Life after Subarachnoid Hemorrhage

SVANTE WALLMARK
Abstract

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with mean age of 59 years. SAH accounts for 5% of all stroke and more than one quarter of potential life years lost through stroke. With the advanced neurosurgical methods of today two thirds of the patients survive. We know, however, that various cognitive, psychiatric and physical impairments are common that affect quality of life, social life, and the ability to work in the aftermath of SAH. The overall aim constituting this PhD dissertation is to better understand some of the challenges often faced by those surviving SAH.

Two SAH patient cohorts have been studied. The first followed 96 consecutively included patients during the first year after ictus. Spasticity and cognitive impairment was assessed after 6 months and the Swedish stroke register follow-up form was used to investigate family support and the use of medical and social services. Return to work was assessed at 12 months. The second cohort assessed attention deficits using the test of variables of attention (T.O.V.A.) at 7 months after ictus in 19 patients with moderate to good recovery.

Spasticity was just as common in our SAH patients as after other stroke, though it was rarely treated pharmacologically. By assessing cognitive impairment at 6 months after ictus using the Montreal cognitive assessment, 68% of the patients could be correctly predicted as having returned/not returned to work at 12 months. Seventeen percent of the patients had not had a follow-up appointment 6 months after ictus. These patients were older, more often living alone, had a lower quality of life, more depressive symptoms and more cognitive impairment compared to those having had a follow-up appointment. Twenty percent had had a follow-up in primary care. Seventy-eight percent of those with moderate to severe disability were living in their own accommodations. Fifty-eight percent of the patients had attention deficits. Challenges after SAH were common and often dealt with in the home environment of the patients.

The results of this thesis highlight the importance of assisting the patients and their relatives in their struggle back to life after SAH.

Keywords: Aneurysmal, Attention deficit, Cognitive impairment, Family medicine, Follow-up appointments, General practice, Intracranial aneurysm, Outcome, Primary care, Primary health care, Return to work, Spasticity, Stroke, Subarachnoid hemorrhage, Sweden

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To my family
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


III Wallmark, S., Lundström, E., Ronne-Engström, E. (2016) Contact with medical and social services after the acute phase of subarachnoid hemorrhage. *Manuscript*


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### Abbreviations

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<tr>
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<th>Full Form</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQol-5D</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow coma scale</td>
</tr>
<tr>
<td>GOS</td>
<td>Glasgow outcome scale</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter quartile range</td>
</tr>
<tr>
<td>NIVA</td>
<td>Neurointensive care unit</td>
</tr>
<tr>
<td>MADRS</td>
<td>Montgomery Åsberg depression rating scale</td>
</tr>
<tr>
<td>MAS</td>
<td>Modified Ashworth scale</td>
</tr>
<tr>
<td>MoCA</td>
<td>Montreal cognitive assessment</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin scale</td>
</tr>
<tr>
<td>ms</td>
<td>Milliseconds</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National institutes of health stroke scale</td>
</tr>
<tr>
<td>n.s.</td>
<td>Not significant</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>SAH</td>
<td>Aneurysmal subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV-Axis I Disorders</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>T.O.V.A.</td>
<td>Test of variables of attention</td>
</tr>
<tr>
<td>WFNS</td>
<td>World federation of neurological surgeons scale</td>
</tr>
</tbody>
</table>
Background

General review of aneurysmal subarachnoid hemorrhage

Prevalence of intracranial aneurysms

Intracranial aneurysms are abnormal dilatations of cerebral arteries occurring frequently in arterial bifurcations. The prevalence of intracranial aneurysms was 3.2% in a systematic review with a population with mean age of 50 years and 50% men. The prevalence ratio for women compared with men was 1.6. Prevalence ratio was 6.9 for people with autosomal dominant polycystic kidney disease, and 3.4 for a positive family history of intracranial aneurysm or subarachnoid hemorrhage. In another systematic review, aneurysms were found in 2% of adults without risk factors for subarachnoid hemorrhage and the annual risk of rupture for small aneurysms was 0.7%.

Most aneurysms are round shaped, so-called saccular aneurysms, and make up 66% to 98% of the aneurysms. The most common nonsaccular aneurysms are fusiform aneurysms, which are sausage like dilatations of an entire segment of artery that are usually associated with elongation and tortuosity of the artery. Eighty-five percent of saccular aneurysms occur on the anterior circulation and 15% on the posterior; this is the same percentages as for ruptured aneurysms. The 3 most common sites of aneurysms are the anterior communicating artery region (30%), posterior communicating artery region (25%), and middle cerebral artery (14%). Of the 15% of aneurysms located on the vertebrobasilar system, 50% are at the basilar apex.

Etiology of intracranial aneurysms

The pathogenesis of intracranial aneurysms has been debated for many years and is still unclear. Saccular aneurysms develop during the course of life and are rarely found in children. The most plausible explanation is that aneurysms are acquired degenerative lesions – the effect of hemodynamic stress, structural, genetic and environmental changes. A study using the 14C birth dating technique to measure the age of collagen in cerebral aneurysm samples found a relatively young collagen type, nearly all samples contained collagen <5 years old, suggesting there is an ongoing collagen remodeling in aneurysms, and that this process is significantly more rapid in
patients with risk factors\textsuperscript{10}. These findings challenge the concept that cerebral aneurysms are present for decades and that they undergo only sporadic episodes of structural change.

There are several heritable conditions associated with intracranial aneurysm formation, including autosomal dominant polycystic kidney disease, neurofibromatosis type I, Marfan’s syndrome and Ehlers-Danlos syndrome type IV\textsuperscript{11}. Several loci on chromosomes show suggestive linkage to intracranial aneurysms\textsuperscript{12}. Different inheritance patterns arise in different families with autosomal recessive being the most common followed by autosomal dominance\textsuperscript{13}. There is, however, no diagnostic test for specific genetic risk factors to identify first-degree relatives of patients with aneurysmal subarachnoid hemorrhage (SAH) who are at high risk of developing intracranial aneurysms\textsuperscript{12}. The risk of having an aneurysm is about four times higher for a close relative than for someone from the general population\textsuperscript{14}. Multiple aneurysms occur in approximately 20-30% of patients with intracranial aneurysms\textsuperscript{15} and is associated with a familial predisposition for intracranial aneurysms\textsuperscript{16}. In Finland and Japan, the higher incidence of SAH is not explained by a higher prevalence of unruptured intracranial aneurysms\textsuperscript{17}, implicating higher risks of rupture\textsuperscript{2,18}.

In a case-control study smoking, hypertension and family history of stroke increased the risk of unruptured intracranial aneurysm\textsuperscript{19}. Patients with previous SAH have a substantial risk for new aneurysm formation and enlargement of untreated aneurysms\textsuperscript{20}.

Harboring an unruptured intracranial aneurysm is associated with a decreased overall quality of life and qualitative data suggests that a factor contributing to poorer reported psychosocial functioning is fear about the untreated aneurysm\textsuperscript{21}. Treatment of unruptured intracranial aneurysms has considerable short-term negative impact on functional health and quality of life in most patients, despite the low rates of impairments. Outcome improves markedly but not completely within 1 year after operation\textsuperscript{22}.

Epidemiology of subarachnoid hemorrhage

**Incidence**

The overall incidence of subarachnoid hemorrhage is approximately 9 per 100 000 person-years\textsuperscript{23}. The incidence varies between countries\textsuperscript{24} and is highest in Japan\textsuperscript{25} and Finland\textsuperscript{26}. Subarachnoid hemorrhage accounts for approximately 5% of all stroke\textsuperscript{27}. Ruptured aneurysms are the cause of subarachnoid hemorrhage in 85% of the patients, whereas 10% fit into the pattern of so-called non-aneurysmal perimesencephalic hemorrhage, a relatively innocuous condition. The remaining 5% are caused by various rare causes, such as inflammatory lesions of cerebral arteries, malformations, arterial dissections, sickle cell disease, tumors, and drugs\textsuperscript{28}. Throughout this thesis
the phrase “subarachnoid hemorrhage” refers to a subarachnoid hemorrhage with the origin of bleeding not specified, whereas the abbreviation “SAH” means a subarachnoid hemorrhage caused by bleeding from an intracranial aneurysm. Having had an aneurysmal subarachnoid hemorrhage (SAH) was one of the inclusion criteria for the patients in Paper I-IV in this thesis.

A nationwide study on subarachnoid hemorrhage in Sweden found incidence rate of 12.4 per 100 000 person-years\textsuperscript{29}. The incidence increased from 11.4 per 100 000 person-years in the south of Sweden to 15.2 in the north, a geographical gradient more evident in women. Similar incidence rates have been reported in regional studies from the south\textsuperscript{24, 30, 31} and north \textsuperscript{32} of Sweden. The studies did, however, not differentiate between aneurysmal and other types subarachnoid hemorrhages. A specified study on SAH from Uppsala showed an incidence of 5.5 per 100 000 person-years\textsuperscript{33}. This study did, however, only include patients having a potential to survive.

**Mortality and cause of death**

Subarachnoid hemorrhage accounts for approximately 5\% of all stroke and 27\% of all stroke-related years of potential life lost before age 65\textsuperscript{27, 34}. Both a Swedish study using the Swedish hospital discharge and cause of death registries on subarachnoid hemorrhage, and a systematic literature review on SAH have showed that 12\% of patients die before reaching the hospital\textsuperscript{29, 35}.

Approximately 85\% of all spontaneous hemorrhages into the subarachnoid space arise from rupture of an aneurysm\textsuperscript{7}. Aneurysms in the posterior circulation have a higher estimated probability of sudden death\textsuperscript{35, 36}.

The case fatality rate of subarachnoid hemorrhage at 28 days is 32\%, which increases sharply with age and is slightly higher in women than in men\textsuperscript{20, 37}. At 6 months, the case fatality of SAH is 40\%\textsuperscript{37}. 10 years after admission for SAH, 64\% of the patients are still alive\textsuperscript{38}.

During the first month after SAH, most deaths are due to the initial bleeding\textsuperscript{38}, and between 2 and 12 months after ictus the most common cause of death is a complication to the disease (e.g. chest or other infections)\textsuperscript{39}. One year after ictus, the most common causes of death are cardiac or cancer-related\textsuperscript{39, 40}.

Patients having survived SAH have an excess mortality rate even after successful treatment. Therefore, SAH should be viewed more as one aspect of a chronic general vascular disease\textsuperscript{41}.

**Risk factors**

**Gender**

Several studies have shown an increase in the risk of SAH in women\textsuperscript{23, 42-44}. The incidence is 1.24 times higher in women than in men; a gender difference starting at age 55 years and increasing thereafter\textsuperscript{23}. The effect of hor-
mone replacement therapy is uncertain. There are no sex differences in predisposing risk factors or admission-related factors.

Age
SAH is rare in children. The incidence of SAH increase with age but level off at 60 years of age in men and at 70 years of age in women. The mean age of SAH have increased over the last decades and is approximately 59 years.

Genetics
First-degree relatives of subarachnoid hemorrhage patients run at least 3 to 7 times greater risk than the general population. The occurrence of SAH is also associated with heritable disorders. The most common heritable disorder associated with SAH is autosomal dominant polycystic kidney disease having a five times higher risk of intracranial aneurysms than the general population. Autosomal dominant polycystic kidney disease is found in 2% of all SAH patients.

Smoking
Smoking is a well-established risk factor for subarachnoid hemorrhage. There is a dose-response relationship between number of cigarettes smoked and risk of subarachnoid hemorrhage. 10 years after having quit smoking the risk of subarachnoid hemorrhage have reached the risk in those who have never smoked. Cessation of smoking is pivotal for SAH survivors even though the effectiveness of smoking cessation in this particular subset of patients has not been formally studied.

Hypertension
The risk of subarachnoid hemorrhage is increased among people with hypertension. The relative risk of subarachnoid hemorrhage among people with hypertension is 2.5 compared to those without hypertension.

Alcohol consumption
Use of alcohol is associated with subarachnoid hemorrhage. There is a dose-response relationship between the alcohol consumption 24 hours before ictus and the risk of SAH.

Aneurysm rupture
71% of ruptured aneurysms are smaller than 10 mm in diameter, and 13% are less than 5 mm in diameter. SAH occurs during physical or emotional stress in 43% of the patients, during non-stressful activities in 34%, and during rest or sleep in 12%. Season influence the occurrence of SAH, with
SAH occurring less often in summer than in winter, and most often in January\textsuperscript{60}.

**Clinical presentation of aneurysm rupture**

The most common presenting symptom of subarachnoid hemorrhage is an unusually severe headache starting instantaneously. It is often accompanied with loss of consciousness, seizure, double vision and vomiting\textsuperscript{61}. One study has shown that in patients with acute severe headache - female sex, the presence of seizure, a history of loss of consciousness, focal symptoms, vomiting or physical exertion increase the probability of SAH\textsuperscript{61}. In patients with such clinical presentation it is straightforward that they should be referred to a hospital. Only 50% of the patients with SAH, however, have an instant development of the headache; a symptom also occurring among two thirds of patients with benign thunderclap headache\textsuperscript{61}.

**Acute severe headache in general practice**

In a study from the Netherlands, where virtually all initial medical contacts are with the GP, almost half of the SAH patients had first contact with the GP, 42\textsuperscript{62}. Sixty-six percent of these had isolated headache. In these patients, presenting with isolated headache to the GP, 58\% had a delayed referral (>2 hours). Factors increasing the probability of delayed referral were GP’s unawareness of the acute onset of the headache, a history of headache and late presentation by the patient. Misdiagnosing SAH is associated with smaller hemorrhage and normal mental status, but among individuals who initially present in good clinical condition, misdiagnosis is associated with increased mortality and morbidity\textsuperscript{63, 64}. From a practical perspective, if the GP can make a diagnosis of a primary headache disorder and, in particular, migraine, the likelihood of subsequent pathology is very small\textsuperscript{65}.

In a study from Netherlands in 1994, acute severe headache in general practice indicated a serious neurological disorder in 37\% and SAH in 25\% of the patients\textsuperscript{66}. The absence of other SAH associated symptoms in a patient with sudden severe headache should not cause hesitation in immediate referral of this patient to a hospital for additional diagnostic evaluation. In Sweden, most patients visiting a GP have first contact with a nurse, usually over phone, and patients with acute severe headache should immediately be readressed to an emergency room, without first visiting the primary care center.

The notion of a “warning leak” or a “sentinel” headache is perpetuated in textbooks and review articles. It has been suggested that the term is misleading and should be abandoned as it may represent a small bleed\textsuperscript{67}. The emphasis must be on educating doctors to recognize the significance of an acute onset headache, and ensure that such patients are referred and investigated properly at the time of presentation.
Diagnosis

The subarachnoid hemorrhage diagnose is usually verified using a CT. There is an ongoing debate whether lumbar puncture can be withheld in patients with a head CT scan performed <6 hours after headache read negative by a staff radiologist. If an aneurysm caused the bleeding, the pattern of blood on the CT often suggests the location of the underlying aneurysm.

To investigate if the subarachnoid hemorrhage has aneurysmal origin, CT angiography is the first-hand method. It reveals most aneurysms, though the sensitivity for small aneurysms is limited. If CT is negative but aneurysmal origin is highly suggestive, a digital subtraction angiography is performed. The digital subtraction angiography is the golden standard for detecting aneurysms. Due to it’s invasive nature, however, the digital subtraction angiography causes neurological complications in 2.6% of examinations and permanent stroke is seen after 0.1% of examinations.

Neurointensive care

During the late 1970’s and 1980’s a number of clinical studies were published advocating early surgery (within 3 days), use of nimodipine, and hypertensive, hypervolemic, and hemodilution therapy to prevent and combat delayed ischemic deterioration. Management principles were introduced affecting referral guidelines, diagnostic and monitoring methods, and pharmacological and surgical treatment. SAH patients were now being managed within a neurointensive care setting and a neurointensive care unit was inaugurated at Uppsala University Hospital in 1990. Close monitoring of factors such as the patients’ neurological status, intracranial dynamics, and systemic vital functions became the mainstay of neurointensive care. This enabled therapy for impending cerebral ischemic states before irreversible damage occurred. These advances in treatment and preventions led to improvements in overall outcome, though there are still formidable challenges ahead.

Grading scales

Grading scales are used to clinically measure the severity of neurologic injury in SAH patients, to provide prognostic information, to guide treatment decisions and to standardize patient assessment across medical centers for the purpose of scientific study. The most commonly used SAH grading scales are the Hunt and Hess scale, Fisher scale, Glasgow coma scale (GCS) and world federation of neurological surgeons scale (WFNS). Several grading scales have been proposed, modified, and evaluated. Below follows a short description of some of the most commonly used scales used in SAH patients.
Glasgow coma scale

In 1974, Teasdale and Jennet reported a bedside system for assessing the depth and duration of impaired consciousness and coma\textsuperscript{81}, the Glasgow coma scale (GCS). Three aspects of behavior were independently measured – motor responsiveness, verbal performance, and eye opening. The authors emphasized the need to be able to assess and to record changing states of altered consciousness reliably. The observations, which previously had been recorded as a descriptive comment, now became formalized. The GCS was plotted on chart together with temperature, pulse, respiration, pupil size and focal motor signs.

In the original version the aspects of behavior were not graded using numbers. Today each aspect of behavior (or axis) is graded according to Table 1 and the three axes are totaled to produce a final comprehensive grade between 3 and 15. Another difference from today’s version is that the original version did not differ between “Flexion withdrawal to pain” and “Abnormal flexion (decorticate rigidity) to pain”.

Table 1. The Glasgow Coma Scale as the three axis are used today

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td></td>
</tr>
<tr>
<td>Open spontaneously</td>
<td>4</td>
</tr>
<tr>
<td>Open to verbal command</td>
<td>3</td>
</tr>
<tr>
<td>Open to pain</td>
<td>2</td>
</tr>
<tr>
<td>No eye opening</td>
<td>1</td>
</tr>
<tr>
<td>Best motor response</td>
<td></td>
</tr>
<tr>
<td>Obey to verbal command</td>
<td>6</td>
</tr>
<tr>
<td>Localized to painful stimulus</td>
<td>5</td>
</tr>
<tr>
<td>Flexion withdrawal to pain</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion (decorticate rigidity) to pain</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal extension (decerebrate rigidity) to pain</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Best verbal response</td>
<td></td>
</tr>
<tr>
<td>Oriented and converses</td>
<td>5</td>
</tr>
<tr>
<td>Disoriented and converses</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

WFNS

The world federation of neurological surgeons committee proposed the WFNS in 1988\textsuperscript{82}. The committee was of the opinion that the GCS\textsuperscript{81} should be used for evaluating the level of consciousness and that major neurological deficit (aphasia and/or hemiparesis or hemiplegia) should be used to differentiate between grade II and III, see Table 2. The WFNS is being used by the neurointensive care unit (NIVA) at Uppsala University Hospital to measure the clinical condition at admission.
Table 2. The world federation of neurological surgeons scale (WFNS) and the Glasgow coma scale (GCS)

<table>
<thead>
<tr>
<th>WFNS grade</th>
<th>GCS score</th>
<th>Motor Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>Absent</td>
</tr>
<tr>
<td>II</td>
<td>14-13</td>
<td>Absent</td>
</tr>
<tr>
<td>III</td>
<td>14-13</td>
<td>Present</td>
</tr>
<tr>
<td>IV</td>
<td>12-7</td>
<td>Present or absent</td>
</tr>
<tr>
<td>V</td>
<td>6-3</td>
<td>Present or absent</td>
</tr>
</tbody>
</table>

**Reaction level scale 85**

Swedish scientists introduced the reaction level scale 85 (RLS 85), see Table 3, in 1988 for the assessment of overall responsiveness. The RLS 85 is used at both admission and discharge from Uppsala University Hospital.

Table 3. The reaction level scale 85 (RLS 85)

<table>
<thead>
<tr>
<th>RLS 85</th>
<th>Description</th>
<th>Mentally responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No delay in response</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy or confused. Responsive to light stimulation</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Very drowsy or confused. Responsive to strong stimulation</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Unconscious. Localizes but does not ward off pain</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Unconscious. Withdrawing movements on pain stimulation</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Unconscious. Stereotype flexion movements on pain stimulation</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Unconscious. Stereotype extension movements on pain stimulation</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Unconscious. No response to pain stimulation</td>
<td>No</td>
</tr>
</tbody>
</table>

**Fisher scale**

In 1980 Fisher et al. attempted to determine whether the amount and distribution of subarachnoid blood detected by CT early after aneurysmal rupture correlated with the later development of cerebral vasospasm visualized angiographically. The patients studied were 47 cases of verified ruptured saccular aneurysms. They found that when there was no subarachnoid blood or it was diffusely distributed, severe vasospasm was almost never encountered, whereas in the presence of blood clots and thick layers of blood, severe vasospasm followed almost invariably. The amount and distribution of subarachnoid blood detected by CT was classified into four grades, see Table 4. Almost all patients with severe vasospasm were found in grade 3.

Table 4. The Fisher scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No blood detected.</td>
</tr>
<tr>
<td>2</td>
<td>A diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern), less than 1 mm thick</td>
</tr>
<tr>
<td>3</td>
<td>Localized clots and/or vertical layers of blood 1 mm or greater in thickness</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots</td>
</tr>
</tbody>
</table>
A classification problem occurs when patients present with thick layers of blood and intracerebral or intraventricular blood\textsuperscript{79}. Another limitation is that the scale was developed when the imaging technology had roughly one-tenth of the resolution currently available\textsuperscript{79}. Today, grade 1 and 2 are quite uncommon\textsuperscript{79} compared with the original study from 1980 when these two groups represented 38\% of all cases.

When assigning patients with Fisher scale 0 (unruptured), 1 or 2; to one group and 3 and 4 to another group, the scale has high inter-rater reliability with a kappa value of 0.9\textsuperscript{86}.

**Modified Rankin scale**
The modified Rankin scale (mRS) is an ordinal scale from 1988 graded between 0 and 5 to assess disability after stroke\textsuperscript{87-89}, see Table 5. It is commonly used and allows comparison between patients with different kinds of neurological deficits. The mRS is a modification of the original Rankin scale devised in 1957\textsuperscript{90}. The original Rankin Scale did not contain Grade 0, defined Grade I as “No significant disability: able to carry out all usual duties.” and defined Grade II as “Slight disability: unable to carry out some of previous activities...”.

The validity in stroke outcome and inter-rater reliability have been well documented for the mRS\textsuperscript{80}. The best available information should be used from the patient, next of kin, or caregiver. To improve the agreement between raters, a structured interview can be used\textsuperscript{91}. mRS is mostly used in the rehabilitation phase and not during the intensive care period.
Table 5. The modified Rankin scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Question in the structured interview\textsuperscript{91}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
<td>Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptoms resulting from stroke?</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms: able to carry out all usual duties and activities</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance</td>
<td>Has there been a change in the person’s ability to work or look after others if these were roles before stroke? Has there been a change in the person’s ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability: requiring some help, but able to walk without assistance</td>
<td>Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
<td>Is assistance essential for eating, using the toilet, daily hygiene, or walking?</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: bedridden, incontinent, and requiring constant nursing care and attention</td>
<td>Does the person require constant care?</td>
</tr>
</tbody>
</table>

Glasgow outcome scale (GOS) and extended GOS (GOSE)

One year after Teasdale and Jennet introduced the GCS in 1974 the Glasgow outcome scale (GOS) was introduced by Jennet and Bond\textsuperscript{92}. They reported a lack of an objective scale leading to vague and over-optimistic estimates of outcome, which obscured the ultimate results of early management. At the time, the state of health of survivors after brain damage was often described in vague terms which made it difficult to judge what degree of recovery that had really occurred. Much of the difficulty which doctors experienced in making decisions about brain-damaged patients, both in the acute stage and during recovery, resulted from uncertainty about the outcome. The original GOS had 5 categories (1-5).

The GOS became the most commonly used scale for assessing outcome after head injury and non-traumatic acute brain insults. Over the years, however, the GOS was recognized to have important shortcomings. In 1998 an extended version of the GOS was introduced (GOSE) together with a standardized format for the interview\textsuperscript{93}, see Table 6.
### Table 6. The Glasgow outcome scale (GOS) and the extended version (GOSE)

<table>
<thead>
<tr>
<th>GOS&lt;sup&gt;92&lt;/sup&gt;</th>
<th>GOSE&lt;sup&gt;93&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>5</td>
<td>Good recovery</td>
</tr>
<tr>
<td>4</td>
<td>Moderately disabled (disabled but independent)</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability (conscious but disabled)</td>
</tr>
<tr>
<td>2</td>
<td>Persistent vegetative state</td>
</tr>
<tr>
<td>1</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

**Complications in the acute phase**

SAH patients having survived the initial bleed are still at risk of a devastating outcome due to complications during the intensive care period. These complications may cause secondary brain injury. Also, rebleeding is a serious complication that may have a large impact on the overall outcome.

**Rebleeding**

In most cases, the initial bleeding from a ruptured aneurysm spontaneously arrests. A platelet plug reinforced by the deposition of fibrin is built up at the surface of the rupture point. This seal is unstable and rupture of the plug may result in rebleeding. In the most common pattern of hemostatic mechanism (79%), the surface of the aneurysm rupture point is sealed from the outside by a platelet plug or fibrin net. In 10% of aneurysms a thrombus or platelet plug is attached to the rupture point from the inside of the aneurysm<sup>94</sup>.

Rebleeding is suspected when a patient experience an additional period of headache, loss of consciousness, or a sudden increase in intracranial pressure. It is the most important preventable cause of death in hospitalized patients with subarachnoid hemorrhage<sup>95</sup> and occurs more frequently within the first 6 hour after SAH<sup>96</sup>. Risk factors associated with rebleeding is high systolic pressure, the presence of intracerebral or intraventricular hematoma, poor Hunt-Hess grade, aneurysm in the posterior circulation, and aneurysm >10 mm in size<sup>96</sup>.

**Vasospasm and brain ischemia**

Cerebral vasospasm is a gradual onset and prolonged constriction of the cerebral arteries in the subarachnoid space after subarachnoid hemorrhage.
The significance of vasospasm is that flow through the constricted arteries may be reduced sufficiently to cause cerebral infarction. Vasospasm occurs most frequently 7 to 10 days after aneurysm rupture and resolve spontaneously after approximately 21 days. Laboratory examinations and a repeat brain CT scan are needed to exclude other causes, especially hydrocephalus and systemic complications.

There are two definitions of cerebral vasospasm – angiographic and clinical – that may not be used interchangeably. Angiographic vasospasm occurs in 70% of SAH patients, but only 25% develop symptomatic vasospasm. Morbidity remains high with approximately 50% infarction rates in affected patients.

Risk factors for vasospasm include admission hypertension, poor clinical grade, thick cisternal clot and intraventricular hemorrhage. Currently accepted medical options include nimodipine (a calcium channel blocker), and triple-H therapy (hypertension, hypervolemia and hemodilution). Nimodipine remains the only modality proven to reduce the incidence of infarction. Although widely used, the triple-H therapy has not been demonstrated to significantly change overall outcome after cerebral vasospasm.

**Intracerebral hematoma**

Depending on the size and location of an aneurysm, a rupture may result in an intracerebral hemorrhage. These patients have higher mortality and poorer mental outcome.

**Hydrocephalus**

Hydrocephalus should be suspected when a patient who is initially alert undergo a gradual reduction in consciousness. A CT scan confirms the diagnosis and there may be reason for ventricular drainage. Nineteen percent of patients with subarachnoid hemorrhage have hydrocephalus on the initial CT scan.

**Infection**

The most common nosocomial infections during the intensive care period in patients with subarachnoid hemorrhage are pneumonia, urinary tract infection, bloodstream infection and meningitis/ventriculitis. The presence of infection is associated with delayed neurological deficits, and pneumonia and bloodstream infection have been shown to independently predict poor outcome. Infections are associated with longer hospitalizations and higher charges.

The diagnosis of ventriculitis and meningitis are challenging in patients with SAH since the disease itself induces a massive inflammatory reaction in the cerebrospinal compartment and is associated with fever, headache, neck stiffness, meningeal signs, cranial nerve signs, and irritability – signs also
characteristic for infection\textsuperscript{109}. This has resulted in various definitions of infection in SAH patients\textsuperscript{106, 109}.

**Paresis**
Due to the brain damage in the acute phase, patients with SAH may present with paraparesis\textsuperscript{110-112}, hemiparesis\textsuperscript{113} or monoparesis\textsuperscript{114}. Exercises done regularly and under observation is important from the viewpoint of obtaining functional recoveries\textsuperscript{115}.

**Aneurysm treatment**
The risk of rebleeding can be effectively reduced by early treatment of the ruptured aneurysm. The goal of such treatment is to occlude the aneurysm and exclude it from the cerebral circulation preserving the blood flow to the brain. Surgical obliteration of the aneurysm was the mainstay of treatment for decades\textsuperscript{7}, but during the last two decades, endovascular occlusion has largely replaced surgical occlusion as the intervention of choice for the prevention of rebleeding\textsuperscript{28}.

In patients with SAH, for which both endovascular coiling and neurosurgical clipping are therapeutic options, and the patients’ treatment method is randomized, the outcome in terms of survival free of disability at 1 year is significantly better with endovascular coiling\textsuperscript{116}. There are, however, aneurysms difficult to reach using an endovascular approach, such as the pericallosal artery. Another problematic site is the trifurcation of the middle cerebral artery because one or more of the branches often originate from the aneurysm\textsuperscript{7}.

**Surgical clipping**
Surgical clipping requires a craniotomy and dissection of the vessels surrounding the aneurysm. The morbidity rate from elective surgery is 4.1-10.9\% and mortality rate 1.0-2.6\%\textsuperscript{117, 118}. The risk for rebleeding of a surgically treated aneurysm is approximately 2\% per year\textsuperscript{119}.

**Endovascular coiling**
Advances in the early 90’s led to a new treatment modality of intracranial aneurysms using detachable coils via an endovascular approach\textsuperscript{120}. When using this method, 54\% of the aneurysms can be completely occluded\textsuperscript{121}. Completely occluded aneurysms are very unlikely to rebleed\textsuperscript{122}. The morbidity rate from elective endovascular coiling is 7\% and mortality rate 0.6\%\textsuperscript{123}. Permanent complications of embolization with controlled detachable coils occur in 4\%\textsuperscript{121}.
Challenges in the postdischarge phase

Although only 1-7% of all stroke are attributed to subarachnoid hemorrhage\(^1\), the disease accounts for 27% of all stroke-related years of potential life lost before the age of 65\(^2\). Patients with SAH are younger than other stroke patients, 30% have school-aged children\(^3\) and 44% are unable to return to work\(^4\). For many patients, the disease has a major impact on life following the acute treatment.

The patients usually stay at NIVA for 10 days and are thereafter referred to a rehabilitation unit or a local hospital. Future contact with neurosurgeons is usually limited to follow-up of the neurosurgical treatment, such as hydrocephalus. Apart from these problems, patients may experience various cognitive, psychiatric and physical deficits that affect quality of life, social life and ability to return to work. In Sweden, there is no standardized approach to aftercare for cognitive, emotional or physical problems. The postdischarge care varies based on services available in the patient’s catchment area. Sometimes a GP manages the patient, though the knowledge in general practice about postdischarge challenges is usually scarce. It has been observed that substantial problems may occur after discharge because of a hiatus in care and support by community-based services\(^5\).

Health-care professionals generally accept that a good recovery equates to one where there is an absence of physical deficit; there does not appear to be a general acceptance of the impact of the less obvious cognitive or psychological difficulties\(^6\).

Spasticity

Spasticity is an impairment that can hamper rehabilitation after stroke. It is characterized by hyperactive tendon jerks and an increase in resistance to rapid muscle stretch. Slowly applied stretch of a muscle in a patient with spasticity may elicit little resistance. As the speed of the stretch is progressively increased, resistance to the stretch also increases progressively. Spasticity occurs when losses of the upper motor neuron leads to decreased inhibition of lower motor neurons, which in turn causes an increase in nervous activity that manifests as spasticity\(^7\).

The most commonly used definition of spasticity is that of Lance from 1980\(^8\). “Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (‘muscle tone’) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome.”. It is observed after lesions of the cortical motor areas or the corticofugal descending tracts and is often associated with exaggerated reflexes and clonus.

The definition of spasticity proposed by Lance has been debated. This definition points out that spasticity is only one component of the upper mo-
tor neuron syndrome and also that spasticity is a sign at clinical examination but not with regard to impact on motor ability or need for treatment. Most studies do not use the definition by Lance but equate spasticity with increased muscle tone or provide no definition. A commonly used grading scale for assessing spasticity is the modified Ashworth scale (MAS) from 1987, see Table 7. This is a modification of the Ashworth scale from 1964 that did not have the 1+ grade and had slightly different descriptions of the other grades (except grade 0 that was not changed in the MAS).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in muscle tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension</td>
</tr>
<tr>
<td>1+</td>
<td>Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in muscle tone, passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Affected part(s) rigid in flexion or extension</td>
</tr>
</tbody>
</table>

Treatment for spasticity should be given when spasticity causes problems for the patient’s functioning or care provision. Therefore, the MAS alone is not sufficient defining the threshold above which spasticity is an undesirable impairment. Sometimes spasticity, especially in the lower limb, can be functionally useful in helping patients walk, stand and maintain posture.

As mentioned above, a difficulty with spasticity is how to measure this phenomenon. The performance of the MAS is not standardized; neither the position of the limb nor the speed of the movement is specified. Also, the MAS has only moderate to substantial test-retest reliability and inter-rater reliability and there are some evidence that the inter-rater reliability of the MAS is higher when the scale is used for less heavy limbs.

The management of spasticity involves identification and elimination of triggers, neurophysiotherapy, oral medications such as baclofen, tizanidine, and dantrolene, focal injection of botulinum toxin, alcohol or phenol, or baclofen delivered intrathecally through a pump, and neurosurgical resection of selected dorsal roots of the spinal chord.

Cognitive impairment

Patients having survived SAH do not usually present with classical signs of stroke, such as hemiparesis or facial paresis. Even though they may be able to take care of them selves, the patients may suffer from vague but serious
impairments resulting in difficulties in their relationships and the inability to return to work. Cognitive impairment is an important cause of these impairments and can persist over several years. Patients classified with good recoveries may still have significant cognitive deficits.

There are several tests of cognition having been used on patients with SAH and the prevalence of cognitive impairment after SAH varies widely between studies. This can be attributed in part to the use of different standardized tests and raises questions about the accuracy of cognitive tests after SAH. Another problem is that the test result is dependent on the time having past after the insult. There is discordance between cognitive complaints and results on objective cognitive results, and the absence of subjective complaints is not necessarily related to better objective conditions, but can rather be due to inadequately optimistic life orientation. Memory, executive function and language are domains in which SAH patients show frequent impairments.

One of the most commonly used instruments to assess cognitive functions after stroke is the mini-mental state examination. It has, however, been considered insensitive to the more subtle memory problems often encountered after SAH. Instead, the Montreal cognitive assessment (MoCA) has been suggested as a screening method for cognitive impairment that is caused by or associated with vascular factors. It seems that the MoCA is superior to the mini-mental state examination in diagnosing cognitive impairment after SAH. It is also correlated to functional outcome after SAH.

Depression

Depression is a common neuropsychiatric disorder following stroke. The peak prevalence of post-stroke depression is around 3-6 months after the stroke and ranges varies across studies between 9-34%. Post-stroke depression is related to a variety of adverse health outcome including cognitive dysfunctions, a low response on activities of daily living, functional recovery and higher mortality risk.

Most studies on the prevalence of depression after SAH have used depression-rating scales with cut-offs defining a threshold above which a patient is considered to suffer from depression. This is not in line with clinical practice and has resulted in various frequencies of depression, ranging from 5 to 40%. The depression diagnose requires a full medical and psychiatric evaluation by a qualified physician. Depression rating scales facilitate data and process symptoms elicited by the physician but should not be used as the only diagnostic tool when diagnosing depression. Hedlund et al. used the structured clinical interview for DSM-IV axis I disorders (SCID-I) and found 20% of the patients having major depression 7 months after ictus and 5% minor depression.
The Montgomery Åsberg depression rating scale (MADRS) is the most commonly used screening tool for depressive symptoms in Sweden\(^\text{161}\). There are not many studies, though, using MADRS after SAH. Two studies used MADRS in the acute phase when other factors than depression may affect the MADRS-score\(^\text{162,163}\). One study reported a depression prevalence of 12% using a cut-off score of 4\(^\text{155}\).

MADRS was not designed to diagnose depression but to follow symptoms identified as sensitive to treatment effects. The MADRS should therefore not be used as a diagnostic tool for depression (which is common among general practitioners in Sweden) but can be used to assess depressive symptoms. Recently the mini international neuropsychiatric interview (MINI) has gained increasing interest and may be used more commonly in both research and clinical practice\(^\text{164}\).

Quality of life

The world health organization have defined quality of life as “individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”.\(^\text{165}\) Quality of life is reduced up to 5 years after ictus compared to reference populations\(^\text{166-169}\). Aspects of quality of life relating to a patients health is referred to as health-related quality of life\(^\text{170}\). Factors affecting the health-related quality of life in SAH patients are the severity of the clinical condition at admission, fatigue and depressed mood, physical disability and cognitive impairment, female gender, higher age, neuroticism, and passive coping\(^\text{171}\); though a meta-analysis revealed that physical disability is the only consistent determinant of health-related quality of life in patients with SAH\(^\text{172}\). Frequently impaired quality of life domains are physical problems\(^\text{173}\) and emotional functioning\(^\text{174}\). Deficits in quality of life are variable and depend on the follow-up interval\(^\text{175}\).

The EuroQol-5D (EQ-5D) is a self-report questionnaire for assessing quality of life described in the 1980s\(^\text{176}\) (see Appendix). It has acceptable concurrent and discriminant validity for the measurement of health-related quality of life after stroke\(^\text{177}\) and acceptable test-retest reliability\(^\text{178}\).
Attention deficits

In order to understand attention deficits, one must reflect on the concept of attention. What is attention? There is no universal definition of attention, but several attempts have been made. Experimental psychologists have been exploring the nature of normal attentional processes for decades, yet agreement on mechanisms of attention is far from universal.

"Every one knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatterbrained state which in French is called distraction, and Zerstreutheit in German." – William James 1910

"Attention is the greatest gift you can give another person." – Chris Holder, CEO The T.O.V.A. Company

The phrase paying attention may be confusing as it combines several different behaviors. To illustrate, statements like the following are frequently made by head-injured individuals: “I start watching a TV show and then just kind of drift off”; “I can’t cook or drive or talk with someone while the radio is on. Any distraction upsets me”; and “I can’t listen to a lecture and take notes at the same time.”

Sohlberg and Mateer developed a clinical model of attention in 1989 based on the experimental attention literature, clinical observations, and patients’ subjective complaints. Their model addresses five levels of attention:

**Focused attention:** This is the ability to respond discretely to specific visual, auditory, or tactile stimuli.

**Sustained attention:** This refers to the ability to maintain a consistent behavioral response during continuous and repetitive activity.

**Selective attention:** This level of attention refers to the ability to maintain a behavioral or cognitive set in the face of distracting and competing stimuli. It incorporates the notion of “freedom from distractibility”.

**Alternating attention:** This level of attention refers to the capacity for mental flexibility that allows individuals to shift their focus of attention and move between tasks having different cognitive requirements.

**Divided attention:** This is the highest level of attention and refers to the ability to respond simultaneously to multiple tasks or multiple task demands.
Even though there is a debate whether divided attention exists (perhaps the brain instead quickly shifts the attention between tasks) the model by Sohlberg and Mateer is still in use for psychological education purposes.

There are measurable, neuropsychological components underlying attention and several studies have reported problems with attention after SAH\textsuperscript{181-185}. Most studies, however, have used examiner-administered neuropsychological instruments to assess attention deficits, which has resulted in non-consistent results. Two studies found no difference when comparing SAH patients to healthy controls\textsuperscript{186, 187}, while other studies support that SAH patients have concentration difficulties\textsuperscript{181} and that the patients suffer from attention deficits more often than normative samples\textsuperscript{182, 183}.

Parallel to the research on attention deficits after SAH there has been a technical development that has not comprised the SAH research field. In the 50’s the first continuous performance test was invented\textsuperscript{188}. Today, several computerized neuropsychological assessment devices are available and they are receiving increasing attention in clinical practice, research and clinical trials\textsuperscript{189}. They have several potential advantages such as ease of administration, reduced costs and the capacity to test a large number of individuals during more standardized conditions. Further, it allows computerized data treatment for clinical and research purposes\textsuperscript{189}.

There are only two studies using computerized neuropsychological assessment devices on SAH patients. One, study, using a battery of computerized decision-making tests, showed that the patients did not have the same adjustment in behavior with changing expectation or reward, and they took more risks at unfavorable odds compared to matched controls\textsuperscript{190}. Yoo et al.\textsuperscript{184} evaluated characteristics of cognitive impairment according to the location of the aneurysm using a computerized neuropsychological test and found that patients with non-anterior communicating artery aneurysms took significantly more time in the auditory and visual continuous performance tests. They found severe dysfunctions in attention tests among the SAH patients regardless of the aneurysm location.

The test of variables of attention (T.O.V.A.) is a continuous performance test measuring how well a patient pays attention by continuously monitoring how quickly and successfully a repetitive task is performed during 21.6 minutes\textsuperscript{191}. The average attention span in adults is 20 minutes. The T.O.V.A. was developed and is mainly used for diagnosing attention deficit hyperactivity disorder and to objectively assess and monitor medication effects. The test has, however, also been used in other patient categories such as tonsillectomy\textsuperscript{192}, prenatal cocaine exposure\textsuperscript{193} and HIV\textsuperscript{194}. T.O.V.A. has also been used identifying improvements after traumatic brain injury using hyperbaric oxygen therapy\textsuperscript{195}. Also, it has been used to identify silent cerebral infarcts in children with sickle cell disease\textsuperscript{196}, but has apart from that not been used in stroke patients\textsuperscript{196}.
In order to better understand the complex symptomatology seen after SAH, e.g. concurrent fatigue, cognitive impairment and attention deficits, it is necessary to investigate attention deficits more thoroughly than what is possible using examiner-administrated neuropsychological instruments. The potential application of computerized neurological assessment devices to medical and neuropsychiatric conditions seems limited only by the available knowledge and recognition of neurocognitive symptoms. For this reason, the clinical application of computerized neuropsychological assessment devices is expected to increase in the coming years.

Return to work

Two-thirds of the patients having worked before SAH are able to return to their previous position. Returning to work is a major issue for SAH patients and not returning to work is associated with reduced life satisfaction and is of economical interest for both patients and society. Returning to work is important after stroke and can have a positive impact on the psychological wellbeing and life satisfaction, and fulfill many psychosocial needs.

A retrospective study using telephone interviews 1-2 years after SAH showed that illness perception and marital status were independent predictors of return to work; a logistic regression model used in the study correctly predicted 66.7% of the outcomes for return to work.

Epileptic seizure

Seizures are well-recognized complications after SAH and treatment of these events with prophylactic antiepileptic drugs remains controversial. The reported incidence of onset seizures varies, probably because the events may be difficult to distinguish from true seizures. Often, the description of these events is provided by non-medical bystanders with insufficient background to differentiate tonic events from seizures. The average time to late seizure is 7 months.

Predictors for seizure

A variety of variables have been associated with the development of epilepsy after SAH. In a study that randomly assigned SAH patients to neurosurgical clipping or endovascular coiling, the risk was lower in those allocated to endovascular treatment. In a study not using the randomization process, patients treated with clipping had similar incidences of seizures or epilepsy compared with patients treated with coiling. Onset seizures have been linked to several disease severity markers, with correlations found with hem-
iparesis, Fisher scale >2, and cerebral infarction. Independent predictors of epilepsy (defined as two or more unprovoked seizures after hospital discharge) include subdural hematoma and cerebral infarction.

**Antiepileptic drugs**

The most commonly used anticonvulsants are phenytoin and valproic acid. In patients suffering a seizure during hospitalization, the literature describes continuation of antiepileptic drug therapy for a variable period (6 weeks to 6 months) and there is no strong data to support a particular treatment duration. Routine long-term use of anticonvulsants is not recommended but anticonvulsants may be considered for patients with risk factors such as prior seizure, parenchymal hematoma, infarct, or middle cerebral artery aneurysms. Antiepileptic drugs have a variety of adverse effects occurring in 21% of treated patients requiring switching in 14% of the patients. The most common adverse effects are deranged liver function tests, thrombocytopenia and rash. Steven-Johnson syndrome has been reported in 0.7% of cases.

**SAH in primary health care**

Most studies on SAH in general practice have focused on the acute onset and there are only a few published papers on the general practitioner’s role after SAH. As part of a clinical governance’ initiative in the UK 2001, a study was designed to determine the psychosocial outcome of patients with SAH. This study showed some findings regarding SAH in general practice. The authors concluded that substantial problems occur after discharge because of a hiatus in care and support by community-based services that are linked to basic communication problems. Even though patients with SAH are mainly very positive about their in-patient experience, 60% were not confident in the general practitioner’s knowledge about SAH. A main theme in this study concerns issues arising after discharge from the neurointensive care, an apparent lack of support and a sense of isolation. The study showed that an average general practitioner may see 6 or 8 patients having had SAH during her or his medical career and the authors conclude that this makes the management of relatively uncommon conditions inherently difficult for the general practitioner-led community services.

A follow-up study in general practice on patients having been diagnosed with idiopathic thunderclap headache showed that 14% of the patients developed new tension headache or migraine, 9% had recurrent attacks of idiopathic thunderclap headache, but no subsequent SAH was diagnosed during the 5 year follow-up.

The cost of SAH in primary health care is 0.4% of all health care costs. Apart from the studies mentioned above, there is not much published on aftercare in general practice of SAH patients.
Riksstroke

Riksstroke is the Swedish national quality register for stroke care primarily aimed at health professionals and decision makers in health care. It collects, analyzes and follow-up data on morbidity and hospital stay and was established in 1994 and since 1998 all hospitals admitting acute stroke patients participate. The aim of the register is to support high and consistent quality of care for stroke patients throughout Sweden, ultimately to ensure patient benefit in the form of the best possible care.\textsuperscript{212}

SAH patients are not included in Riksstroke though there is an ongoing process and hopefully they will be included during 2017. Riksstroke has a 3-months follow-up form\textsuperscript{213} and a 12-months follow-up form\textsuperscript{214}.

Common questions from patients and relatives

The following questions and answers come from the driving and vehicle licensing agency in the United Kingdom\textsuperscript{215} and the brain and spine foundation booklet providing information on SAH designed as guides for patients, their families and carers.\textsuperscript{216}

**Can I drive?**

The UK guideline includes not only cars, but also motorcycles, lorries and busses.\textsuperscript{215}

*No source of bleeding*

Provided comprehensive cerebral angiography normal, may resume driving following recovery.

*Intracranial aneurysm*

If any other procedure is undertaken e.g. VP shunt, craniotomy for a hematoma etc., then the standards for that procedure shall apply.

If the aneurysm was treated successfully without complications: drive on clinical recovery.

**Can I fly?**

There are no Swedish guidelines for when flying after SAH is advisable. The brain and spine foundation booklet advise to avoid flying for at least 10 days after a craniotomy. And up to 6 weeks after the operation, you should inform the airline with whom you are travelling.

**Will the coils or clips affect airport security machines?**

No.
Can I play sports?
Yes, but you should avoid all contact sports like rugby, boxing or martial arts, and strenuous exercise like lifting weights, for at least 6 months. You can then discuss with your specialist the possibility of resuming these sports if you wish to.

Can I swim?
Swimming is fine once any wounds have healed, but it’s a good idea to be accompanied for the first few months while the risk of having seizures is at its highest.

Can I have sex?
Yes, there is no risk. Women are advised to avoid become pregnant for the first 6 months. Avoiding becoming pregnant for the first 6 months is not a recommendation that is used in Sweden.

Can I drink alcohol?
You should not drink alcohol for the first 3 weeks. After that, small amounts are safe. There is a risk of provoking a seizure if you drink too much.

When can I go back to work?
It is common for people who have had SAH to take several months off work. Many people find it helpful to go back part-time or for a few hours each week before returning to full-time work. You might like to see if there are any clubs or voluntary organizations with whom you can volunteer as a stepping stone to returning to work.

Can I have MRI scans?
Yes. Modern platinum coils and plastic or titanium clips are designed to be safe with MRI scanning equipment. However, each individual case should be discussed with the consultant neuroradiologist. Scanning equipment varies in different hospitals.
Aims of the study

This thesis investigates the challenges often faced by SAH patients and their relatives after the acute treatment at the neurointensive care unit, with special focus on spasticity, cognitive impairments, return to work, contact with medical services, and attention deficits.

Paper I: The objectives of the present study were to estimate the prevalence of spasticity 6 months after SAH, to identify risk factors in the acute phase for spasticity after SAH, and to investigate the extent to which patients receive pharmacological anti-spastic treatment.

Paper II: The objective of this study was to investigate the predictive value of MoCA assessed 6 months after ictus on return to work at 12 months.

Paper III: The aim of this study was to investigate patients’ contacts with medical and social services after the acute phase of SAH.

Paper IV: The aim of this pilot study was to assess attention deficits in a group of SAH patients using the T.O.V.A. We also compared the T.O.V.A. with the concentration and attention domains in MADRS and MoCA, 2 examiner-administrated neuropsychological instruments.
Methods

Patients

Paper I-III

All patients aged 18 years or over, admitted with first time SAH to the Department of Neurosurgery at Uppsala University hospital, Sweden, between January 6, 2010 and July 13, 2011 and with no previous history of spasticity were eligible. A flow chart is provided in Figure 1 showing that 191 patients were investigated of which 96 patients were included; see Table 8 for patient characteristics. Secondary insults were treated according to the neuro-intensive care unit’s protocols for programmed care\textsuperscript{217}. Inclusion was performed within 10 days after ictus. The department has a catchment area of 2 million inhabitants. The aim was to include 100 patients. The sample size was based on previous research on spasticity after stroke\textsuperscript{218-225} and on the following assumption: It was assumed that 20\% of the patients would develop severe paresis, and of those, 70\% would develop spasticity. In addition, 30\% of the patients without severe paresis were assumed to develop spasticity. With the above proposed sample size, these approximations would provide a power of 90\% to detect a difference between those with and those without spasticity at a significance of 5\%, which was considered acceptable.

![Flow chart of patients in Paper I-III](image_url)

Figure 1. Flow chart of patients in Paper I-III
Table 8. Characteristics of the patients included in Paper I-III at inclusion and at 6-months follow-up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study cohort, n=96</th>
<th>6-months follow-up, n=86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>59 (12)</td>
<td>58 (12)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>63 (66)</td>
<td>54 (63)</td>
</tr>
<tr>
<td>Education, mean years (SD)</td>
<td>11.3 (3.8)</td>
<td>11.3 (3.9)</td>
</tr>
<tr>
<td>WFNS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48 (50)</td>
<td>48 (56)</td>
</tr>
<tr>
<td>2</td>
<td>12 (13)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>3</td>
<td>4 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>4</td>
<td>26 (27)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>5</td>
<td>6 (6)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Fisher scale, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>2</td>
<td>23 (24)</td>
<td>23 (27)</td>
</tr>
<tr>
<td>3</td>
<td>44 (46)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>4</td>
<td>26 (27)</td>
<td>22 (26)</td>
</tr>
<tr>
<td>Aneurysm location, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>83 (86)</td>
<td>74 (86)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>13 (14)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular coiling</td>
<td>62 (65)</td>
<td>58 (67)</td>
</tr>
<tr>
<td>Surgical clipping</td>
<td>34 (35)</td>
<td>28 (33)</td>
</tr>
<tr>
<td>Vasospasm, n (%)</td>
<td>23 (24)</td>
<td>22 (26)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage, n (%)</td>
<td>24 (25)</td>
<td>24 (28)</td>
</tr>
<tr>
<td>Hydrocephalus, n (%)</td>
<td>34 (35)</td>
<td>33 (38)</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>46 (48)</td>
<td>38 (44)</td>
</tr>
<tr>
<td>Brain ischemia, n (%)</td>
<td>37 (39)</td>
<td>37 (43)</td>
</tr>
<tr>
<td>RLS 85 at discharge, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>82 (85)</td>
<td>74 (86)</td>
</tr>
<tr>
<td>4-8</td>
<td>12 (12)</td>
<td>11 (13)</td>
</tr>
</tbody>
</table>

Paper IV

In this pilot study, 19 patients were recruited at 17 months (SD 20) after having had SAH. They had been treated for SAH at the Department of Neurosurgery at Uppsala university hospital between 2007 and 2012 and had a routine magnetic resonance imaging control planned 2013. The patients had either a good recovery or moderate disability (GOS 4-5). For patient characteristics see Table 18 (page 57, All patients).
Data collection

Paper I-III

Paper I-III were based on 3 data collections, see Table 9. The first data collection was performed at the neurointensive care unit within 10 days after ictus, the second at 6 months, and the third at 12 months.

Table 9. Data collected at the 3 data collections for Paper I-III

<table>
<thead>
<tr>
<th>The acute phase</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D</td>
<td>EQ-5D</td>
<td>EQ-5D</td>
</tr>
<tr>
<td></td>
<td>Riks-Stroke 3-months follow-up form</td>
<td>Riks-Stroke 12-months follow-up form</td>
</tr>
<tr>
<td>mRS</td>
<td>mRS</td>
<td></td>
</tr>
<tr>
<td>Pain Questionnaire</td>
<td>Pain Questionnaire</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>NIHSS</td>
<td></td>
</tr>
<tr>
<td>Spasticity</td>
<td>Spasticity</td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>Reflexes</td>
<td></td>
</tr>
<tr>
<td>Babinski</td>
<td>Babinski</td>
<td></td>
</tr>
<tr>
<td>Sensory assessment</td>
<td>Sensory assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MoCA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MADRS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distance between home and primary care center</td>
<td></td>
</tr>
<tr>
<td>Paresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of ictus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
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</tr>
<tr>
<td>RLS 85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WFNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasospasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data collected in the acute phase

The following parameters were collected from medical records or by asking the patients or patients’ relatives: age, years of education, occupational status (employed, unemployed, student, retired, sick-listed), gender, date of ictus, and presence of hypertension, diabetes, cardiac disease, hypercholesterolemia, smoking, and use of alcohol.
The following parameters were collected from admission records at Uppsala University hospital: RLS 85, GCS, WFNS, aneurysm location (anterior circulation includes aneurysms on the internal carotid artery, anterior cerebral artery and middle cerebral artery; and posterior circulation those on the basilar and vertebral arteries), and the amount of blood visualized at the diagnostic CT scan graded using the Fisher scale. There was no standard approach to measure paresis; paresis was defined as weakness in at least one limb at arrival to Uppsala university hospital according to the neurosurgeon’s assessment.

The following parameters were collected at the NIVA: Medications, spasticity according to the MAS, reflexes in biceps-, brachioradialis-, triceps-, patellar- and Achilles tendon, Babinski sign, sensory investigation using touch, sharp and cold in all extremities, pain drawing, pain questionnaire, EQ-5D and mRS. Neurological deficits was assessed using the Swedish 42-point version of the national institutes of health stroke scale (NIHSS) with 11 items. Infections were considered present when proven by bacterial cultures and treated. Vasospasm was considered present when no other cause to a neurological deterioration was found, e.g. hydrocephalus or intracerebral clots. Hydrocephalus, brain ischemia, and intracerebral hemorrhage were considered present when diagnosed in the patients’ medical records and CT- or MRI-report; when there was any doubt the CT- or MRI-scan was re-evaluated by an experienced neurosurgeon (ERE).

Data collected at 6-months follow-up
The patients were assessed either at the neurology department or in the patients’ home. The Riks-Stroke 3-months follow-up questionnaire (including medications), was completed. mRS and NIHSS were collected. Reflexes and Babinski was investigated as well as pain drawings and pain questionnaires.

Spasticity was assessed in the upper limb (shoulders, elbows, wrists and fingers) and the lower limb (hips, knees, and ankles) using the MAS. Spasticity in the shoulders was examined in abduction and adduction with the elbow in 90° flexion, and the other joints were examined in flexion and extension. Each joint was examined separately at different velocities with the patient lying in the supine position. Spasticity was defined as having a MAS score of 1 or more in a least one joint. Information about the use of anti-spastic treatment during the first 6 months came from interview questions and medical records. The medical records during the first 6 months after ictus were gathered (e.g. from Uppsala University hospital, patients’ local hospital, nursing home and primary health care) for all patients presenting with spasticity. The distance from the patient’s home to the closest primary care center or hospital was measured in kilometers using Google Maps.

The Swedish version of MoCA (see Appendix) was administered. MoCA is a 30-point test usually administered within 10 minutes. It evaluates the
following cognitive domains: visuospatial/executive, naming, attention, language, abstraction, delayed recall and orientation. An additional point is given for education ≤ 12 years.

Depressive symptoms were assessed using the MADRS (see Appendix). It is an observer rating scale for mood assessment assessing depressive symptoms. 10 domains are each rated between 0 and 6 and the total score ranges from 0 to 60. The domains assessed are apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The higher score the more depressive symptoms.

Also at 6 months, quality of life was assessed using EQ-5D (see Appendix). The first part of EQ-5D is the EQ-Index measuring health in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored as one of three levels: 1 = no or minor problems, 2 = some or moderate problems and 3 = large problems. From the results of the five dimensions, an EQ-Index value is derived using the “time trade-off” technique. Several studies on general populations have been conducted to elicit preference weightings for the EQ-Index. In these studies, the respondents were asked to select a length of time (x) in full health that they regard as equivalent to 10 years in the target state. In case of states regarded as worse than dead, the choice was between dying immediately vs. spending a length of time (x) in the target state followed by (10-x) years in the target state. States regarded better than dead are calculated as x/10. States regarded worse than dead are calculated as x/10-1, hence, scores are bounded by -1 and 1. The second part of EQ-5D, the EQ-VAS, is a vertical visual analogue scale measuring health state that takes values between 0 (worst imaginable health state) and 100 (best imaginable health state). The EQ-VAS is also presented in the Appendix.

Data collected at 12-months follow-up

At 12 months after ictus the Riks-Stroke 12-months follow-up questionnaire (including medications) and EQ-5D was mailed to the patients. The Riks-Stroke questionnaire contains questions regarding whether the patients have been able to return to work and to what extent. The patients are also asked whether they have received work related rehabilitation such as a rehabilitation plan, rehabilitation tools, change of assignments or working hours, vocational training, reallocation or work related education, and if they have received enough work related rehabilitation. The patients not answering the questionnaires were reminded 3 times.

Paper IV

Data was collected by a research nurse when the patients visited the hospital for a routine 3.0-Tesla MRI follow-up of the treated aneurysm. The MRI
was used to describe brain ischemia, hydrocephalus and intracerebral hemorrhage. After the MRI, attention deficits was assessed using the T.O.V.A. Thereafter, cognitive functions were estimated with the MoCA and depressive symptoms were assessed using the MADRS. Health-related quality of life was measured with EQ-5D. Fatigue was assessed using a visual analogue scale between 0 and 100 in which the patient stated his/her subjective energy (low scores for low energy). The patients answered questionnaires regarding profession, medications and whether they had been able to return to work and to what extent.

**T.O.V.A.**
The T.O.V.A. is a computerized test measuring attention.

There is a visual and an auditory version of the T.O.V.A. The visual T.O.V.A.’s stimuli are two easily discriminated geometric figures on a computer screen flashing every 2000 ms. Because of a possible risk for epileptic seizures in SAH patients exposed to flashing screens, we chose to use the auditory T.O.V.A. In the auditory T.O.V.A. two different tones are played in a predefined order for 21.6 minutes. Each tone is played for 100 ms at 2000 ms interval. When a high tone is played (G above middle C), this is called a target and the patient is supposed to press a button as soon as possible. When a low tone is played (middle C), this is called a non-target and the patient is supposed not to press the button.

There are four possible responses, see Table 10; when a patient presses the button on a target, this is a correct response and when a patient do not press the button on a non-target this is a correct non-response. When, however, a patient fails to press the button on a target, this is called an error of omission, and when a patient presses the button on a non-target, this is called an error of commission.

<table>
<thead>
<tr>
<th>Possible responses in the T.O.V.A.</th>
<th>Target = High tone (signal to press button)</th>
<th>Non-target = Low tone (signal to not press button)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient presses button</td>
<td>Correct response</td>
<td>Error of commission</td>
</tr>
<tr>
<td>Patient does not press button</td>
<td>Error of omission</td>
<td>Correct non-response</td>
</tr>
</tbody>
</table>

**Test setup**
The test is divided into two halves, both being 10.8 minutes long. The first half is called the infrequent half with a target appearing randomly and infrequently with a target: non-target ratio of 1:3.5. This half is boring and the
patient must pay close attention to press the button on each target. The second half is called the frequent half in which a target appears randomly and frequently with a target: non-target ratio of 3.5:1. During this half the patient must press the button most of the times and inhibit the tendency to press the button on the non-targets. In the evaluation of data, each half, is divided into two quarters, adding up to 4 quarters. See Figure 2 and Figure 3 for an example of a normal test result of one of the patients. Also, see Figure 4 and Figure 5 for a patient with a pathological test result.

Figure 2. T.O.V.A. test summary of a patient with a normal test result
Figure 3. T.O.V.A. raw data graph of a patient with a normal test result
Figure 4. T.O.V.A. summary of a patient with a pathological test result
Figure 5. T.O.V.A. raw data graph of a patient with a pathological test result
Data collected in the T.O.V.A.

The response time of each response is measured in milliseconds. Response time variability is a measure of the variability in the patient’s reaction time for accurate responses and is the most sensitive measure in the T.O.V.A. The response time variability is defined according to the following equation:

\[
\text{response time variability} = \frac{\sum (\text{response times} - \text{mean correct response time})^2}{\# \text{ correct responses}}
\]

The number of correct responses and number of correct non-responses are added to a total of correct responses. The number of commissions and omissions are presented. The data is reported by quarters, halves, and total.

Comparison to normative sample

The comparison to the normative sample is built into the software. The auditory T.O.V.A. test has been normed on children 6 to 19 years, n=2551, recruited from elementary and high schools in the Minneapolis metropolitan area, Minnesota, and were predominately Caucasian (99%, 1% other). Additional normative data for the adult sample is not yet available. Testing adult subjects is to be considered experimental for the auditory version. The visual T.O.V.A. (not used in this thesis) has been normed on children and adults, ages 4 to 80+ years.

Another advantage with the visual T.O.V.A. is that an attention performance index providing information about the patient’s overall performance is included. It is a single number that could be useful in a clinical trial to detect improvement/deterioration of a patient’s T.O.V.A. results over time.

The results of the response time, response time variability, commission errors, and omission errors are compared to the normative sample, stratified by age and gender, and presented in standard scores. The higher standard scores the better. The standard scores are defined as having an average of 100 and a standard deviation of 15. Scores above 85 are considered to be in the normal range, scores between 80 and 85 are considered borderline, and scores below 80 are considered not within normal limits. Scores less than 70 are considered significantly below normal range. The comparison to normative sample is reported by quarters, half, and total.

Test interpretation

By comparing the patients’ test result to the normative sample, the test result is categorized into being normal (within normal limits), borderline, or pathological (not within normal limits). If all standard scores are above 85 the test is considered normal. If no standard score is below 80 but there is a standard score between 80 and 85 the test is considered borderline. If any standard score is below 80, the test is considered pathological.
Statistics

Paper I
Simple regression analysis was used to compare possible risk factors for spasticity between patients with and without spasticity. Student’s t-test, chi-square test, Fisher’s exact test, and Mann-Whitney U test were used where appropriate. A risk factor with a $p<0.05$ was considered significant. WFNS was dichotomized in good (WFNS 1-2) or worse (WFNS 3-5). The significant risk factors were selected for a multiple logistic regression model using backward stepwise (likelihood ratio) method. Odds ratio (OR) for spasticity were calculated and are presented with 95% confidence interval (CI). Data was analyzed using STATA 10.0 software for Microsoft Windows.

Paper II
The following variables from the acute phase were dichotomized for the statistical analysis: better or worse clinical condition at admission (WFNS 1-2 vs. 3-5), less or more blood on the first CT (Fisher 1-2 vs. 3-5), and aneurysm location in anterior and posterior circulation. MoCA was compared between groups using Mann-Whitney U test. Linear regression was used in the comparison of MoCA and age. Logistic regression models were used to analyze the predictive value of MoCA on return to work. The predictive value of MoCA on return to work was further evaluated using the area under the receiver operating characteristic curve (ROC curve). A difference with a $p$ value $<0.05$ was considered statistically significant. Data was analyzed using StatSoft, Inc. (2012), STATISTICA 11.

Paper III
Mann Whitney-U was used to analyze differences between patients having had a follow-up appointment to those not having had a follow-up appointment in age, education, NIHSS, EQ VAS, MADRS, MoCA and distance to primary care center or hospital; and chi-square test in sex and whether the patients were living alone or not. A difference with a p-value $<0.05$ was considered statistically significant. Data was analyzed using StatSoft, Inc. (2013) STATISTICA (data analysis software), version 12 (www.statsoft.com).

Paper IV
Mann-Whitney U test was used to analyze differences between patients with normal and pathological T.O.V.A. in age, education, WFNS, Fisher scale, fatigue, MADRS, and MoCA; and chi-square test in sex, vasospasm, aneurysm location, treatment, infection, hydrocephalus, brain infarction, and intracerebral hemorrhage.
Ethics

The studies included in this thesis were approved by the regional ethics review board in Uppsala and the patients were included after written informed consent either directly from the patients, or from next of kin.
Results

Paper I

Eighty-seven patients were examined for spasticity at the 6-months follow-up. Spasticity was defined as having a MAS score of 1 or more in at least one joint. Nineteen patients (22%) had developed spasticity, see Table 11.

Table 11. Distribution of patients according to the highest score on the modified Ashworth scale

<table>
<thead>
<tr>
<th>MAS grade</th>
<th>Description</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in muscle tone</td>
<td>68 (78)</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase</td>
<td>6 (7)</td>
</tr>
<tr>
<td>1+</td>
<td>Slight increase</td>
<td>7 (8)</td>
</tr>
<tr>
<td>2</td>
<td>A more marked increase</td>
<td>3 (3)</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase</td>
<td>1 (1)</td>
</tr>
<tr>
<td>4</td>
<td>Rigid</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

Thirteen of the patients had mild spasticity, defined as MAS grade 1 or 1+. Seventeen (20%) had spasticity in the upper limb, 14 (16%) in the lower limb and 12 (14%) had spasticity in both the upper and lower limb. Of the 19 patients presenting with spasticity, 2 had developed spasticity in the elbow, 13 in the knee, 7 in the wrist, 6 in the ankle, 5 in the hip, and 4 in the fingers. One patient had been treated with a single shot of intramuscular botulinum toxin, and this was the only patient with spasticity having received pharmacological anti-spastic treatment.

The patients with spasticity had a worse functional outcome, measured with mRS, compared to those without spasticity (p<0.001), see Table 12.

Table 12. Association between functional status and spasticity

<table>
<thead>
<tr>
<th>modified Rankin scale</th>
<th>No Spasticity n (%)</th>
<th>Spasticity n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1</td>
<td>25 (37)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>2</td>
<td>17 (25)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>3</td>
<td>13 (19)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>4</td>
<td>2 (3)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>4 (21)</td>
</tr>
</tbody>
</table>
Risk factors for spasticity

Simple regression analysis showed that patients with spasticity were in significantly worse clinical condition at admission, had more blood on the CT scan, and more often had paresis at admission. Furthermore, they were more likely to have had vasospasm, intracerebral hemorrhage, hydrocephalus, and to have been treated for infections, see Table 13.

Table 13. Differences in clinical characteristics at the neurointensive care unit between patients presenting with spasticity and those not presenting with spasticity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spasticity</th>
<th>No spasticity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>19 (22)</td>
<td>68 (78)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>61 (12)</td>
<td>56 (12)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>12 (63)</td>
<td>42 (62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WFNS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>4 (21)</td>
<td>52 (76)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>3-5</td>
<td>15 (79)</td>
<td>16 (24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fisher grade, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (11)</td>
<td>21 (31)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (42)</td>
<td>31 (46)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9 (47)</td>
<td>13 (19)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm location, n (%)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>17 (89)</td>
<td>58 (85)</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>2 (11)</td>
<td>10 (15)</td>
<td></td>
</tr>
<tr>
<td>Initial paresis, n (%)</td>
<td>8 (44)</td>
<td>7 (10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vasospasm, n (%)</td>
<td>10 (53)</td>
<td>13 (19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intracerebral hemorrhage, n (%)</td>
<td>9 (47)</td>
<td>16 (24)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hydrocephalus, n (%)</td>
<td>13 (68)</td>
<td>21 (31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>16 (84)</td>
<td>22 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Brain ischemia, n (%)</td>
<td>11 (58)</td>
<td>23 (34)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

When entering the significant factors into a multiple logistic regression model using backward selection we found that the following variables had an independent effect on the development of spasticity:

WFNS 3-5: OR 10.2; 95% CI 2.4-43.2
Infection: OR 7.4; 95% CI 1.6-33.8
Vasospasm: OR 4.8; 95% CI 1.2-19.0

CT-verified brain ischemia was marginally not significant in the simple regression analysis (p=0.057), but was also tried in the same model. However, it was not found to be an independent risk factor.
Paper II

Predicting cognitive impairment

Cognitive impairment was assessed in 86 of the patients at the 6-months follow-up using the MoCA. Eighty-one of the 86 patients investigated (94%) were able to complete the MoCA (4 patients had a clinical condition not allowing cognitive testing, and 1 patient did not speak Swedish). The median score of all patients having completed the MoCA was 25, interquartile range 22-28, mean MoCA score 23.96, SD 5.20. The total score on MoCA of the 81 patients having completed the MoCA is presented in Figure 6.

![Histogram of MoCA scores](image)

**Figure 6.** Total score of the Montreal cognitive assessment

In simple regression high age, high WFNS score, infection, and brain ischemia were associated with a low score on MoCA, see Table 14.
Table 14. The score of the Montreal cognitive assessment (MoCA) by patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median MoCA-score (IQR)</th>
<th>Median MoCA-score (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>WFNS</td>
<td>1-2: 26 (22-28)</td>
<td>3-5: 24 (21-26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fisher scale</td>
<td>1-2: 26 (21.5-28)</td>
<td>3-4: 25 (22-28)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td>Anterior circulation: 25 (22-28)</td>
<td>Posterior circulation: 25.5 (22-27.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Endovascular coiling: 25 (22-28)</td>
<td>Surgical clipping: 25 (22-28)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>Yes: 24.5 (22.5-28)</td>
<td>No: 25 (21-28)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>24 (22-27)</td>
<td>26 (22-28)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>25 (21-27)</td>
<td>26 (22-28)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Infection</td>
<td>23 (20-26)</td>
<td>26.5 (24-28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Brain ischemia</td>
<td>24 (20-26)</td>
<td>26.5 (23-28)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

When entering these independent variables into a multiple ordinal logistic regression model using backward selection, with MoCA score as the dependent variable, we found that the following two variables independently affected the risk of scoring low on MoCA:

- High age: OR 0.95; 95% CI 0.92-0.98, p=0.03
- Brain ischemia: OR 0.31; 95% CI 0.14-0.68, p<0.004

The score in each domain of MoCA is presented in Figure 7. The most frequently missed domain was the delayed recall with 93% of the patients not having full score. Forty-one percent of all lost points on the whole MoCA test were points missed in the delayed recall domain.
Figure 7. The score in each domain of the MoCA
Predicting work status

Seventy-five patients answered the 12-months questionnaire regarding work status. Fifty (67%) had a regular work before the SAH. Seventeen of these (34%) had completely returned to work, 9 (18%) had returned partially, and 24 (48%) not at all. Hence, 52% of the patients had been able to return to work to at least some extent. Those having returned to work had scored significantly better on MoCA, 28 points, compared to those not having returned to work, 24 points, (p=0.001), see Figure 8.

![Figure 8. Montreal Cognitive Assessment (MoCA) score at 6 months divided into those having returned to work at 12 months and those not having returned to work](image)

Figure 9 shows that by using a cut-off of <27 on MoCA, the sensitivity is 71%, specificity is 65%, negative predictive value is 71%, positive predictive value is 65%, and 68% of the patients could be correctly classified (accuracy) as returned/not returned to work. The predictive value of MoCA on return to work was evaluated using the ROC curve and showed an area of 0.75 (95% CI 0.62-0.89).
Figure 9. Sensitivity, specificity, negative predictive value, positive predictive value, and accuracy for different cut-off values of the MoCA at 6 months after ictus when predicting return to work at 12 months.

There were no factors from the acute phase (e.g., those describing the severity of the disease, localization of the aneurysm or treatment mode of the aneurysm) that significantly predicted return to work, though there was a tendency that higher age \( (p=0.09) \) and infection \( (p=0.10) \) increased the risk of not returning to work. To investigate if the MoCA test, together with data from the acute phase, would better predict return to work than the MoCA test alone, a logistic regression was performed with return to work as the dependent variable and MoCA, age, and infection as independent variables. Seventy percent of the patients could be correctly classified using this model, which is a 2% increase compared to the MoCA test alone using the cut-off of <27, as described above.

**Paper III**

**Living conditions**

Of the 85 patients investigated at the six-months follow-up, there were 77 (91%) living in their own accommodations, see Table 15.
Table 15. This table presents answers to the question “Where are you staying at present?” investigated 6 months after ictus.

<table>
<thead>
<tr>
<th>Accommodation Type</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In own accommodation without community home-help services</td>
<td>67</td>
<td>(79)</td>
</tr>
<tr>
<td>In own accommodation with community home-help services</td>
<td>10</td>
<td>(12)</td>
</tr>
<tr>
<td>Arranged accommodation (e.g. nursing home, old people’s home, service flat with full board, temporary accommodation, sheltered housing, alternate accommodation or equivalent)</td>
<td>5</td>
<td>(6)</td>
</tr>
<tr>
<td>At acute-care ward (e.g. medical, neurological or surgical ward)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>At geriatric or rehabilitation unit</td>
<td>3</td>
<td>(4)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>(0)</td>
</tr>
</tbody>
</table>

Functional outcome is presented in Figure 10 showing that 78% of those with moderate to severe disability (mRS 3-5) were living in own accommodations. Fifty-five percent stated they were dependent upon family or friends for help or support.

Figure 10. This figure presents functional outcome six months after SAH divided into those living in own accommodations and those not living in own accommodations. mRS 0 means no symptoms, 3 means moderate disabilities, and 5 means severe disability.
Support from medical services or the municipality
The type of support or help received from the medical services or the municipality is presented in Table 16. Seventy-six percent of the patients had received at least one type of support. The most common municipality support was day-care rehabilitation/team rehabilitation followed by home-help services. Forty-one percent, however, felt their requirements for support or help had not been completely fulfilled.

Table 16. This table presents answers to the question “What type of support or help did you receive from the Medical Services or the Municipality after your hospitalization? (More than one option may be applicable)” investigated 6 months after ictus.

<table>
<thead>
<tr>
<th>Type of Support</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-care rehabilitation / team rehabilitation</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Home rehabilitation</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Temporary accommodation</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Other support (e.g. from physician, nurse, physiotherapist, occupational therapist, counselor or speech therapist)</td>
<td>34 (41)</td>
</tr>
<tr>
<td>Home-help service</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

Follow-up appointments
Seventy patients (83%) had had a follow-up after discharge. A majority of the follow-up appointments had been conducted in a hospital, though 17 (20%) of the patients had had a follow-up appointment in a primary care center. Fourteen patients (17%) had not had a follow-up appointment after their SAH; see Table 17 (one patient did not remember whether a follow-up appointment had been conducted). The patients not having had a follow-up appointment were older (p=0.04), had lower quality of life (p=0.03), had more depressive symptoms (p=0.03), more cognitive impairment (p=0.03), and were more often living alone (p=0.01) compared to the patients having had a follow-up appointment. There were no differences between the two groups in gender, education, NIHSS, or distance to primary care center or hospital.
Table 17. This table presents patient characteristics divided into those having had a follow-up appointment and those not having had a follow-up appointment.

<table>
<thead>
<tr>
<th></th>
<th>Have had follow-up appointment n=70</th>
<th>Not had follow-up appointment n=14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 (11)</td>
<td>63 (14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>44 (63)</td>
<td>8 (57)</td>
<td>0.69</td>
</tr>
<tr>
<td>Education, mean years (SD)</td>
<td>11.6 (3.7)</td>
<td>9.9 (4.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>NIHSS score at 6 months, mean (SD)</td>
<td>1.1 (2.7)</td>
<td>1.7 (3.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>EQ VAS at 6 months, mean (SD)</td>
<td>72 (17)</td>
<td>58 (21)</td>
<td>0.03</td>
</tr>
<tr>
<td>MADRS at 6 months, mean (SD)</td>
<td>6.5 (6.1)</td>
<td>12.7 (10.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>MoCA at 6 months, mean (SD)</td>
<td>23.9 (5.1)</td>
<td>20.3 (6.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Distance, mean (SD)</td>
<td>6 (8)</td>
<td>6 (10)</td>
<td>0.17</td>
</tr>
<tr>
<td>Living alone at 6 months, n (%)</td>
<td>15 (21)</td>
<td>8 (57)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Paper IV

Initially, 6 patients had a normal and 13 patients a pathological T.O.V.A. performance according to the computer software. The results from 2 patients with pathological T.O.V.A. were, however, considered normal after analysis indicated that the pathological results were because of external distractions. After these considerations 8 patients had a normal T.O.V.A. and 11 patients (58%) had a pathological T.O.V.A. All patients with infection during the acute phase had pathological results on the T.O.V.A., see Table 18.

Table 18. Patient characteristics for all patients in Paper IV, for those with normal T.O.V.A., and for those with pathological T.O.V.A.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=19)</th>
<th>Normal T.O.V.A. (n=8)</th>
<th>Pathological T.O.V.A. (n=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>57 (14)</td>
<td>50 (14)</td>
<td>62 (12)</td>
<td>0.10</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (79)</td>
<td>5 (63)</td>
<td>10 (91)</td>
<td>0.13</td>
</tr>
<tr>
<td>Education in years, mean (SD)</td>
<td>13 (4)</td>
<td>14 (2)</td>
<td>11 (4)</td>
<td>0.08</td>
</tr>
<tr>
<td>WFNS, median (IQR)</td>
<td>1 (1-3)</td>
<td>1 (1-1.5)</td>
<td>1 (1-4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Fisher scale, median (IQR)</td>
<td>3 (3-4)</td>
<td>3 (3-3.5)</td>
<td>3 (3-4)</td>
<td>0.84</td>
</tr>
<tr>
<td>Vasospasm, n (%)</td>
<td>6 (32)</td>
<td>2 (25)</td>
<td>4 (36)</td>
<td>0.60</td>
</tr>
<tr>
<td>Anterior aneurysm, n (%)</td>
<td>17 (89)</td>
<td>8 (100)</td>
<td>9 (82)</td>
<td>0.20</td>
</tr>
<tr>
<td>Coiling, n (%)</td>
<td>18 (95)</td>
<td>8 (100)</td>
<td>10 (91)</td>
<td>0.38</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>7 (37)</td>
<td>0 (0)</td>
<td>7 (64)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hydrocephalus, n (%)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Brain ischemia, n (%)</td>
<td>8 (42)</td>
<td>4 (50)</td>
<td>4 (36)</td>
<td>0.55</td>
</tr>
<tr>
<td>Intracerebral hemorrhage, n (%)</td>
<td>4 (21)</td>
<td>1 (13)</td>
<td>3 (27)</td>
<td>0.44</td>
</tr>
</tbody>
</table>
The standard scores are presented in Figure 11. The dominating pattern was a worsening of performance in the second half of the test, commonly a failing to react to correct stimuli (omission errors).

![Figure 11](image)

Figure 11. The response time, response time variability, commission errors, and omission errors reported in standard scores of all 19 patients. Standard scores <80 (grid line) are considered pathological.

The patients with pathological T.O.V.A. scored lower on the fatigue scale compared to those with normal T.O.V.A. (mean 44 and 64, respectively; p=0.01). There were no differences in the concentration and attention domains of MADRS or MoCA when comparing patients with normal T.O.V.A. to those with pathological (p=0.21 and p=0.49, respectively).
Discussion

Spasticity

As mentioned in the methods-section, a difficulty with spasticity is how to define and measure this phenomenon. In order to compare our results with other studies we used the MAS and defined spasticity as a MAS score of 1 or more, which is the most commonly used definition in stroke studies.

There are 2 previous studies on spasticity after SAH. Blicher and Nielsen\textsuperscript{233}, investigated 42 patients with subarachnoid hemorrhage in Denmark defining spasticity by clinical signs found in the physical examination by the therapist, and/or if the patient received medical treatment for spasticity. Forty percent of the patients had spasticity one year after ictus. Singer et al.\textsuperscript{234} in Australia, used the Ashworth scale\textsuperscript{131} to define spasticity in patients with acquired brain injuries (SAH, n=25; traumatic causes, n=63; and other, n=17). After 20 weeks, 13% were predominantly spastic in this mixed sample. These two studies had patients that were selected to represent severe injuries with admission GCS less than 10 and 12, respectively. In our study, no such exclusion was done, we defined spasticity using the MAS, and we investigated SAH patients that were consecutively included.

The prevalence of spasticity found in our study on patients with SAH is similar to most studies on patients with cerebral ischemia and/or intracerebral hemorrhage, showing prevalence between 17-22\textsuperscript{18,218-221,225}. Some studies report higher prevalence, up to 43\%\textsuperscript{222,223}, which may be due to differences in inclusion criteria or in the method of assessing spasticity. For example, Urban et al.\textsuperscript{222} only included patients with central paresis, and Watkins et al.\textsuperscript{223} used a slightly different definition of spasticity that combined the MAS and the tone assessment scale.

Our results indicate that high MAS-scores in patients with SAH are rare. This may explain why only one patient had received pharmacological treatment. Other explanations to the low number of treated patients could be the unawareness of problems associated with spasticity among healthcare personnel or the side effects of oral anti-spastic drugs.

Risk factors for spasticity

Although SAH is a hemorrhagic event, much of the pathophysiology is based on a number of ischemic events. At the rupture of the aneurysm there is often a transient global brain ischemia due to the high intracranial pres-
sure. This is followed, after some days, by the development of vasospasm, which can lead to hypoperfusion and brain ischemia. Infections increase the metabolism and frequently result in fever, which is one of the secondary insults of the neurointensive care unit’s care targets.

In our sample, we found that vasospasm and infections were independent predictors of spasticity. These are factors that compromise substrate delivery and could increase the metabolic demand on the brain. This supports the theory that ischemia is an important factor in the development of spasticity. In our study, however, CT verified brain ischemia was marginally not significant in the simple regression analysis. The reason for this may be that CT is too crude of a method to adequately quantify ischemia, especially in the acute and sub acute phase. MRI would provide more reliable information, and should be used in further studies to identify risk factors in the acute phase for the development of spasticity.

Another factor that may be associated with spasticity in the rehabilitation phase is spasticity in the acute phase. Spasticity was, in fact, measured at inclusion but the data was not considered reliable; a temporary reduction in the medications and removal of intubation would have enabled a more reliable assessment. Future research may assess spasticity already at the emergency unit, which may give a more reliable assessment than our assessment at the neurointensive care unit.

Using neuropsychological assessment scales

Patients having survived SAH may have challenges that can be looked upon from different neuropsychological angles, e.g. a patient may describe difficulties shopping clothes in a store, which is a difficulty that is often described by patients with depression, but also by patients with cognitive impairment or attention deficits. Another problem in the evaluation of a patient’s neuropsychological symptoms is that the assessment scales used to evaluate these symptoms may be overlapping, e.g. concentration difficulties can be looked upon as a depressive symptom yielding scores on MADRS, but also as an expression of an attention deficit measurable in T.O.V.A., or as a cognitive impairment yielding scores on the attention domain at MoCA. This raises the question: What are we really measuring?

Most neuropsychological assessment scales used in SAH patients have not been developed for this specific patient category, e.g. MADRS was developed to be sensitive to treatment effects with focus on patients with depression, MoCA was developed as a screening tool for mild cognitive impairment with focus on Alzheimer’s disease, and T.O.V.A. was developed with focus on attention deficit hyperactivity disorder (ADHD).

An assessment scale can be of great use when there is a strict cut-off defining which patients that benefit from a specific treatment. When it comes
to SAH patients, however, there are a few problems with this approach. Firstly, cut-offs are not usually based on SAH patients but on other patient categories. Secondly, relevant cut-offs may be different between geographical regions. Thirdly, there is usually no treatment to be used against the neuropsychological challenges often experienced by SAH patients. These problems limit the use of assessment scales for neuropsychological challenges after SAH.

There are, however, times when a neuropsychological assessment scale can be useful. If a patient scores well on a scale, this may be interpreted as an absence of treatable symptoms, e.g. a patient scoring 0 at MADRS would probably not benefit from anti-depressive treatment. Also, when dealing with practical problems, such as trouble returning to work, taking care of children, or not being able to drive, neuropsychological assessment scales can be useful in contact with social insurances, when discussing preschool hours, and in the communication with transport administration. Assessment scales can also be useful when allocating money between patient categories and in the comparison of different patient categories.

Oftentimes a poor outcome on an assessment scale can be difficult to interpret. In these cases it may be valuable to investigate the results of each query separately in order to correctly characterize the patient’s symptoms. In other cases, the result of the whole test can be more valuable in a clinical situation. But in some cases, a poor result on a neuropsychological assessment scale does only give a vague description of a patient’s complex symptomatology and the result should be looked upon as a rough measurement of the patient’s general status.

Cognitive impairment

Comparison of cognitive functions to other studies

We wanted to compare our results on the MoCA to what is expected in the general population\textsuperscript{146, 235-238}. Unfortunately, there is no Swedish study with normative data. The normative study with the ethnically and culturally most similar population is from Ireland\textsuperscript{236} and our SAH patients scored 2.0 points lower than this normative population.

In an attempt to compare our results to other SAH studies, we used the cut-off for cognitive impairment of <26 suggested by Nasreddine\textsuperscript{146}. This cut-off is based on only 90 healthy Canadian controls with a high mean age of 73 years, and there is a need for caution when applying the proposed cut-off in lower education or ethnically diverse samples\textsuperscript{239}. Approximately half of our patients scored <26 on MoCA, 52%, which is in the same range as Schweizer et al.\textsuperscript{144} finding 42% scoring <26 in their cohort of younger, more well-educated SAH patients with good recovery assessed more than 6
months after ictus. Wong et al.\textsuperscript{148} presented the highest percentage of patients scoring <26 on MoCA, 73\%. However, they assessed MoCA already at 3 months after ictus. This implies that the MoCA score could improve with time passed after ictus, which is in line with the previously showed increase of cognitive functions that can be observed over time\textsuperscript{140, 141}. This indicates that the statistical measures of the performance of MoCA in predicting return to work presented in Paper II should be used cautiously if applied at other follow-up times than 6 months after ictus.

The most frequently missed domain was the delayed recall. This is consistent with the literature of SAH\textsuperscript{183, 185} as well as normative studies\textsuperscript{237}.

**Predicting cognitive impairment**

Our results, with high age and brain ischemia independently predicting cognitive impairment, are in line with previous research\textsuperscript{148, 240-242}. In our patient material there was, however, a correlation between age and education with lower education level in higher ages (p=0.002). Education level is therefore a confounding factor difficult to account for since it affects both the MoCA score (1 additional point for \(\leq 12\) years of education) and is correlated with age.

**Cognitive testing as a predictor of future work status**

The convalescence after SAH is usually a long period during which the patients gradually recovers. Many suffer from neurological deficits of various extents. It is an open question when outcome best can be assessed and this probably depends on what outcome variable that is interesting. Factors describing the severity of the acute disease have been demonstrated to predict if the patient will return to an independent life or not. However, these factors are usually not possible to influence, e.g., age, clinical condition at admission, and the extent of the hemorrhage. When studying return to work, we found it more adequate to measure a parameter that also gives information that could be used in the rehabilitation process. The timing of this should be careful so that the patients have a fair chance for basic recovery first. We chose to measure the patients’ cognitive status, using MoCA, at 6 months after SAH. This is in our experience a time point when many functions have improved but most patients have not returned to work due to remaining problems. In other words, at this time point, probably a lot more could be done in order to help patients return to work.

Returning to work is a major issue for SAH patients\textsuperscript{198} and is of economic interest for both patients and society\textsuperscript{124}. Attempts so far to predict future work status using clinical factors have had limited success\textsuperscript{243, 244}. Harris et al.\textsuperscript{125} included demographic variables, clinical variables, and variables from telephone interviews in a logistic regression model and showed that the model correctly predicted 67\% of the outcomes for return to work. In Paper II, by only using the MoCA, 68\% of the patients could be correctly predict-
Very little predictive power was gained by including clinical and demographic features. Therefore we believe that cognitive testing is a promising approach when predicting return to work. The threshold of <27 was selected on the basis of the current patient group, so results on other groups may not be as good. On the other hand, this same threshold has been used elsewhere in the literature as a marker of cognitive dysfunction. Although the MoCA is a well-validated method for assessing cognitive functions, seven of the 24 patients with MoCA ≥27 did not return to work. This indicates that returning to work does not solely depend on cognitive performance and that other factors must be considered. For example, many patients suffer from mood and posttraumatic stress disorders that can interfere with work. Nine of the 26 patients with MoCA <27 actually did work after 12 months. A factor that should be considered in these cases is that the work situation can sometimes be adapted to reduced performance, allowing people to return to work in spite of cognitive impairments and other problems after their SAH. Probably the classification failures in this study reflect the fact that this is a multifactorial problem.

Attention deficits
This paper is published as a brief report. The pattern of poor performance in the second half of the T.O.V.A. test, when there were frequent targets, brings up the question whether the patients fatigued, had trouble working under pressure, or both. The patients with pathological T.O.V.A. expressed more problems with fatigue, indicating that fatigue would be associated with attention deficits. Paper IV also raises the question whether infection in the acute phase affects attention after SAH.

The T.O.V.A. results were not correlated to the concentration and attention domains in MADRS or MoCA. One explanation is that continuous performance tests are qualitatively and technically different from examiner-administered instruments. Also, MADRS and MoCA are instruments originally designed for assessing depressive symptoms and cognitive functions, respectively. It could therefore be difficult to compare the 3 methods, as they do not seem to measure the same expression of attention deficits.

Living conditions
Being able to return home after SAH is essential and Paper III showed that a majority of the patients, 91%, were living at home 6 months after ictus. Furthermore, 78% of the patients with moderate to severe outcome had been able to return home. This shows that challenges after SAH are often dealt with in the patients’ home environment.
The high proportion of patients living in own accommodations is reflected in the support and help provided by the municipality. Day-care rehabilitation, home-help services and home rehabilitation were commonly utilized. Nonetheless, 41% felt their requirements for support or help had not been completely fulfilled. This may put a large burden upon family members or friends. In the present study, 55% of the patients were dependent upon family or friends. This indicates that the patients’ families have a central role during the rehabilitation phase, which may have implications when planning rehabilitation.

Follow-up appointments

The patients having received a follow-up appointment were more often living with a partner compared to those not having had a follow-up appointment. It seems possible that living with someone increases the chance that the patient receives a follow-up appointment. Being younger also increased the chance that the patient would receive a follow-up appointment. There may, however, be a covariation between age and civil status but a sub-analysis was not performed due to the limited number of patients living alone. The initiative to seek help may also come from colleagues or be a part of a sick leave investigation.

Apart from being older and more often living alone, those not having had a follow-up appointment had lower quality of life, more depressive symptoms and more cognitive impairments. This shows that follow-up appointments are not prioritized towards those with the poorest outcome, which reveals a shortcoming in the follow-up procedure of SAH patients where the patients with the most serious symptoms are not the ones being followed-up. It cannot be expected of those to initiate the rehabilitation process themselves. The initiative to make such contact should lie upon the healthcare provider. Therefore, this study suggests that in order to find and treat the patients with the poorest outcome in terms of quality of life, depression, and cognitive impairment, routine follow-up appointments of all patients is motivated during the first 6 months after ictus.

Primary care

Since >90% of the patients in Paper III lived at home after 6 months it seems important to early involve the primary care. Many medical issues often faced by patients after SAH, e.g. depression, sleep disturbances, treatment of vascular risk factors etc., are issues commonly treated by general practitioners. Such issues are preferentially dealt with in primary care and for the general practitioner to get a comprehensive view of a patient it is important that
medical issues are treated by the physician most suited to that end. The primary health care also has an important role together with the municipality in assisting the patients to find his/her way back to a normal life after the SAH.

In order for primary care to establish early contact with the patients after discharge it is essential for primary care to be notified when a patient is discharged from hospital after SAH. As this study showed that the patients with the most serious symptoms are not the ones being followed-up, such notification should also include a request for the general practitioner to arrange a first meeting with the patient at the health center. Some of the patients’ challenges may, however, be of neurosurgical nature and the general practitioners should have easily accessible specialist support regarding individual patient matters, and information on how contact could be established between the general practitioner and the responsible neurosurgeon should be included in the notification sent from the neurosurgical apartment in connection to discharge. In order to improve treatment after the acute phase of SAH it is essential that neurointensive care units routinely notify primary care when a SAH patient is discharged and that appropriate information is included in such notification.

One strategy to improve SAH rehabilitation would be to implement a method for structured functional assessment in general practice, assessing the multitude of physical and cognitive impairments experienced by many of those surviving a SAH. Such assessments have shown to change GPs sick-listing practices. Changing GPs behavior may be important, as 60% of SAH patients do not believe their GP knows sufficiently about SAH to deal with their care. Assessments using a multidisciplinary approach has been suggested though it is uncertain whether multidisciplinary care involving GPs improves outcome in patients with completed stroke. A more wide ranging approach is an organized multidisciplinary outpatient clinic after discharge dedicated to patients and their proxies in which patients are seen 6 weeks after discharge by a neuropsychological assistant, a stroke nurse, and a rehabilitation physician. The outpatient clinic approach does, however, overlook the facts that patients may have difficulties travelling to such clinic and that it is not designed to manage the long-lasting and chronic challenges often met by the patients. The GP is ideally placed to meet the patients’ community-based psychosocial needs and has the advantage of supporting patients over time.

Having personnel that are specialized in treating SAH patients after the acute phase working in primary care could have use of the advantages of the primary care setting and would also provide the specialist knowledge required for dealing with patients’ often complex symptomatology. A pilot project providing a specialist liaison nurse providing a link between neurosurgery and the community showed significant reductions in time off work and the project was clinically and fiscally cost-effective. However, a study
with a randomized design aiming at evaluating the use of liaison personnel in the primary care setting is still lacking.

Limitations

The MAS assessment was performed by more than one person, which may have influenced the results, since the inter-rater and intra-rater reliability of the MAS have been discussed\textsuperscript{133}. Physiotherapy given to the patients was not studied. This would have been of interest since the treatment of spasticity is primarily physical and pharmacological treatment should be considered as a supplement\textsuperscript{250}. In future research, MRI should be used to quantify ischemia in the acute phase. The results about follow-up visits rely on the patients’ answers and adding data from medical records could have changed the description of the follow-up process as some patients may have declined a follow-up appointment. The T.O.V.A. study is a pilot study on a selected group of patients that were not consecutively included, and a larger study including a more general SAH population would provide results more representative of SAH patients. A disadvantage using the auditory T.O.V.A. is that its normative data has only been normed in children.
Conclusions

Spasticity after SAH occurred with the same prevalence as after other stroke. Risk factors for spasticity were worse clinical condition at admission and the occurrence of infection and vasospasm during the intensive care period. Estimating cognitive functions at 6 months after SAH using the MoCA allowed us to predict return to work correctly in 68% of the cases; adding data from the acute phase resulted in marginal improvement of the prediction. Follow-up appointments after SAH seem not to be targeted towards those with the poorest outcome. Challenges after SAH are often dealt with in the patients’ home environment. Attention deficits, measured by the T.O.V.A., were common after SAH.
Summary in Swedish - Sammanfattning på svenska

Aneurysmal subarakanoidalblödning (SAH) är en allvarlig stroke som drabbar unga människor mitt i livet. Med modern neurokirurgisk intensivvård kan man idag rädda flesta av patienterna, men bland de som överlever är det tyvärr vanligt med bestående hjärnskador. Denna avhandling belyser de utmaningar som patienterna ofta ställs inför efter utskrivning från sjukhuset.


I det andra delarbetet (Paper II) användes ett kognitivt test där patienterna bland annat fick räkna, komma ihåg ord och rita en tredimensionell figur. Med hjälp av testet gick det att i 68 % av fallen korrekt förutsäga vilka av patienterna som senare återgick i arbete.

Det tredje delarbetet (Paper III) visar att 83 % av patienterna hade haft ett uppföljande besök efter utskrivning. Dock hade endast 20 % av patienterna följts upp i primärvården. De patienter som inte hade haft ett uppföljande besök hade mer kognitiva och depressiva problem och hade lägre livskvalitet. En viktig slutsats är att utan rutinmässig uppföljning av samtliga patienter riskerar de med störst besvär att inte bli uppföljda.


Resultaten från denna avhandling ger en deskriptiv bild av den komplexa symptomatologi som patienter ofta upplever efter SAH. Slutsatserna tyder på en möjlighet till förbättrad rehabilitering och att SAH här har lyfts fram ur ett allmänläkarperspektiv kommer förhoppningsvis att leda till bättre uppföljningsmöjligheter. Studierna lågger också grunden för förnyad forskning, varav det fjärde delarbetet redan lett till en större studie om uppmärksamhetsstörningar efter SAH.
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Appendix

MoCA

English Original and Swedish version of MoCA published with permission from MoCA Institut & Clinique, September 1, 2016, Kathleen Gallant.
EQ-5D

EQ-5D-3L\textsuperscript{176} Swedish version published with permission from EuroQol Research Foundation, September 2, 2016, Bianca Smit.

Hälsoenkät

Svensk version för Sverige

(Swedish version for Sweden)
Markera, genom att kryssa i en ruta i varje nedanstående grupp (så här ☑), vilket påstående som bäst beskriver Ditt hälsotillsstånd i dag.

**Rörlighet**
- Jag går utan svårigheter ☐
- Jag kan gå men med viss svårighet ☐
- Jag är sängliggande ☐

**Hygien**
- Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädningsdrift ☐
- Jag har vissa problem att tvätta eller klä mig själv ☐
- Jag kan inte tvätta eller klä mig själv ☐

**Huvudsakliga aktiviteter** (t.ex. arbete, studier, hushållssysslor, familje- och insatsaktiviteter)
- Jag klarar av mina huvudsakliga aktiviteter ☐
- Jag har vissa problem med att klara av mina huvudsakliga aktiviteter ☐
- Jag klarar inte av mina huvudsakliga aktiviteter ☐

**Smärtor / besvär**
- Jag har varken smärtor eller besvär ☐
- Jag har mättliga smärtor eller besvär ☐
- Jag har svåra smärtor eller besvär ☐

**Oro / nedstämdhet**
- Jag är inte orolig eller nedstämd ☐
- Jag är orolig eller nedstämd i viss utsträckning ☐
- Jag är i högsta grad orolig eller nedstämd ☐
Till hjälp för att avgöra hur bra eller dåligt ett hälsotillstånd är, finns den termometer-liknande skalan till höger. På denna har Ditt bästa tänkbara hälsotillstånd markerats med 100 och Ditt sämsta tänkbara hälsotillstånd med 0.

Vi vill att Du på denna skala markerar hur bra eller dåligt Ditt hälsotillstånd är, som Du själv bedömer det. Gör detta genom att dra en linje från nedanstående ruta till den punkt på skalan som markerar hur bra eller dåligt Ditt nuvarande hälsotillstånd är.
MADRS

English version of MADRS\textsuperscript{16} published with permission from The Royal College of Psychiatrists, September 6, 2016, Lucy Alexander.

© 1979 The Royal College of Psychiatrists. Montgomery, S.A. & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. \textit{British Journal of Psychiatry}, \textbf{134}, 382-389. Written permission must be obtained from the Royal College of Psychiatrists for copying and distribution to others or for republication (in print, online or by any other medium).

1. Apparent Sadness
Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

2. Reported sadness
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.
3. **Inner tension**
Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.
   - 0 Placid. Only fleeting inner tension.
   - 1 Occasional feelings of edginess and ill-defined discomfort.
   - 2 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
   - 3 Unrelenting dread or anguish. Overwhelming panic.

4. **Reduced sleep**
Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.
   - 0 Sleeps as usual.
   - 1 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
   - 2 Sleep reduced or broken by at least two hours.
   - 3 Less than two or three hours of sleep

5. **Reduced appetite**
Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.
   - 0 Normal or increased appetite.
   - 1 Slightly reduced appetite.
   - 2 No appetite. Food is tasteless.
   - 3 Needs persuasion to eat at all.
6. Concentration difficulties
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty.

7. Lassitude
Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. Inability to feel
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.
9. **Pessimistic thoughts**
Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.
1 2 Fluctuating ideas of failure, self-reproach or self depreciation.
3 4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5 6 Delusions of ruin, remorse or unredeemable sin. Self-accusation which are absurd and unshakable.

10. **Suicidal thoughts**
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.
1 2 Weary of life. Only fleeting suicidal thoughts.
3 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.
References


23. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: A systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78:1365-1372


neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366:809-817


48. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: A meta-analysis. Lancet Neurol. 2009;8:635-642


68. Claveau D, Dankoff J. Is lumbar puncture still needed in suspected subarachnoid hemorrhage after a negative head computed tomographic scan? Cjem. 2014;16:226-228


90. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2:200-215
95. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke. 1994;25:1342-1347


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181. Hutter BO, Gilsbach JM. Which neuropsychological deficits are hidden behind a good outcome (glasgow = i) after aneurysmal subarachnoid hemorrhage? *Neurosurgery*. 1993;33:999-1005; discussion 1005-1006


191. Greenberg LM. The test of variables of attention (version 8.0) (computer software). 2011


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