

# Aneurysmal Subarachnoid Hemorrhage

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**Abstract:** Aneurysmal subarachnoid hemorrhage (SAH) is a worldwide health burden with high fatality and permanent disability rates. The overall prognosis depends on the volume of the initial bleed, rebleeding, and degree of delayed cerebral ischemia (DCI). Cardiac manifestations and neurogenic pulmonary edema indicate the severity of SAH. The International Subarachnoid Aneurysm Trial (ISAT) reported a favorable neurological outcome with the endovascular coiling procedure compared with surgical clipping at the end of 1 year. The ISAT trial recruits were primarily neurologically good grade patients with smaller anterior circulation aneurysms, and therefore the results cannot be reliably extrapolated to larger aneurysms, posterior circulation aneurysms, patients presenting with complex aneurysm morphology, and poor neurological grades. The role of hypothermia is not proven to be neuroprotective according to a large randomized controlled trial, Intraoperative Hypothermia for Aneurysms Surgery Trial (IHAST II), which recruited patients with good neurological grades. Patients in this trial were subjected to slow cooling and inadequate cooling time and were rewarmed rapidly. This methodology would have reduced the beneficial effects of hypothermia. Adenosine is found to be beneficial for transient induced hypotension in 2 retrospective analyses, without increasing the risk for cardiac and neurological morbidity. The neurological benefit of pharmacological neuroprotection and neuromonitoring is not proven in patients undergoing clipping of aneurysms. DCI is an important cause of morbidity and mortality following SAH, and the pathophysiology is likely multifactorial and not yet understood. At present, oral nimodipine has an established role in the management of DCI, along with maintenance of euvolemia and induced hypertension. Following SAH, hypernatremia, although less common than hyponatremia, is a predictor of poor neurological outcome.

**Key Words:** subarachnoid hemorrhage, intracranial aneurysm, delayed cerebral ischemia

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## SUBARACHNOID HEMORRHAGE (SAH) IS A WORLDWIDE HEALTH BURDEN WITH HIGH RATES OF FATALITY AND PERMANENT DISABILITY

The estimated worldwide incidence of SAH is 9/100,000 persons/y with regional variation.<sup>1</sup> One systematic review found the incidence to be lower in South and Central America (4.2/100,000 persons/y) and higher in Japan (22.7/100,000 persons/y) and Finland (19.7/100,000 persons/y).<sup>1</sup> Interestingly, the prevalence of intracranial aneurysm is not found to be higher in Japan or Finland,<sup>2</sup> but the risk for rupture is higher.<sup>3</sup> The incidence is also reported lower in China (2.0 //100,000 persons/y).<sup>4</sup> SAH accounts for only 5% of all strokes,<sup>5</sup> but it has high mortality and permanent disability rates. A retrospective cohort study in 2 large Norwegian populations between 1984 and 2007 reported a 30-day case fatality rate of 36%.<sup>6</sup> A nationwide Danish study reported a similar 30-day mortality at 38%.<sup>7</sup> World Health Organization Multinational Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA stroke study), a large observational study on 11 populations, in Europe and China, reported a 30-day case fatality rate of 42%.<sup>4</sup> A review of data from the Swedish hospital discharge and cause of death registry from 1987 to 2002 on 18,443 patients with SAH showed a 28-day case fatality rate of 31.7%.<sup>8</sup> Another study from Australia and New Zealand placed the 28-day case fatality rate at 39%.<sup>9</sup> The risk for permanent disability is high among survivors, and the dependency rate is approximately 50%.<sup>10–12</sup>

The incidence of new cases of SAH in the United States is about 30,000/y or 10/100,000 persons/y.<sup>13,14</sup> Ruptured cerebral aneurysms account for 75% to 85% of SAH for nontraumatic SAH.<sup>15,16</sup> One systematic review of prospective studies estimated prevalence at 3.6% to 6.0% on the basis of autopsy and angiographic studies.<sup>17</sup> Most of the aneurysms were small (< 1 cm) with an annual risk for rupture of 0.7%.<sup>17</sup> A recent systematic review placed the prevalence rate at 3.2%.<sup>2</sup>

## RISK FACTORS FOR DEVELOPMENT AND RUPTURE OF INTRACRANIAL ANEURYSMS

### Risk Factors for Development of Aneurysms

The important risk factors for the development of cerebral aneurysms are hypertension, smoking, chronic alcohol use,<sup>18–20</sup> family history of intracranial aneurysms in first-degree relatives<sup>2,21–23</sup> and female sex.<sup>1,2,5,8,9,12,23,24</sup> In the United States, the incidence of aneurysmal

subarachnoid hemorrhage (aSAH) is higher in the African American and Hispanic population compared with whites.<sup>23-25</sup> In New Zealand, the incidence of aSAH is found to be higher in native Maori and Pacific Islanders than in the white population.<sup>9</sup> Autosomal dominant polycystic kidney disease is an inherited systemic disorder that is strongly associated with intracranial aneurysms. Autosomal dominant polycystic kidney disease has a prevalence rate 2 to 4 times higher than the general population.<sup>2,14,17,26,27</sup> Other conditions such as Marfan syndrome, Ehlers-Danlos syndrome type IV, neurofibromatosis type 1, and fibromuscular dysplasia are weakly associated with intracranial aneurysms (Table 1).<sup>14,22,27-29</sup>

**Risk Factors for Rupture of Intracranial Aneurysms**

Both the location and type of aneurysm are important considerations in describing the risk for rupture. Most aneurysms occur in the anterior circulation of Circle of Willis, whereas aneurysms of the posterior circulation of the vertebral and basilar systems account for only 12% of intracranial aneurysms, according to the prospective component of the International Study of Unruptured Intracranial Aneurysms (ISUIA) involving 4060 patients with unruptured intracranial aneurysms.<sup>30</sup> About 35% of the patients had >1 aneurysm in this study. Saccular berry aneurysms account for 90% of the total aneurysm morphology and their rupture is the most common cause of SAH. Fusiform aneurysms account for the remaining 10%; their most common location is posterior circulation.<sup>31</sup> Atherosclerosis and dissection are suggested as possible mechanisms for formation of fusiform aneurysms.<sup>32</sup> The risk factors for aneurysm rupture are female sex,<sup>3,14,22</sup> Japanese or Finnish descent,<sup>3</sup> size and location of aneurysms,<sup>3,20,30,33</sup> hypertension,<sup>33-35</sup> smoking,<sup>3,23</sup> older patients,<sup>3,33,36</sup> and cocaine abuse.<sup>23,37</sup>

**TABLE 1.** Risk Factors for the Formation of and Rupture of Intracranial Aneurysms

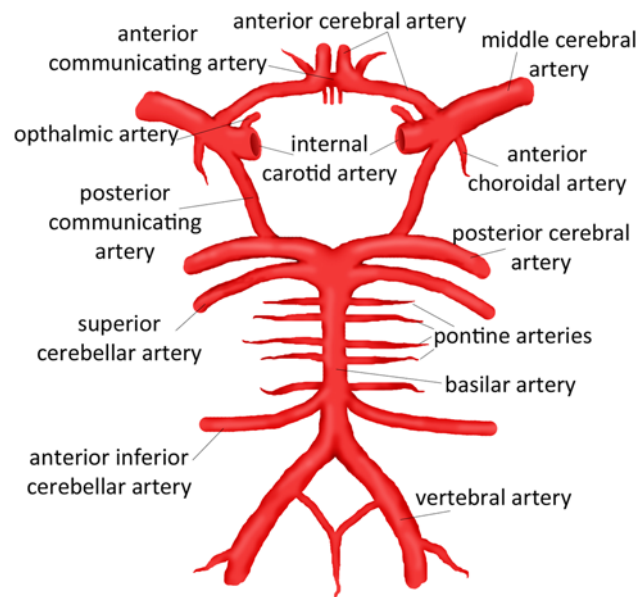
Formation of intracranial aneurysms	Hypertension Smoking Chronic alcohol intake Female sex Family history first-degree relatives Inherited diseases: Strong association Autosomal dominant polycystic kidney disease Weak association Marfan syndrome Neurofibromatosis type 1 Ehler-Danols syndrome Fibromuscular dyplasia
Rupture of intracranial aneurysms	Female sex Japanese and Finnish descent Smoking Hypertension Cocaine abuse Posterior circulation aneurysms Giant aneurysms

The retrospective component of ISUIA identified the risk for rupture to be 0.05% a year for aneurysms <1 cm, whereas aneurysms >1 cm and posterior circulation aneurysms carried a higher risk for rupture.<sup>20</sup> The prospective arm of the ISUIA trial revealed a 5-year cumulative risk for rupture of 0% for aneurysms <7 mm in anterior circulation and 2.5% for posterior circulation aneurysms of similar size.<sup>30</sup> The risk for rupture is higher for giant aneurysms with a size >2.5 cm. Giant aneurysms in the anterior circulation have a 40% risk, whereas those in the posterior circulation carry a 50% risk for rupture.<sup>30</sup> In 2007, a meta-analysis also reported a higher incidence of rupture for posterior circulation aneurysms compared with the anterior circulation of Circle of Willis.<sup>3</sup> The posterior circulation aneurysms most likely to rupture are those located at the basilar tip, the posterior cerebral artery, the vertebrbasilar distribution, and the origin of the posterior communicating artery.<sup>3,38</sup> However, a recent large Japanese cohort study showed similar incidence of rupture for anterior and posterior circulations. In addition, the authors reported a higher incidence of rupture for anterior communicating artery and posterior communicating artery aneurysms. This study found an overall annual rate of rupture of 0.95%<sup>39</sup> (Fig. 1).

**CLINICAL PRESENTATION, ASSESSMENT OF SEVERITY, AND PREOPERATIVE PREPARATION**

**Clinical Presentation**

Most aneurysms remain undetected during one’s lifetime or until rupture. An aneurysm is often an incidental finding during investigations for other causes of intracranial pathology.<sup>40</sup> Aneurysms may present in



**FIGURE 1.** Circle of Willis. Source: Chiu et al.<sup>286</sup> Reprinted with permission from Children’s Hospital of Wisconsin. <https://www.chw.org/display/PPF/DocID/48513/Nav/1/router.asp>.

**TABLE 2.** Clinical Features of Intracranial Aneurysms Based on Location

Location of the Aneurysm	Clinical Features
Anterior communicating artery	Bilateral temporal hemianopsia Bilateral lower extremity weakness
Posterior communicating artery	Third nerve palsy
Intercavernous internal carotid artery	Facial or orbital pain  Epistaxis Progressive vision loss and/or ophthalmoplegia
Posterior circulation aneurysms	Brainstem dysfunction

several ways: headache,<sup>23,41</sup> bilateral temporal hemianopsia and bilateral lower extremity weakness (anterior communicating artery aneurysm),<sup>23,41,42</sup> unilateral third nerve palsy (posterior communicating artery aneurysm),<sup>41</sup> facial or orbital pain, epistaxis, progressive vision loss and/or ophthalmoplegia (intercavernous internal carotid artery),<sup>43</sup> and symptoms of brainstem dysfunction (posterior circulation aneurysms).<sup>14</sup> The most common presenting feature of an aneurysm is SAH. SAH most commonly presents as a severe headache most often described by the patient as “This is the worst headache of my life.”<sup>44,45</sup> An SAH headache is most often associated with nausea, vomiting, neck rigidity, and photophobia.<sup>23</sup> As many as 30% to 40% of the patients may present with a sentinel headache; a warning headache occurring a few weeks before the major bleed possibly due to a warning leak.<sup>46–49</sup> Depending on the severity of SAH, the patient may present with drowsiness, confusion, focal neurological deficits, hemiparesis, and even coma (Table 2).

### Assessment of Severity

The severity of SAH is clinically assessed and graded using either the Hunt and Hess classification or the World Federation of Neurosurgeons Scale (WFNS). The prognostic advantage of one scale over the other is uncertain, these scales have limitations due to intra-observer and interobserver variability.<sup>50</sup> The WFNS scale, widely used, is composed of focal neurological deficits and the Glasgow Coma Scale. Higher grades on both scales are associated with the worst outcomes. Neurological status should also be assessed using the Glasgow Coma Scale, which has a prognostic value and less observer variability.<sup>50</sup> Mortality is commonly caused by neurological injury resulting from the initial bleeding and rebleeding and from delayed cerebral ischemia (DCI). Mortality is a function of the volume of initial hemorrhage and initial neurological status following SAH.<sup>51,52</sup> Elderly patients and patients with coexisting medical conditions are at higher risk for mortality.<sup>51</sup> The clinical goal is to prevent rebleeding and DCI.

Noncontrast head computed tomography (CT) is the initial imaging modality of choice.<sup>53,54</sup> The presence of SAH requires further evaluation with CT angiography (CTA) or cerebral angiography.<sup>54</sup> Noncontrast CT followed by CTA provides diagnosis in aSAH in 99% of the cases.<sup>55,56</sup> In the presence of a normal noncontrast

CT scan, lumbar puncture remains necessary to avoid potential misdiagnosis.<sup>13,54,57</sup> The Fisher scale is used to classify the appearance of SAH on a CT scan. This scale is based on the amount of blood in the subarachnoid space on a cranial CT scan and is a predictor of cerebral vasospasm, DCI, and possibly the overall patient outcome.<sup>58–60</sup>

### Cardiac Manifestations

Patients following subarachnoid bleed are likely to show a wide variety of electrocardiographic abnormalities including ST and T wave changes, suggestive of myocardial ischemia and QT prolongation and U waves. In addition, SAH may present with supraventricular and ventricular arrhythmias, elevated troponin levels, and myocardial dysfunction without coronary vasospasm.<sup>61–63</sup> The exact mechanism is not known. The likely cause is sympathetic activation along with parasympathetic dysfunction resulting in inflammation of cardiac myocytes.<sup>63</sup> The degree of troponin elevation is associated with an increased risk for cardiovascular complications and vasospasm-induced DCI and poor neurological outcome.<sup>61,62</sup> An exploratory analysis of 413 patients from the CONSCIOUS-1 (Clazosentan to Overcome Neurological iSChemia and Infarct OccUring after Subarachnoid Hemorrhage) database showed an association between QT prolongation, tachycardia, and development of angiographic vasospasm.<sup>64</sup> Thus these cardiac changes primarily reflect the severity of neurological injury, but are reversible in the majority of cases and are likely to resolve.<sup>65,66</sup> However, patients with severe myocardial dysfunction may need inotropic support and rarely temporary intra-aortic balloon counterpulsation.

### Neurogenic Pulmonary Edema (NPE)

NPE is thought to be due to a massive sympathetic discharge resulting from neurological injury and is associated with reduced global and segmental left ventricular systolic function.<sup>67</sup> NPE reflects the severity of the subarachnoid bleed and is associated with poor outcome.<sup>68,69</sup>

### Hypertension

Elevated blood pressure (BP) following aSAH is associated with higher mortality.<sup>70,71</sup> However, aggressive management of hypertension following aSAH is always a matter of concern, given that a higher BP is required to maintain cerebral perfusion pressure (CPP), in the presence of elevated intracranial pressure (ICP).<sup>15</sup> Sympathetic activation following SAH is an important cause of hypertension. Elevated ICP is not the solitary cause. Sustained elevation of BP increases the risk for aneurysmal rupture and rebleeding. A recent large randomized controlled trial (RCT), INTENSIVE Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT-2), with 2794 participants reported that systolic BP reduction to <140 mm Hg within an hour of intracerebral hemorrhage compared with <180 mm Hg systolic had similar mortality and severe disability rate at the end of 90 days.<sup>72</sup> The IntraCerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT)

involving 75 patients did not show reduction in perfusion in the vulnerable penumbra around the hematoma in patients in whom the BP was lowered to 150 mm Hg systolic compared with 180 mm Hg systolic in the control group.<sup>73</sup> The perfusion was measured within 2 hours of postrandomization using CT perfusion imaging. The results of these trials can be applied to patients with aSAH. On the basis of these results it can be concluded that BP can be reduced safely to 140 mm Hg systolic to decrease the risk for rebleeding without increasing the risk for ischemic complications. Another phase III trial, Anti-hypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II, is currently underway.<sup>74</sup> This trial compares aggressive BP reduction with intravenous (IV) nicardipine to systolic 140 mm Hg with the control group in which BP reduction is limited to systolic 180 mm Hg. The outcomes compared are death and disability rates at the end of 90 days. The BP reduction is done within 3 hours of randomization. This trial will provide further clarification to the issue of aggressive BP management.

Labetalol, esmolol, and nicardipine are commonly used agents to reduce hypertension in patients with aSAH.<sup>23,70</sup> Vasodilators such as nitroglycerine, hydralazine, and sodium nitroprusside should be avoided because vasodilatation may increase cerebral blood flow and is likely to worsen ICP.<sup>70</sup> Nicardipine provides better BP control compared with labetalol in patients with aSAH.<sup>75</sup> However, one should note that vasodilators were used to reduce the BP in the INTERACT-2 trial without worsening neurological outcome.

### Hyperglycemia

Patients with SAH who develop hyperglycemia are at increased risk for poor clinical outcome.<sup>76-78</sup> Hyperglycemia was found to be associated with increased length of ICU stay, and increased risk of death and disability in one retrospective cohort study.<sup>78</sup> Analysis of data from 1000 patients in the Intraoperative Hypothermia for Aneurysms Surgery Trial (IHAST II) revealed that patients with SAH, secondary to ruptured aneurysm, who underwent clipping, and whose blood sugar levels were > 129 mg/dL, had long-term cognitive dysfunction. Patients with blood sugar levels > 152 mg/dL had deficits in gross neurological function.<sup>79</sup> Glycemic control with aggressive hyperglycemia management is associated with improved outcome, but further studies are required to confirm these results.<sup>80</sup> Hyperglycemia should be treated in the perioperative period; however, there are insufficient data available to make a recommendation on target blood sugar levels.

### EARLY VERSUS LATE INTERVENTION?

Early therapy with either surgical clipping or neuroradiologic intervention with endovascular coiling will prevent rebleeding and will enable safe and effective management of vasospasm. However, early surgery on an edematous brain makes the surgical task difficult. In the past, early intervention was advocated for better neurological grades, now surgical intervention is done for

higher grades as well. An 11-year database of 230 consecutive ruptured aneurysms from an Australian center found that either early surgical clipping or endovascular coiling within 24 hours was associated with improved clinical outcome.<sup>81</sup> Another meta-analysis also found that early intervention within 72 hours is associated with improved clinical outcome and that the degree of improvement is a function of the clinical condition on admission.<sup>82</sup> An observational study from the Netherlands involving 8 centers and 1500 patients did not show a difference in outcome with either early or late intervention to secure the aneurysm, in good grade patients.<sup>83</sup> However, patients with poor neurological grades at admission fared better with early intervention. An analysis of data from a Nationwide Inpatient Sample on 32,048 US patients with aSAH from 2005 to 2008 revealed that patients treated early (within 48 h of hospital admission) with coiling or surgery are more likely to be discharged with little or no disability.<sup>84</sup>

Whenever a delay is anticipated in definitive treatment, a short course (< 72 h) of antifibrinolytic agents such as tranexemic acid and aminocaproic acid prevents rebleeding without increasing the risk for DCI.<sup>23,70,71,85-90</sup> However, delayed and prolonged therapy with antifibrinolytic agents is not recommended, as it may increase the risk for thrombotic events and DCI.<sup>23</sup> The role of antifibrinolytic agents in terms of overall patient outcome is yet to be demonstrated in RCTs.<sup>85,87,88,90</sup>

## CLIP VERSUS COIL?

### Ruptured Aneurysms

The International Subarachnoid Aneurysm Trial (ISAT),<sup>91,92</sup> a prospective international multicenter RCT involving 42 centers, located mainly in the United Kingdom (77% of the recruits) and Europe, used death or dependency at 1 year as the primary outcome measure. In this trial 9559 patients with SAH were screened and 2143 patients were included; 1070 patients were assigned to the surgical clipping group and 1073 were included in the coiling group. Patients with good neurological grades (WFNS I-III) were included in this study. The ISAT results reported in 2002 showed that the primary outcome measure (death or dependency rate) was better with the coiling group (23.5%) compared with the surgical clipping group (30.9%). However, the rate of rebleeding at the end of 1 year was higher in the coiling group (2.6%) compared with the surgical clipping group (1%). A 5-year follow-up of results from the ISAT trial in 2009 also showed a reduced death rate in the coiling group compared with the clipping group (11% vs. 14%).<sup>93</sup> In addition, the percentage of survivors who were independent did not differ between the groups. Thus at the end of 5 years the advantage of coiling in death or dependency rate decreased from 7.4% to 3%. This 5-year follow-up also confirmed an increased risk for recurrent bleeding in the coiling group compared with the surgical clipping group. The risk for seizure at the end of the first and fifth year was lower in the endovascular coiling group compared with the neurosurgical clipping group.<sup>91,93</sup> The

difference in outcome for patients younger than 40 years of age in the ISAT trial is similar for both the coiling and the clipping group.<sup>94</sup> Surgical clipping provides better protection from recurrent SAH in younger patients. Inadequate primary occlusion of an aneurysm is the primary cause of recurrent bleeding in the coiling group.<sup>95</sup> Intramural thrombus and wide neck increases the risk for inadequate occlusion during coiling. Dissolution of thrombus and subsequent aneurysm growth leads to late reopening and increases the risk for potential future rupture.<sup>96</sup>

Before a definitive conclusion of the superiority of endovascular coiling over surgical clipping, ISAT design limitations should be considered.<sup>93,97,98</sup> Only 22.4% of the total patients screened were recruited in the trial (2143 of 9559). Ninety-seven percent of the recruits had anterior circulation aneurysms and only 3% had posterior circulation aneurysms. The middle cerebral artery aneurysms (MCA) were also underrepresented (< 15%) in the trial because they were considered unsuitable for coiling at the time of randomization. Ninety-two percent of the aneurysms were < 1 cm in diameter and are likely to have a better outcome.<sup>20,30</sup> Although the selection criteria were designed to include WFNS grades I-III, 88% of the recruits belonged to grade I-II. Because of these limitations in the selection process, the ISAT results can be reliably applied to small, anterior circulation aneurysms with good neurological grades. These results cannot be extrapolated to patients with larger aneurysms, posterior circulation aneurysms, WFNS grade III-IV patients, and patients with complex aneurysm morphology. The average time for coiling was 1.1 days compared with 1.5 days for surgical clipping; this delay would have influenced the outcome. The experience parameter of 30 coiling procedures was set for participating physicians performing the coiling procedure and no such standard was set for the surgeon performing the surgical clipping. It was not mandatory to perform angiography to confirm the surgical clipping since this procedure would have required a change in the institutional practice of participating centers. In addition, rigorous angiographic surveillance was not required for surgical clipping patients unlike their coiling counterparts in the trial. Incomplete obliteration and residual neck remnants possibly resulted in adverse outcome in surgical patients. Patients older than 70 were excluded in the trial and the choice of technique in these patients cannot be ascertained using the results of the ISAT trial. Moreover, patients were assessed using the modified Rankin scale, a subjective assessment by patients, reported through a postal questionnaire rather than an objective assessment. Although the modified Rankin scale is a commonly used measure of outcome in clinical studies, there is the possibility of bias in patients reporting their outcome because of interobserver variability.<sup>98,99</sup> Despite these caveats, ISAT is the first landmark study comparing the outcome measure of endovascular coiling with surgical clipping and changed practice in favor of coiling. The endovascular coiling technique is currently increasingly used in the United States according to a recent Nationwide Inpatient Sample database review on cerebral aneurysms.<sup>100</sup>

The Barrow Ruptured Aneurysm Trial (BRAT), a recent prospective RCT involving 471 patients, found improved clinical outcome for endovascular coiling at the end of 1 year.<sup>101</sup> Crossovers from one treatment group to the other were allowed in this trial on the basis of the discretion of the treating physician. A subsequent analysis of the 349 patients who were available for evaluation at the end of 3 years did not confirm this overall benefit. The 3-year data showed that a significant number of patients assigned to the coiling group were crossed over to the surgical clipping group (38%). No significant difference in outcome was found in anterior circulation aneurysms, but the coiling group had a better outcome for aneurysms located at the posterior circulation (anterior circulation  $n = 339$ , posterior circulation  $n = 69$ ).<sup>102</sup> Because of crossovers, secondary to study design, the reported significance of benefit of coiling in a small group of posterior circulation aneurysms is questionable.

To address the issues raised in the aftermath of ISAT trial, ISAT II, a multicenter international trial involving 50 centers, began in 2012 and is currently recruiting patients and is estimated to complete in 2024. The study design also includes aneurysms > 1 cm in diameter, posterior circulation aneurysms, patients with WFNS grade 3-4, and patients over the age of 70, which were not studied in the original ISAT trial.<sup>103</sup> Non-invasive angiographic surveillance is planned for both the coiling and the clipping group (such follow-up was not mandatory for the clipping group in the original ISAT trial). However, the primary outcome measure is similar to the original ISAT trial, which also includes assessment of dependency using the modified Rankin scale.

## Unruptured Aneurysms

A retrospective study of unruptured aneurysms used data from 429 US hospitals in 18 states covering 58% of the US population. During the years 1998 to 2000, there were 2535 unruptured aneurysms evaluated. The results of this study favored endovascular coiling over surgical clipping.<sup>104</sup> There are no randomized trials comparing the clipping and coiling technique for unruptured aneurysms. The unruptured aneurysms are likely to be smaller and they are likely to be located in anterior circulation. The results of the ISAT trial can be predictably extrapolated to unruptured aneurysms, as the ISAT recruits predominantly had anterior circulation aneurysms < 1 cm in diameter and 87% of the recruits were neurological good grade patients (WFNS scale I and II). The role of conservative management for unruptured small aneurysms, particularly of anterior circulation, which otherwise have low risk for rupture, is not known. An RCT comparing conservative management, coiling, and clipping is not feasible and likely to face recruitment problems and would meet the same endpoint as the Trial on Endovascular Aneurysm Management (TEAM trial), which was stopped after recruiting only 80 patients.<sup>105</sup> The TEAM trial was designed to compare the role of conservative management and endovascular coiling for unruptured intracranial aneurysms.

### Choice of Technique for Management of Intracranial Aneurysms

The choice of technique for non-ISAT type of aneurysms is yet to be studied in the ISAT II trial. Certain aneurysms are not suitable for endovascular coiling, such as giant aneurysms, wide neck aneurysms (a neck to dome ratio >0.5), fusiform aneurysms, and aneurysms at certain anatomic locations, such as arterial bifurcation.<sup>23</sup> However, aneurysms located in the vertebrobasilar distribution can be easily accessed by an endovascular approach compared with surgical clipping.<sup>13,23,106</sup> In particular, basilar tip aneurysms are not amenable to surgery because of deep location and difficulty in proximal control. These aneurysms can be safely treated with an endovascular approach, with or without stent use.<sup>107-109</sup> Cavernous sinus internal carotid aneurysms (ICA) are the most difficult aneurysms to treat, because of their close proximity to venous structures and cranial nerves. Surgical access is difficult for aneurysms at this location.<sup>110</sup> Aneurysms located at the intercavernous ICA can be managed with balloon occlusion of the parent vessel and coiling.<sup>111,112</sup> MCA aneurysms are difficult to treat by coil embolization and are better suited for surgical clipping; however, recent evidence suggests that these aneurysms can be safely treated with coiling embolization.<sup>113-118</sup> Ruptured aneurysms with mass effect are better suited for surgical therapy as it enables the surgeon to evacuate a hematoma and thereby decreases the incidence of vasospasm.<sup>23</sup> In younger patients, surgical clipping is preferred as it provides better protection from future SAH.<sup>94</sup> Coiling is suitable for older patients and patients with comorbid conditions (Table 3).<sup>119</sup>

#### ENDOVASCULAR FLOW DIVERSION

This is a relatively new endovascular technique whereby an endovascular device with a porous, tubular tight mesh and high metal ratio is deployed across the neck of the aneurysm to redirect the flow from the aneurysm to the parent vessel. This flow diversion eventually leads to intra-aneurysmal thrombosis; subsequently, reendothelialization of the arterial wall intima covers the stent.<sup>120,121,123</sup> This results in reconstruction and remodeling of the parent artery and occludes the aneurysm/parent vessel interface. Thus a combination of flow diversion hemodynamics, thrombosis, inflammation,

and endothelial regrowth results in endoluminal reconstruction and overall aneurysm obliteration.<sup>120,121,123</sup> Larger aneurysms may require a combined technique of flow diversion and coiling. The advantage of the endovascular flow diversion technique is that coiling is not required and thereby aneurysmal perforation secondary to coiling can be avoided. After the deployment of endovascular flow-diverter devices, patients require dual antiplatelet therapy.<sup>120,121,123</sup> The duration of the antiplatelet therapy is currently debated. The combination of aspirin 325 mg and clopidogrel 75 mg is used for 6 months in most of the centers.<sup>120,123</sup> The pipeline embolization device (PED), silk flow diverter (SFD), Surpass flow diverter (SURPASS), and the flow redirection endoluminal device (FRED) system are the 4 flow-diverter devices CE marked in Europe for clinical use and available in other parts of the world. PED is the only device approved by the US Food and Drug Administration. SURPASS and FRED are new-generation devices, and have recently obtained CE marking. Currently limited data are available on their use.

The recognized problems with this technique are intraprocedural aneurysmal perforation or rupture, ischemic stroke, perianeurysmal cerebral edema, early and delayed distal intraparenchymal hemorrhages (IPH), perforator infarction, side branch occlusion, delayed aneurysm rupture, and late parent artery stenosis/occlusion from neointimal overgrowth.<sup>120-129</sup> The perforator infarction is more common in posterior circulation compared with anterior circulation.<sup>122</sup> Ischemic stroke is thought to be due to stent occlusion from thrombus formation and thromboembolism.<sup>120,122</sup> The neointimal overgrowth may cause parent artery stenosis/occlusion and late cerebral infarction.<sup>123</sup> The exact mechanism of IPH is not known. The proposed mechanisms are hemorrhagic reperfusion of the ischemic stroke, hemodynamic alteration from flow-diverter placement, and dual antiplatelet therapy.<sup>120,122,123</sup> The intra-aneurysmal thrombosis results in an inflammatory process and extension of such an inflammatory process around the aneurysm is the most likely mechanism of perianeurysmal cerebral edema.<sup>120,123</sup> Such edema may result in headache and worsening of presenting compressive signs and symptoms.<sup>123</sup> The early SAH can occur due to intraprocedural rupture. The flow diversion technique does not occlude the aneurysm immediately and requires a latency period. Rupture can occur during this latency period.<sup>120</sup> The late SAH is caused by aneurysmal rupture due to inadequate occlusion. In addition, there are other theories to explain the delayed aneurysmal rupture. The inflammatory process resulting from intra-aneurysmal thrombosis may contribute to weakening and breakdown of the aneurysmal wall and subsequently rupture causing delayed SAH.<sup>120,123</sup> The proximal migration of the flow-diverter device may redirect the flow from the parent vessel to the aneurysmal sac resulting in its rupture.<sup>120</sup> A meta-analysis involving 29 studies with 1654 aneurysms treated with PED and SFD reported the total occlusion rate as 76% at 6 months.<sup>122</sup> The periprocedural mortality and morbidity rate was 4% and 5%, respectively. The overall

**TABLE 3.** Choice of Technique for Intracranial Aneurysms

Endovascular coiling	Posterior circulation aneurysms
	Basilar tip aneurysms
	Intercavernous internal carotid artery aneurysms
	Elderly patients
	Patients with comorbid conditions
Surgical clipping	Middle cerebral artery aneurysms
	Fusiform aneurysms
	Giant aneurysms
	Aneurysms with wide neck
	Aneurysms at arterial bifurcations
	Ruptured aneurysms
	Younger patients

incidence of ischemic stroke was 6% and the rate of IPH was 3%.<sup>122</sup> Another meta-analysis involving 1018 aneurysms treated with SFD and PED reported the total occlusion rate of the aneurysms at 9 months as 76.2%.<sup>124</sup> The reported early neurological morbidity was 7.3% and late neurological morbidity was 2.3%.

The currently available data are primarily derived from prospective and retrospective studies involving unruptured aneurysms. The current ongoing trials involving flow-diverter devices have excluded patients with ruptured aneurysms. The ISAT II trial is the only ongoing RCT comparing clinical outcomes for patients with SAH randomized to either endovascular management or surgical management.<sup>103</sup> Within the endovascular study arm the physician may choose the coil type and supplement this with balloon-remodeling, stents, or flow diverters. Considering the uncertain safety profile of the flow diverter, a low enrollment of patients receiving this device is anticipated. The requirement of a latency period for obliteration and inadequate occlusion leaves the already ruptured aneurysm unprotected. In addition, the use of dual antiplatelet therapy is likely to potentiate the risk for hemorrhage. Because of these concerns, the use of flow diverters should be avoided in treating patients with aSAH.

### ANESTHETIC MANAGEMENT OF SURGICAL CLIPPING

Depending on the severity of SAH, cerebrovascular reactivity and cerebral autoregulation are likely to be impaired in these patients. Patients with impaired cerebral autoregulation are at risk for delayed cerebral infarction following SAH.<sup>130,131</sup> In these patients, cerebral perfusion depends directly on the mean arterial pressure. The anesthetic goal is to maintain the transmural pressure gradient (TMPG) across the wall of the aneurysm and to maintain CPP. A sudden increase in BP coupled with a sudden decrease in ICP can cause sudden changes in the TMPG across the wall of the aneurysm, increasing the risk for rupture. If the patient has a lumbar drain, the optimal time for release of the drain is after opening the dura, which will prevent a sudden drop in ICP and change in the TMPG. Smooth induction and maintenance of anesthesia is desired. Hypotension or hypertension at the time of induction, intubation, surgical pinning, incision, and opening the dura should be avoided. An arterial line usually placed before induction and wide-bore venous access is preferred.

#### Choice of Anesthetic Technique: Inhalational Versus IV Anesthesia?

Anesthesia can be maintained with inhalational agents  $\leq 1$  minimum alveolar concentration (MAC), using narcotics such as fentanyl, sufentanil, or remifentanyl, with adequate neuromuscular blockade using non-depolarizing agents. The difference in the cerebral vasodilator effect of modern inhalational agents such as desflurane, isoflurane, and sevoflurane is not clinically relevant when used at 1 MAC or lower.<sup>132,133</sup> The

cerebral vasodilatory effect is dose dependent, halothane > desflurane > isoflurane > sevoflurane.<sup>134,135</sup> However, from a postoperative neurological recovery point of view, desflurane > sevoflurane > isoflurane and this property is dependent on their blood gas solubility coefficients.<sup>136,137</sup> Alternatively, a propofol-based total IV anesthesia (TIVA) technique can also be used. This technique is likely to reduce the cerebral blood flow and ICP.<sup>138,139</sup> However, its superiority over inhalational agents in terms of brain relaxation and neurological recovery is not proven when used at 1 MAC or lower.<sup>140-142</sup>

The studies comparing IV with inhalational technique did not compare the long-term neurological outcome. Alternatively, a combination of IV and inhalational techniques can be used. There is no advantage to using remifentanyl with inhalational or propofol-based TIVA compared with fentanyl with a similar technique in terms of neurological recovery.<sup>141</sup> A recent retrospective analysis of Japanese Diagnosis Procedure Combination Database revealed that remifentanyl use is associated with lower in-house mortality following clipping of ICA aneurysms.<sup>143</sup> The exact cause of such an observation with remifentanyl use is not known, but could possibly be due to a reduced surgical stress response in the remifentanyl group. An RCT reported reduced stress response in the remifentanyl group undergoing supratentorial tumor resection.<sup>141</sup> Urinary catecholamines and cortisol levels were measured as markers of stress response in this trial, which were found to be lower in the remifentanyl group compared with the fentanyl group. However, these beneficial observations with remifentanyl use need to be further studied in large randomized trials with long-term neurological outcome and mortality as a primary outcome measure.

One should note that the RCTs comparing IV and inhalational technique examined patients presenting for supratentorial tumor resection with good neurological condition. However, data are lacking in patients with poor neurological condition with critically elevated ICP. In such patients the above data comparing IV and inhalational agents cannot be predictably extrapolated to make an effective conclusion. Patients with raised ICP, at the upper portion of the intracranial volume-ICP curve, are likely to benefit from a TIVA technique. Deepening of anesthesia during anticipated surgical stimulation (for example surgical pinning) should be done with IV agents rather than volatile agents over 1 MAC. If patients are monitored using evoked potentials, TIVA is preferred, because volatile agents have a significant effect on evoked potentials. Moreover, large randomized trials are required to look into the long-term outcome before a definite conclusion can be made with regard to a choice of technique between IV and inhalational technique.

#### ICP Management

Elevated ICP should be managed along with simple measures such as head end elevation and prevention of jugular venous compression. Clinicians should maintain a low normal arterial carbon dioxide (PaCO<sub>2</sub> of 35 mm Hg) and ensure adequate anesthetic depth; ICP reduction may

require administration of IV mannitol or hypertonic saline (HTS) and slow controlled cerebrospinal fluid (CSF) drainage. Sudden drop of ICP with CSF drainage is to be avoided as it may lead to sudden change in TMPG and possible aneurysm rupture.

### Role of Hyperventilation?

Hyperventilation produces brain relaxation and improves surgical conditions.<sup>144</sup> There are insufficient data with regard to the benefits and risks in terms of neurological outcome with hyperventilation therapy in neurosurgical patients. One RCT reported adverse neurological outcome in severe head injury patients following prolonged hyperventilation.<sup>145</sup> Hyperventilation results in cerebral vasoconstriction with reduction in cerebral perfusion and cerebral tissue oxygen content as per small studies in traumatic brain injury (TBI) patients. These studies did not look into the neurological outcome.<sup>146–149</sup> The effects of hyperventilation comparing normocarbina in terms of neurological outcome need to be studied in a large RCT. Hyperventilation should only be used when all other measures have failed to control the ICP and should be terminated when the indication for its use ceases.<sup>150–152</sup>

### Mannitol Versus HTS?

Mannitol 20% is a commonly used agent to reduce ICP in a dose range of 0.25 to 1 g/kg body weight, with 0.5 g/kg being the most common. Mannitol should be infused intravenously over a period of 10 to 15 minutes to prevent a transient increase in ICP.<sup>151</sup> There are no randomized trials comparing the efficacy of HTS over mannitol in patients with aSAH. Two RCTs proved the benefit of HTS over mannitol in terms of brain relaxation in patients undergoing supratentorial craniotomy.<sup>153,154</sup> However, the ICU days and hospital days were similar in both groups in one of these studies,<sup>153</sup> and the long-term neurological outcomes were not studied in either trial.<sup>153,154</sup> A meta-analysis and systemic review from TBI reported better control of elevated ICP with the use of HTS compared with mannitol.<sup>155</sup> However, the authors cited the limitations of this meta-analysis as lack of patient numbers, limited RCTs, and inconsistent methodology.

HTS administration requires a central venous access because infusion through a peripheral IV line is likely to result in thrombophlebitis. HTS administration may result in hypernatremia, but its association with the development of acute kidney disease and central pontine myelinolysis is not established in the normonatremic patient.<sup>156</sup> Until the superiority of HTS is demonstrated in terms of neurological outcome (long-term benefit in particular) in a large RCT, the use of HTS or mannitol is acceptable during intracranial aneurysm clipping for the control of ICP.

### Neuromonitoring

Neuromonitoring techniques such as electroencephalography (EEG), somatosensory evoked potentials (SSEP), and brainstem auditory evoked potentials

(BAEP) are used for aneurysm surgery, but their role in patient outcome is uncertain. In a recent analysis of 691 consecutive patients, who underwent aneurysm clipping, the overall accuracy of SSEP changes in predicting post-operative stroke rate was reported as a positive predictive value of 30% and a negative predictive value of 94%, with a sensitivity of 25% and a specificity of 95%.<sup>157</sup> SSEP monitoring is useful for aneurysm surgery involving anterior circulation<sup>158</sup>; a combination of SSEP and BAEP monitoring is useful for aneurysms of posterior circulation.<sup>159,160</sup> Transcranial or direct cortical stimulation, motor evoked potential (MEP) monitoring identifies the ischemia of the motor cortex and its pathway secondary to the occlusion of the perforating arteries of middle cerebral and basilar arteries.<sup>161–164</sup> The role of neuromonitoring in terms of neurological outcome needs to be studied in a large placebo controlled trial. Until then, neuromonitoring techniques should be given a consideration when there is a possibility of the application of a temporary clip or if induced hypotension is used to facilitate surgical access. These techniques may identify an improperly applied permanent clip.

### Induced Hypothermia

A large multicenter prospective, randomized partially blinded trial, IHAST II determined that mild induced hypothermia (33°C) is not associated with improved neurological outcome in patients with good neurological grades in patients undergoing surgical clipping of intracranial aneurysms.<sup>165</sup> Ninety-five percent of the recruits belonged to WFNS grades 1 and 2. Because of the limitations of the IHAST II, the role of induced hypothermia cannot be completely ruled out as a neuroprotective strategy.<sup>165–167</sup> The patients in this study were cooled slowly over a period of 5 hours. Target temperature was only reached at or just before clipping. This slow phase of cooling is likely to deny protection from initial ischemic insults from placement of surgical retractors. Cooling time was limited to a mean operating time of 5 to 6 hours. Insufficient cooling might be the cause of the lack of beneficial effect of hypothermia. Rapid rewarming in hypothermia may have contributed to the lack of benefit of induced hypothermia. The outcome measure was based upon the Glasgow Outcome Score (GOS), which is a crude method of outcome assessment and should have been supplemented with the modified Rankin scale for better assessment. In addition, the GOS cannot detect subtotal cognitive beneficial effects. Moreover, even though 1001 patients were recruited in the trial, the study is underpowered to detect a change of one point on GOS. Also, the role of hypothermia has not been studied in patients with poor neurological grades.<sup>168</sup> Because of the above considerations, the role of hypothermia cannot be completely negated in patients with aSAH on the basis of the results of IHAST II trial alone.

### Role of Albumin for Neuroprotection

The Albumin in Subarachnoid Hemorrhage (ALISAH), a multicenter pilot study with 48 patients, reported the



beneficial neuroprotective effect of 25% albumin when administered daily for 7 days.<sup>169</sup> Neurological outcome was measured at the end of 90 days. In severe TBI patients, the Saline versus Albumin Fluid Evaluation (SAFE) study revealed increased mortality at the end of 2 years when patients were resuscitated with 4% albumin compared with 0.9% saline.<sup>170</sup> The cause of the increase in mortality with the 4% albumin resuscitation group is not known, but increased ICP secondary to 4% albumin administration is a likely explanation.<sup>171</sup> One should note that 4% albumin is used in the SAFE study in contrast to 25% hyperoncotic solution in the ALISAH study. A large placebo controlled RCT is needed to confirm the benefit of the ALISAH trial. Until such confirmation one should be cautious with the use of albumin as a neuroprotective agent in light of the results of the SAFE study 2-year follow-up.

### Temporary Clip

Surgeon may apply a temporary clip to the feeding vessel to produce localized hypotension to reduce the vascularity of the aneurysm. This facilitates dissection around the neck of the aneurysm enabling the surgeon to place a permanent clip in difficult cases. The application of a temporary clip also reduces the incidence of intraoperative aneurysm rupture.<sup>172</sup> After the temporary clip is placed, mean arterial pressure should be maintained or elevated to improve perfusion through collateral circulation while avoiding hypotensive episodes. The safe duration of temporary clipping is not entirely known.<sup>173,174</sup> However, temporary clipping for an MCA aneurysm should preferably be limited to < 10 minutes.<sup>173</sup> A duration > 20 minutes of temporary clipping on any intracranial artery puts the patient at risk for ischemia.<sup>175,176</sup> Patients with poor neurological grades, elderly patients, those with delayed surgery (4 to 10 d after SAH), or patients with episodes of multiple clipping increase the risk for ischemia and stroke.<sup>177</sup>

During temporary clipping, burst suppression on EEG using propofol is commonly practiced; however, a beneficial clinical outcome of this practice is not demonstrated, according to the subset analysis of IHAST II in which patients received supplemental drug for neuroprotection when a temporary clip was applied.<sup>178</sup> Intraoperative hypothermia did not affect the outcome of patients who had a temporary occlusion.<sup>178</sup>

### Induced Hypotension

A surgeon may request a brief period of induced hypotension to gain surgical access to the base of the aneurysm. The traditional methods of induced hypotension using nitroprusside and nitroglycerine are likely to result in prolonged hypotension, which may increase the risk for cerebral ischemia. A retrospective data analysis from 2 centers in the United States showed that adenosine can be safely used to produce transient flow arrest without adverse cardiac or neurological outcome in patients with low risk for coronary artery disease.<sup>179-182</sup> A mean duration of 45 seconds of circulatory arrest can be achieved with 0.3 to 0.4 mg/kg of adenosine.<sup>179</sup> However, one should be pre-

pared to manage prolonged asystolic arrest. Pacer pads should be applied for external pacing and equipment should be kept ready for transvenous pacing.

A brief period of induced hypotension with adenosine is particularly useful for paraclinoid aneurysms, basilar tip aneurysms, and large anterior communicating artery aneurysms in which proximal control using a temporary clip is not feasible. In the event of unintentional aneurysmal rupture, rapid onset of adenosine-induced hypotension will aid in quick control of hemorrhage and will facilitate in securing the aneurysm with a permanent clip.

The use of adenosine should be avoided in patients with severe reactive airway disease, severe coronary artery stenosis, and preexisting cardiac conduction abnormalities.<sup>183</sup> In addition, one should be cautious with the use of adenosine in patients who are on dipyridamole, carbamazepine, digoxin, and verapamil. These medications are likely to prolong the duration of action of adenosine. Patients on methylxanthines require larger doses because of antagonistic effects.

### Confirmation of Surgical Clipping

The near-infrared indocyanine green videoangiography technique is increasingly used in many neurological centers for assessment of adequate permanent clip placement. A recent retrospective analysis of 295 consecutive surgical clipping procedures using this technique resulted in clip modification in 15% of the patients.<sup>184</sup> However, small neck remnants < 2 mm wide and small residual aneurysms were missed in 10% of the patients. The combination of near-infrared indocyanine green videoangiography along with intraoperative angiography is likely to improve the success of surgical clipping. Postoperative digital subtraction angiography should be used as a confirmatory method for adequate occlusion.<sup>185</sup>

At the conclusion of the surgery extubation should be considered in patients with good neurological grades. The most common postoperative problems include DCI, rebleeding, hydrocephalus, and fluid and electrolyte abnormalities.

### ANESTHESIA FOR COILING EMBOLIZATION

The requirements and principles of anesthetic management for this procedure are similar to surgical clipping; CPP and TMPG should be maintained. In addition, the procedure requires a still patient during critical periods. Other concerns include the working environment outside the operating room, exposure to radiation, and the need for anticoagulation. An arterial line is usually inserted along with a wide-bore venous access. The procedure is usually performed using general anesthesia with endotracheal intubation and muscle relaxation. However, a recent retrospective analysis reported that the procedure can be safely performed with midazolam and fentanyl in cooperative, good grade patients following SAH, who are alert and able to maintain their airway.<sup>186</sup> Alternatively, the procedure can be performed using dexmedetomidine, an alpha 2 agonist, which provides sedation and analgesia

with minimal respiratory depression.<sup>187</sup> Goals during monitored anesthesia care include anxiolysis, analgesia, maintenance of verbal contact, and patient immobility. The reasons for patient discomfort include injection of contrast resulting in burning sensation and headache due to traction on cerebral vessels.

A parallel can be drawn with the patients presenting for endovascular management of ischemic stroke. The Society for Neuroscience in Anesthesiology and Critical Care (SNACC) consensus statement opined that local anesthesia with anxiolytics can be used in neurologically cooperative patients for anterior circulation stroke who are able to protect the airway.<sup>188</sup> This recommendation lacked evidence from randomized trials. Similarly, endovascular coiling can be done for good grade ruptured aneurysms or unruptured aneurysms with local anesthesia with anxiolytics. Neurological monitoring on an awake patient is an added advantage; but the advantage of such monitoring in long-term neurological outcome is not known. RCTs are needed to compare the outcome of local anesthesia with general anesthesia in neurologically good grade patients.

Possible procedure-specific complications include aneurysm perforation and cerebral ischemia or infarction secondary to thromboembolism, arterial dissection, catheter or coil misplacement, and vasospasm.<sup>189–192</sup> Perforation of the aneurysm during coiling embolization can be identified by extravasation and delay in transit of the contrast medium.<sup>191</sup> When perforation is diagnosed, the procedure should be completed with further coil deposition, if it is deemed safe, anticoagulation should then be reversed.<sup>191</sup> Control of hemostasis may necessitate the use of proximal balloon inflation.<sup>193</sup> This intervention risks thromboembolism following the reversal of anticoagulation. Neurosurgical intervention may be required for open craniotomy for decompression and to secure the aneurysm. In the event of vascular occlusion during coiling secondary to thromboembolism or vasospasm, mean arterial pressure should be increased to maintain collateral circulation. Treatment with heparin and antiplatelet agents may be required as well. Catheter-induced vasospasm may require intra-arterial vasodilator therapy; nimodipine, a calcium channel blocker, is the common agent used.

## DCI

DCI is a serious complication of SAH and is associated with adverse neurological outcome and may occur with or without vasospasm. The term DCI is preferred over vasospasm because cerebral ischemia can occur following SAH without angiographically detected vasospasm.

## Pathophysiology of DCI

The incidence of symptomatic vasospasm, DCI and long-term neurological outcome is comparable in both the surgical clipping and coiling groups.<sup>194–198</sup> Smoking has been identified as a risk factor for the development of DCI.<sup>199</sup> The mechanism of DCI is not definitely known, but likely to be multifactorial with severity a function of the degree of initial hemorrhage. The suggested mecha-

nisms are loss of blood-brain integrity from early brain injury, initial cerebral edema, loss of cerebral autoregulation, cortical spreading depression, and microthrombosis.<sup>200,201</sup> Cortical spreading depression is a depolarization wave in the gray matter that propagates across the brain at 2 to 5 mm/min and depresses the spontaneous and evoked EEG activity. The spreading of clusters of these slow waves results in severe vasoconstriction, impairment of brain ion homeostasis, and recurrent tissue ischemia.<sup>201–204</sup> Microthrombosis is a result of activation of the coagulation cascade following initial hemorrhage.<sup>201</sup>

## Biomarkers for DCI

There are currently no established biomarkers to predict the development of DCI or to monitor its progression. Systemic inflammatory response syndrome following SAH is associated with an increased incidence of delayed ischemic neurological deficit, cerebral infarction, and poor neurological outcome, according to exploratory analysis of data from 413 patients of CONSCIOUS-1 database.<sup>205</sup> Systemic inflammatory markers like C-reactive protein and IL-6 levels are elevated early following SAH; higher levels are associated with poor neurological outcome.<sup>206–208</sup> Thus elevation of systemic and CSF inflammatory markers may play a role in monitoring the development of DCI, but further studies are required to substantiate this possibility.<sup>208,209</sup>

## Management of DCI

DCI is usually managed with nimodipine, maintenance of normal circulating blood volume, and induced hypertension.<sup>70,71</sup> Nimodipine is a calcium antagonist and its oral administration is useful in the management of vasospasm and DCI.<sup>210–212</sup> On the basis of current evidence nimodipine's IV use is not recommended.<sup>210</sup> High-dose IV nicardipine (0.15 mg/kg/h for 14 d) reduces symptomatic vasospasm, but does not improve neurological outcome at 3 months as per the results of a multicenter prospective double-blind RCT.<sup>213</sup> The routine use of IV nicardipine is not indicated.<sup>213</sup> The value of HHH (induced Hypertension, Hypervolemia, and Hemodilution) therapy is not validated and needs to be studied in RCTs.<sup>214,215</sup> Hypertension is the more important component of HHH therapy and increases cerebral blood flow and brain tissue oxygen levels and reverses neurological symptoms.<sup>216–220</sup> There are currently insufficient data to confirm the usefulness of hypervolemic therapy.<sup>216,218–221</sup> Hypervolemic therapy results in a decrease in brain tissue oxygenation, fluid overload, and is associated with deleterious cardiac and pulmonary events. Isovolumic and hypervolemic hemodilution increases global cerebral blood flow, but is associated with decreased oxygen delivery.<sup>219–222</sup> Balloon angioplasty for distal vasospasm, refractory to medical management, is shown to be beneficial in smaller retrospective analyses.<sup>223,224</sup> Intra-arterial papaverine relieves the vasospasm effectively, but its effects are transient lasting for about 3 hours, requiring multiple papaverine infusions.<sup>225–227</sup> Elevated ICP is a frequent complication of intra-arterial

papaverine therapy with adverse neurological outcome.<sup>225,228,229</sup> Papaverine preserved with chlorobutanol may result in selective permanent gray matter changes.<sup>230</sup> The possible cause of this change is unclear, but could be the preservative, papaverine, or both. Other less frequently reported complications include monocular blindness, brainstem dysfunction leading to hemodynamic and respiratory compromise, and seizures.<sup>225</sup> Precipitation of papaverine during infusion can result in arterial embolism. Because of these complications intra-arterial papaverine should be avoided. Transluminal angioplasty and injection of intra-arterial nimodipine proximal to a vasospastic vessel improves clinical outcome as observed in small case studies.<sup>231–236</sup> Balloon angioplasty along with intra-arterial nicardipine is also found to be useful in the management of refractory vasospasm.<sup>227,237</sup> Intra-arterial milrinone has also shown benefit in small case studies.<sup>237–239</sup> The beneficial effect of intra-arterial verapamil has been reported as per a small case series.<sup>240,241</sup> The effects of intra-arterial vasodilator therapy needs to be studied in a large prospective randomized trial. A multicenter RCT, Intra-arterial Vasospasm Trial (IVT), comparing the effects of intra-arterial nicardipine, milrinone, verapamil, and a combination therapy with nicardipine, verapamil, and nitroglycerine is currently underway.<sup>242</sup> Transluminal balloon angioplasty and intra-arterial vasodilator therapy should be considered for the management of symptomatic vasospasm.<sup>70,71,243</sup> Prophylactic intra-arterial vasodilator therapy is not indicated before development of angiographic vasospasm.<sup>70,71</sup>

### Other Pharmacological Agents for the Management of DCI

The Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH) trial, a phase II RCT found that IV magnesium, an arteriolar dilator, improved neurological outcome.<sup>244</sup> This finding was confirmed in other prospective RCTs.<sup>245–247</sup> However, the Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH-2) trial,<sup>248</sup> a phase III trial, did not confirm these beneficial effects on clinical outcome.<sup>248</sup> Similarly, the Intravenous Magnesium for Subarachnoid Hemorrhage (IMASH) trial,<sup>249</sup> a phase III, multicenter RCT, did not support the use of IV magnesium for vasospasm management. Currently, there are insufficient data to support the use of IV magnesium to prevent DCI and to improve neurological outcome.<sup>250,251</sup> At present, there is no evidence to include tirilazad, a nonglucocorticoid aminosteroid, in addition to nimodipine, in the management of vasospasm.<sup>252</sup> Clazosentan, an endothelin-I antagonist, is found to be effective in the prevention and management of vasospasm and in reducing vasospasm-induced morbidity and mortality as shown in a phase II multicenter RCT (CONSCIOUS-1).<sup>253</sup> However, a phase III randomized double-blind placebo controlled trial (CONSCIOUS-2) failed to confirm this benefit in patients who had surgical clipping.<sup>254</sup> Similarly, a phase III trial (CONSCIOUS-3) trial did not show benefit from clazosentan in patients who had endovascular coiling and the trial was prematurely terminated.<sup>255</sup> At present, the available data are not

conclusive to recommend the use of oral statins to prevent vasospasm and DCI.<sup>256–258</sup> The SimvaSTatin in Aneurysmal Subarachnoid Hemorrhage (STASH), a multicenter randomized placebo controlled phase 3 trial, did not identify the beneficial effects of simvastatin in aSAH patients at the end of 6 months as per the outcome data in 782 patients aged 18 to 65 with 1:1 randomization. The study group received simvastatin 40 mg within 96 hours from ictus of aSAH. The authors concluded against the routine use of simvastatin despite the lack of increased adverse events in the simvastatin group.<sup>258</sup> The use of antiplatelet agents is not found to be beneficial in the management of DCI.<sup>259,260</sup> Two randomized trials involving the use of low-molecular weight heparin for the prevention and management of microthrombi in DCI provided contradictory results; further large trials are needed.<sup>261,262</sup> Intercisternal thrombolysis is beneficial in the management of DCI according to a meta-analysis and systemic review, but this review did not have randomized trials.<sup>263</sup> Further large randomized trials are required.

### Monitoring for DCI

Cerebral angiography is the technique of choice for diagnosing intracranial arterial vasospasm, but it is invasive and carries the risk of stroke due to arterial dissection, embolism, and arterial rupture.<sup>264</sup> CTA, magnetic resonance angiography, and digital subtraction angiography are other modalities used to diagnose arterial vasospasm.<sup>265</sup> However, it is practically impossible to use these techniques for daily monitoring in the intensive care unit. Transcranial Doppler (TCD) has the advantage of being a noninvasive technique and is portable, but has a limited role in the diagnosis and monitoring of vasospasm progression and overall neurological outcome.<sup>265–278</sup> An increase in mean blood flow velocity (mBFV) >120 cm/s indicates vasospasm in the MCA.<sup>265,268,271,272,276</sup> A mBFV >200 cm/s in the MCA territory has high positive predictive value for angiographic vasospasm.<sup>265,272</sup> The progressive severity of vasospasm is indicated by an increase in mBFV, an increase in the ratio of mBFV of ipsilateral to contralateral cerebral arteries, and the reversal of diastolic blood flow during serial TCD monitoring.<sup>265,271,275,277</sup> TCD is better for detecting and monitoring vasospasm in the ICA and the MCA distribution than in other circulations.<sup>265,271</sup> TCD is also better in detecting proximal vasospasm than in detecting distal vasospasm.<sup>265,268</sup> Serial TCDs are required to monitor the progression or regression of vasospasm.<sup>265</sup>

### NEUROENDOCRINE ABNORMALITIES

Patients with SAH are likely to present with fluid and electrolyte abnormalities. Hyponatremia is more frequently seen than hypernatremia.<sup>278,279</sup> Hyponatremia is due to cerebral salt wasting syndrome or syndrome of inappropriate secretion of antidiuretic hormone; both conditions may coexist. The etiology of hyponatremia is possibly multifactorial; increased levels of renin, angiotensin-II, natriuretic peptide, arginine vasopressin, hypoadosteronin and an increase in sympathetic tone are likely causes.<sup>280,281</sup> Patients with cerebral salt wasting

**TABLE 4.** Differential Diagnosis Between SIADH, CSWS, and DI

Condition	Intravascular Volume Status	Serum Sodium Levels
SIADH	Normovolemia or mild hypervolemia	Hyponatremia
CSWS	Hypovolemia	Hyponatremia
DI	Hypovolemia	Hypernatremia

CSWS indicates cerebral salt wasting syndrome; DI, diabetes insipidus; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

syndrome typically show a triad of hyponatremia, hypovolemia, and high random urinary sodium concentration (> 50 mmol/L) (Table 4).<sup>282</sup>

Patients with syndrome of inappropriate secretion of antidiuretic hormone are likely to show normovolemia or mild hypervolemia. Hypernatremia may also be found in patients with SAH: it is most likely to be iatrogenic secondary to mannitol or HTS infusion.<sup>281</sup> Rarely, hypernatremia is due to diabetes insipidus, which is most likely due to hypothalamic ischemia. Multifactorial causes of hypothalamic ischemia include: decreased CPP, elevated ICP with a reduction in CPP, vasospastic involvement of anterior cerebral artery, and anterior communicating artery distribution. Hyponatremia is associated with longer hospital stay, but is not associated with increased mortality.<sup>278</sup> However, hypernatremia after SAH is independently associated with adverse outcomes and death.<sup>278,283</sup> Partial hypopituitarism is also seen in these patients, again it is possibly due to pituitary-hypothalamic ischemia secondary to various possible causes including: vasospasm, decreased CPP, and elevated ICP, resulting in reduced CPP.<sup>284,285</sup>

**SUMMARY**

The aSAH is a major health problem in the United States with an incidence of 10/100,000 persons/y. The common mode of presentation of an intracranial hemorrhage is SAH with an acute onset of headache. Patients with good neurological grades at the time of admission have a favorable outcome. NPE and cardiac involvement indicate the severity of SAH. Noncontrast CT scan is a useful initial screening tool, but lumbar puncture is still needed to avoid potential misdiagnosis. Coiling embolization is increasingly used, following the publication of the ISAT results. Surgical clipping is still favored for younger patients, giant aneurysms, fusiform aneurysms, aneurysms located at arterial bifurcations, and MCA aneurysms. Endovascular flow diversion is a new technique, which avoids coiling, but its role is yet to be established in clinical practice.

Hypertension is common following SAH, and systolic BP needs to be lowered to 140 mm Hg to prevent rebleeding based on the most recent evidence from INTERACT-2 trial of intracerebral bleeding. Early intervention following SAH to secure the aneurysm is widely preferred. IV adenosine is found to be useful for induced

hypotension in 2 retrospective analyses and further data are required. The benefit of neuromonitoring and pharmacological neuroprotection during temporary clipping is not proven in terms of neurological outcome. The role of induced hypothermia cannot be completely rejected as the patients with IHAST II trial were subjected to slow cooling, inadequate cooling time, and rewarmed slowly. DCI can occur without angiographic vasospasm and is multifactorial in origin, the mechanism of which is yet to be fully understood. There are no established biomarkers to predict its occurrence and to monitor its progression. The established management of DCI includes induced hypertension, maintenance of euvoolemia, and oral nimodipine. The role of magnesium, tirilazad, statins, and clazosentan is not proven in phase III randomized trials. Sodium abnormalities are common after SAH. Hyponatremia is more frequently found than hypernatremia. Hypernatremia is associated with unfavorable prognosis.

The body of evidence on the neuroanesthetic considerations for the management on aSAH is expanding. Several trials are underway that may offer results that will further enhance the practice of the anesthesiologist and thus improve the short-term and long-term outcomes for aSAH and SAH patients. This review points to the need for further large RCTs to answer some remaining questions.

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