping and endovascular coiling. A meta-analysis of 11 out of 268 studies with a total of 1,814 patients revealed in a comparative evaluation of early *versus* late surgical clipping of ruptured aneurysms that early treatment (within 72 h after SAH) of patients with a good clinical/neurological condition on admission (WFNS 1-3) led to a significantly better outcome. A similar trend, without statistical significance, could be detected in patients with worse WFNS grades 4-5[99]. Even earlier treatment (within 12 h) of SAH patients with WFNS grades IV and V did not increase the number of dependent survivors[100]. Although there are no good evidence-based data, a general long-lasting consensus exists that ruptured aneurysms of patients with good and moderate clinical SAH grades (WFNS 1-4; Hunt and Hess grade I–IV) should be treated in the early phase after the initial bleeding (<72 h after SAH). In patients presenting with multiple intracranial aneurysms, i.e. with one ruptured aneurysm causing SAH and several unruptured incidental aneurysms, the ruptured aneurysm is primarily treated. Subsequent treatment of the unruptured incidental aneurysms depends on the clinical course after SAH, outcome, age, size, location and configuration of the aneurysm.

*Surgical clipping and endovascular coiling*

The decision should be made by a team of neurological, neurosurgical and interventional cerebrovascular experts. ISAT was the only multicenter randomized trial comparing microsurgical and endovascular repair (clipping and coiling but without balloon or stent techniques)[97]. The ISAT study followed the 'uncertainty principle'. The main inclusion criterion of ISAT was that a ruptured aneurysm seemed equally accessible and treatable by either surgical clipping or endovascular coiling ('clinical equipoise'). This inclusion criterion was met by 22.4% of patients (2,143 of 9,559 patients) treated during the study period at the study centers. The remaining 77.6% of patients suffered from aneurysms which were preferably treated by either coiling or clipping. Those patients were not randomized and were excluded from the study. Besides a highly selected patient cohort, ISAT was also criticized for its high (90%) proportion of patients with good clinical grades after SAH (Hunt and Hess grades 1-2) and underrepresentation of middle cerebral artery aneurysms, which are often anatomically more difficult to be coiled than aneurysms in other locations. However, for this subpopulation of ruptured aneurysms, which were equally coilable or clippable, ISAT showed that endovascular coiling had an advantage over surgical clipping, with better clinical outcome: absolute risk reduction of death and severe disability after 1 year was 6.9% in favor of coiling *versus* clipping, based on the observation that 23.7% of endovascular-treated patients (compared to 30.6% of patients after clipping) stayed severely disabled or died after 1 year[97]. The 9-year follow-up of ISAT also revealed a reduction in the relative 5-year mortality risk in favor of coiling. No difference could be observed in the amount of independent SAH survivors between the clip (82%) and coil (83%) group. Both early and follow-up ISAT analysis showed that patients treated with coiling had a higher rebleeding risk, which was comparable to the risk of suffering SAH from a new aneurysm[97,101]. The postoperative risk of rebleeding appears to be associated with the degree of insufficient aneurysm occlusion. Another follow-up study of the patients treated in the ISAT was performed to compare the frequency and consequences of aneurysm recurrence. Retreatment was performed in 17.4% of patients after primary endovascular coiling and in 3.8% of patients after neurosurgical clipping. Late retreatment was 6.9 times more likely after coiling. Younger age, larger lumen size, and incomplete occlusion were the risk factors for late retreatment after coiling[102]. A *post hoc* modeling study with mortality as outcome parameter only after coiling and clipping for patients from the ISAT emphasized that no advantage of coil embolization over clip ligation could be assumed for patients younger than 40 years. For these patients, clipping might even be a better treatment option in terms of life expectancy[103,104]. Because of the highly selected aneurysm subpopulation in ISAT, its results cannot be generalized.

Although in endovascular coiling, the complete obliteration rate can be increased by the addition of a high-porosity stent, this has been associated with an increased risk of complications, especially in patients with SAH, in large part because of the need of periprocedural dual-antiplatelet therapy to prevent arterial thromboembolism[105]. Whether low-porosity flow-diverting stents with or without coils represent a better option for many or most of those presenting with SAH from saccular aneurysms, remains to be studied, but these stents make more conceptual sense for use in the patient with a dissecting aneurysm, in whom vessel sacrifice is not an option and microsurgical solutions carry a higher risk.

Recent advances in technique including the balloon remodeling technique that holds the coils in the aneurysm cavity, liquid polymer coils and embolic agents make treatment of broad neck aneurysm feasible.

Recent studies, which consider increasing endovascular treatment during the last years, could not detect any difference in mortality and morbidity between coiling and clipping[104]. The main concern about endovascular therapy is an increased rate of rebleeding after several years due to coil compaction and aneurysm regrowth at the residual neck.

Given this delicate balance between safety and durability, there have been multiple efforts to identify subgroups of patients who might be best treated with endovascular or microsurgical techniques. The quality of data is modest. Summarizing current studies, ruptured aneurysms are complex lesions.

The primary goal of treatment should be complete occlusion of the aneurysm sack to reduce postprocedural rerupture and bleeding. In case of aneurysms which can be treated equally with clipping or coiling, without stent or balloon, endovascular therapy is preferred. However, indications and treatments should be discussed in an interdisciplinary dialogue. In case of an accompanying space occupying intracerebral hematoma, surgical treatment and clipping is preferred.

As a rough guidance, aneurysms with a wide neck, branching vessels out of the aneurysm sack, middle cerebral artery aneurysms or patients with intracerebral hematoma should preferably be treated by clipping, while aneurysms of the basilar artery or elderly patients (patients >70 years, small aneurysm neck, posterior circulation) should be coiled. Any decision concerning treatment should be interdisciplinary and based on the experience and treatment results of the neurosurgeon and endovascular radiologist together with cerebrovascular neurologist, and should be adapted to the individual aspects including parameters such as age, general state of health, location, configuration and size of the aneurysm, as well as the request of the patient. Patients with aSAH should be treated in centers that offer high-quality treatment with both modalities because the skills of the treating interventionalist or neurosurgeon, as well as the institution, may have great impact on outcome.

***Treatment of ruptured aneurysm – surgical and endovascular methods: recommendations***

1. Ruptured aneurysm should be treated as early as logistically and technically possible to reduce the risk of rebleeding after aSAH; if possible, it should be aimed to intervene at least within 72 h after onset of first symptoms[4] (Class I; Level of Evidence B). The decision should not depend on grading[4] (Class IIb; Level of Evidence C).
2. Complete obliteration of the aneurysm is recommended[3] (Class I; Level of Evidence B).
3. The decision for the best mode of aneurysm treatment, as judged by experienced cerebrovascular neurologists, cerebrovascular surgeons and endovascular specialists, should be multidisciplinary and based on characteristics of the patient and the aneurysm, and the patient should be informed and included in the process of decision making[3,4] (Class I; Level of Evidence C).
4. In general, the decision on whether to clip or coil depends on several factors related to 3 major components: (1) Patient: age, comorbidity, presence of ICH, SAH grade, aneurysm size, location and configuration, as well as the status of collaterals; (2) Procedure: competence, technical skills and availability; and (3) Logistics: the grade of interdisciplinarity[4] (Class IIb, Level of Evidence B).
5. Factors in favor of operative intervention (clipping) in patients with aSAH are: younger age,

presence of space occupying ICH and aneurysm-specific factors such as location (middle cerebral artery and pericallosal aneurysm), wide aneurysm neck and arterial branches exiting directly out of the aneurysmal sack (Class IIb, Level of Evidence B), or other unfavorable vascular and aneurysmal configuration for coiling[4].

6. Factors in favor of endovascular intervention (coiling) in patients with aSAH are: age above 70 years, patients presenting with poor-grade (World Federation of Neurological Surgeons classification IV/V) aSAH, space occupying ICH not present, and aneurysm-specific factors such as posterior location, small aneurysm neck, unilobar shape[4] (Class IIb, Level of Evidence B).
7. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered[3] (Class I; Level of Evidence B).
8. In the absence of a compelling contraindication, patients who undergo coiling or clipping of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (e.g., growing) remnant[3] (Class I; Level of Evidence B).
9. Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded[3] (Class III; Level of Evidence C).

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Sažetak

## OPĆE PREPORUKE ZA LIJEČENJE ANEURIZMATSKOG SUBARAHNOIDNOG KRVARENJA

Subarahnoidno krvarenje je hitno neurološko stanje s visokom stopom smrtnosti i komplikacija. Preporuke su temeljene na dostupnoj literaturi, rezultatima velikih međunarodnih kliničkih ispitivanja i kolektivnom iskustvu autora, a prihvaćene od strane Hrvatskoga društva za neurovaskularne poremećaje, Hrvatskoga društva za neurologiju uključivo i Sekciju za intenzivnu neurologiju, Hrvatskoga društva za neurokirurgiju, Hrvatskoga društva za zbrinjavanje otežanog dišnog puta i Hrvatskoga liječničkog zbora. Cilj ovih preporuka je pomoć liječnicima u donošenju odgovarajućih odluka u dijagnostici i liječenju bolesnika sa subarahnoidnim krvarenjem.

Ključne riječi: *Subarahnoidno krvarenje – dijagnoza; Aneurizma – dijagnoza; Subarahnoidno krvarenje – liječenje; Aneurizma – liječenje; Praktična smjernica*