Subarachnoid Hemorrhage in the Elderly

MATS RYTTLEFORS
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Abstract

Subarachnoid hemorrhage (SAH) is a disease with high risk of mortality and morbidity. Elderly patients have an even higher risk of poor outcome. The incidence of SAH increases with age and the elderly constitute a substantial and increasing proportion of the population. Thus, the management of elderly SAH patients is an imminent clinical challenge. Time trends in clinical management and outcome were investigated in 281 SAH patients aged ≥65 years admitted over an 18-year period. The volume of elderly patients, especially patients ≥70 years and patients in worse clinical condition increased over time. The proportion of patients with favorable outcome increased over time, without an increase in severely disabled patients. Technical results and clinical outcome of endovascular aneurysm treatment (EVT) was investigated in 62 elderly SAH patients. EVT can be performed in elderly SAH patients with high technical success, acceptable aneurysm occlusion degree, acceptable procedural complication rate, and fair outcome results. EVT was compared to neurosurgical clipping (NST) in 278 elderly SAH patients in the International Subarachnoid Aneurysm Trial. In good grade elderly SAH patients, EVT should probably be the favored treatment for internal carotid and posterior communicating artery aneurysms, while elderly patients with middle cerebral artery aneurysms appear to benefit from NST. Occurrence of secondary insults and their impact on clinical deterioration were studied in 99 patients with severe SAH. High intracranial pressure increased and high cerebral perfusion pressure decreased the risk of clinical deterioration. Elderly patients had less intracranial hypertension insults and more hypertensive, hypotensive and hypoxemic insults. Good outcome was achieved in 24% of elderly patients with severe SAH, and the proportion of severe disability was similar to that of younger patients. Patient age was not a significant predictor for vasospasm in 413 SAH patients when admission and treatment variables were adjusted for with multiple logistic regression.

Keywords: subarachnoid hemorrhage, intracranial aneurysm, elderly, outcome, endovascular coiling, neurosurgical clipping, secondary insult, cerebral vasospasm

Mats Ryttefors, Department of Neuroscience, Box 593, Uppsala University, SE-75124 Uppsala, Sweden

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List of papers

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I Changes in intervention and outcome in elderly patients with subarachnoid hemorrhage
Johansson, M.*, Cesarini, K.G., Contant, C.F., Persson, L., Enblad, P.
Stroke 2001;32(12):2845-2849

II Clinical outcome after endovascular coil embolization in elderly patients with subarachnoid hemorrhage
Johansson, M.*, Norbäck, O., Gál, G., Cesarini, K.G., Tovi, M., Solander, S., Contant, C. F., Ronne-Engström, E., Enblad, P.
Neuroradiology 2004;46(5):385-391

III International Subarachnoid Aneurysm Trial of neurosurgical clipping versus endovascular coiling: subgroup analysis of 278 elderly patients
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IV Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration
Ryttlefors, M., Howells, T., Nilsson, P., Ronne-Engström, E., Enblad, P.

V Neurointensive care is justified in elderly patients with severe subarachnoid hemorrhage: an outcome and secondary insults study
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VI Patient age and vasospasm after subarachnoid hemorrhage
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Abbreviations

ACA  Anterior cerebral artery
AComA  Anterior communicating artery
BPs  Systolic blood pressure
CBF  Cerebral blood flow
CI  Confidence interval
CPP  Cerebral perfusion pressure
CSF  Cerebrospinal fluid
CT  Computed tomography
CTA  Computed tomography angiography
DIND  Delayed ischemic neurological deficit
DSA  Digital subtraction angiography
EVT  Endovascular aneurysm treatment
GCS  Glasgow Coma Scale
GOS  Glasgow Outcome Scale
H&H  Hunt and Hess grade
ICA  Internal carotid artery
ICH  Intracerebral hematoma
ICP  Intracranial pressure
ISAT  International Subarachnoid Aneurysm Trial
IVH  Intraventricular hemorrhage
MAP  Mean arterial pressure
MCA  Middle cerebral artery
OR  Odds ratio
PComA  Posterior communicating artery
SAH  Subarachnoid hemorrhage
SDH  Subdural hematoma
SpO2  Arterial oxygen saturation
T°  Body temperature
TCD  Transcranial Doppler
WFNS  World Federation of Neurological Surgeons
Introduction

During the last century the population structure in Sweden has changed due to lowered mortality and lowered nativity, altering the shape of the “population pyramid”. The elderly now constitute a substantial proportion of the population. In Sweden today, 17% of the population is 65 years or older \(^1\). The improvement in the general health of the population has not only been evident in the longer life expectancies. Also the elderly are healthier and have more active life-styles today than before \(^2\). This has increased the possibilities and the expectations to treat serious and life threatening diseases in higher and higher age groups.

Subarachnoid hemorrhage (SAH) is a devastating disease with a high risk of mortality and morbidity \(^3\). The incidence of SAH increases with age \(^4, 5\), and along with the increasing elderly population, the number of elderly patients with SAH is increasing substantially. Only a few decades ago elderly SAH patients rarely received active treatment because of the poor outcome results \(^6-8\). Today a more active approach in the treatment of SAH is used also in the elderly. However, special considerations must be made in the management of the elderly SAH patients:

The frequency of concurrent diseases increases with age \(^9\). Along with age-related decline in muscle mass and in cardiovascular \(^10\), respiratory \(^11\) and renal function \(^12\), elderly patients are more prone to develop organ dysfunction and are more vulnerable for complications. Furthermore, the elderly are less amenable to rehabilitation efforts after brain injury.

In order to meet the imminent challenge of managing the increasing number of elderly SAH patients in the future, it is urgent to increase the knowledge of different aspects of SAH specifically in the elderly.
Background

General review of subarachnoid hemorrhage

History
In the eighteenth century, Morgagni (1761) and Biumi (1765) published the first descriptions of intracranial aneurysms. In 1813, Blackall described the clinical presentation and the corresponding autopsy findings of a ruptured intracranial aneurysm in a young woman. William Gull described the typical sudden severe headache as the presenting sign of SAH in 1859. In 1875, Hutchinson described the clinical appearance of an internal carotid artery aneurysm with palsy of third and sixth cranial nerves and proposed carotid ligation as treatment. Cooper performed the first premeditated carotid ligation in 1805 and this technique became widely practiced during the nineteenth century. Proximal artery ligation techniques with clamps were further developed by Dott, Selverstone, Poppen, Crutchfield and Logue. Later, direct surgical attack of the ruptured aneurysm replaced the proximal occlusion techniques. The technical development of cerebral angiography in the end of the 1920ies by Egas Moniz was important for the pre-operative diagnosis of intracranial aneurysms and operative planning. Dott conducted the first planned direct surgical attack of an intracranial aneurysm in 1931. He packed muscle against a carotid bifurcation aneurysm, which ruptured intra-operatively, and managed to stop the bleeding and the patient made an excellent recovery and had no further hemorrhages. In 1937, Dandy clipped the neck of a preoperatively diagnosed aneurysm using a metal clip. Hemostatic silver clips were introduced already by Cushing in 1911, but they were not suitable for aneurysms. Spring clips were developed by Schwartz and Mayfield to be appropriate for aneurysm surgery. An important contribution to the management of SAH patients was the invention of the intraventricular catheter for continuous intracranial pressure monitoring by Nils Lundberg. The introduction of the operating microscope in neurosurgery by Jacobson was the advent of microneurosurgery. The field of microneurosurgical treatment of anterior and posterior circulation aneurysms was developed by Yasargil and Drake.
Cause

Approximately 85% of all spontaneous SAH are caused by the rupture of an intracranial saccular aneurysm located on one of the basal cerebral vessels near the circle of Willis. 10% of spontaneous SAH are non-aneurysmal perimesencephalic hemorrhages with excellent prognosis. The remaining 5% are caused by a number of rare conditions such as arterial dissection, cerebral arteriovenous malformations, dural arteriovenous fistulas, septic aneurysms, vascular lesions around the spinal cord, pituitary apoplexy, cocaine abuse and trauma.

There is no clearly defined theory on the formation of intracranial aneurysms and their pathogenesis is still debated. It is likely that the pathogenesis is multifactorial, involving hemodynamic stress, structural alterations in cerebral arteries, and genetic and environmental factors. It was early thought that intracranial aneurysms were congenital, or that congenital defects in the tunica media of the arterial wall was a prerequisite for aneurysm formation. Others emphasized acquired changes to the internal elastic lamina to be the key factor for aneurysm formation. However, the most plausible explanation is that intracranial aneurysms are formed during life due to degenerative changes in the cerebral arterial wall subjected to hemodynamic stress caused by the pulsating blood stream at the relatively unsupported arterial divisions.

Evidence also supports a role of genetic factors involved in the formation of intracranial aneurysms. Numerous inherited connective tissue diseases have an increased prevalence of intracranial aneurysms and an increased risk of SAH, the most important being autosomal dominant polycystic kidney disease, Ehler-Danlos Syndrome type IV, Marfan’s syndrome and neurofibromatosis type I. Several studies have also shown an increased risk for intracranial aneurysms and SAH in relatives of SAH patients. The inheritance pattern of familial intracranial aneurysms is not uniform. In a Finnish study on 346 families with intracranial aneurysms, the inheritance pattern was autosomal recessive in 57%, autosomal dominant in 36%, autosomal dominant with incomplete penetrance in 5.5% and in 0.9% no known pattern of inheritance could be elucidated. This implies that also other factors are involved in the formation of intracranial aneurysms.

The most important modifiable risk factors for SAH consistent in several studies and meta-analyses are cigarette smoking, hypertension, excessive alcohol consumption, and oral contraceptives. Some studies have also implicated low body mass index, serum cholesterol levels, and coffee consumption more than 5 cups a day to be a risk factor for SAH. In a systematic review, hormone replacement therapy, hypercholesterolemia and diabetes appeared to be risk-reducing factors while the use of oral contraceptives did not influence the risk of SAH and data was inconsistent with level of physical activity and body mass index.
Epidemiology

The prevalence of intracranial aneurysms in the population is estimated to 2.3%, but vary widely depending on the study design: 0.4% in retrospective autopsy studies to 6.0% in prospective angiography studies. The average risk of rupture of a previously unruptured aneurysm is 0.6–1.3% per year. Factors associated with increased risk of aneurysm rupture include patients >60 years, female gender, smoking, aneurysm size >5 mm, posterior circulation aneurysm and Finnish and Japanese descent.

The incidence of SAH is approximately 9/100000 person-years, but varies widely depending on region, gender and age. The incidence rates in Japan and Finland are much higher than in other parts of the world, whereas South and Central America have lower incidence rates. In Sweden, the overall incidence of SAH is 12.4/100000 person-years, and increases with latitude, from 11.4/100000 person-years in the southern region, over 12.8/100000 person-years in the central region to 15.2/100000 person-years in the northern region. Similar incidence rates of SAH in Sweden have previously been reported.

Women have a higher relative risk for SAH than men do overall. However, the gender difference is age-dependent. Before the age of 55 the incidence is higher in men then in women, but in the age group 55–85 years the incidence is significantly higher in women than in men. The incidence of SAH increases with advancing age, but levels off at 60 years in men and at 70 years in women.

Symptoms and diagnosis

The presenting sign of SAH is sudden severe headache, typically described as “worst-ever” or “explosive”, which develops over seconds rather than minutes, often accompanied with nausea and vomiting. A period of altered consciousness or prolonged unconsciousness occurs in over half of the cases, and focal neurological signs may develop at the time of ictus or shortly thereafter. In the following hours neck stiffness, neck pain, low-grade fever and photophobia may develop.

Computed tomography (CT) reveals the characteristically hyperdense appearance of extravasated blood in the basal cisterns, Sylvian fissures and/or the sulci over the brain convexities. If the history is strongly suggestive of SAH, but CT scanning does not reveal any subarachnoid blood, lumbar puncture should be undertaken before ruling out SAH. The hemoglobin in the red blood cell is degraded to oxyhemoglobin and bilirubin, which gives the typical yellow tinge (xanthochromia) to the cerebrospinal fluid (CSF) after centrifugation. On spectrophotometry absorbance is increased at 415 nm (oxyhemoglobin) and 455 nm (bilirubin). It is essential to wait at least 6 and preferably 12
hours after ictus before performing the lumbar puncture to allow for sufficient red blood cell lysis and formation of oxyhemoglobin and bilirubin. The first-hand method for diagnosis of intracranial aneurysms is, nowadays, computed tomography angiography (CTA), which reveals most intracranial aneurysms, but the sensitivity for small aneurysms is limited. If CTA does not disclose an aneurysm but the SAH is highly suggestive of an intracranial aneurysm, a digital subtraction angiography (DSA) is performed. DSA has a higher sensitivity in detecting an intracranial aneurysm and is considered the gold standard for this purpose, but has a higher risk of complications than CTA due to its invasive nature.

Natural course and overall clinical outcome

SAH from a ruptured intracranial aneurysm is a devastating disease. Although it constitutes only approximately 3% of all strokes, it accounts for 5% of stroke deaths and nearly one third of potential life years lost through stroke.

The mortality rate was 60% at 6 months following SAH in a community-based study, and in an early study of the natural history of SAH, the mortality rate was 61% at 6 months after SAH of the conservatively treated patients. In a hospital-based study where patients were randomly allocated to conservative treatment 42% were deceased at 6 months.

Population-based studies generally reports higher case fatality rates than hospital-based studies or surgical series, because also patients never reaching hospital or are dead on admission and patients in such poor clinical grade that active treatment is not deemed feasible are included. 12–17% of all SAH patients die before reaching hospital and 20% are in too poor clinical condition for surgical treatment.

A prospective randomized trial in the late 1950ies showed that surgical aneurysm treatment could alter the natural course of the disease in some circumstances (depending on the aneurysm location). Since then the case fatality rates have improved, due to advances in management and treatment, but are still high. In a meta-analysis of 21 studies from 1960 to 1992 the case fatality rates ranged between 32–67% and the case fatality rates had improved by 15% over these 30 years. The overall case fatality rate of SAH at 28 days was 32% in a study covering all cases of SAH in Sweden during 1987–2002. The case fatality rate increased steeply with age, reaching 70% at 1 year in patients 80 years or older.

In a longitudinal study from our department, improved overall management results over time were demonstrated when a management policy of early referral, modern neurointensive care protocol and early surgery in good grade patients was adopted. Overall mortality was reduced from 34% to 15% and the proportion of favorable outcome increased from 58% to 66%.
The major causes of death and disability after SAH can be attributed to the primary cerebral injury caused by the initial rupture, re-bleeding of the aneurysm and cerebral vasospasm 76-78.

Primary brain injury

The aneurysm rupture causes a dramatic rise in intracranial pressure (ICP) that may reach the level of mean arterial pressure (MAP) causing an arrest in the global cerebral circulation for a period of seconds to minutes, and the bleeding ceases 79-81. Intracranial compensatory mechanisms (movement of CSF to the spinal canal) decrease the ICP allowing the blood circulation to return to the brain. The transient cerebral circulatory arrest causes a global ischemia of varying degree and seems to put the brain in a vulnerable state more susceptible to further ischemic events. The aneurysm rupture can cause intracerebral hematoma (ICH) and/or intraventricular hemorrhage (IVH) in addition to the SAH if the jet from the aneurysm is pointed towards the brain parenchyma and/or ventricles. The resulting neuronal damage in the brain at the site of the hemorrhage is instant and irreversible. The irreversible ischemic and hemorrhagic injury to the brain sustained, or at least initiated, at the time of aneurysm rupture is defined as the primary brain injury. The duration of the initial unconsciousness and the neurological condition of the patient at the time of admission reflect the severity of the primary brain injury.

It has been estimated that 60% of the mortality and morbidity could be ascribed to the primary aneurysmal rupture, while the remaining 40% could be ascribed to potentially avoidable causes of unfavorable outcome, such as re-bleeding and ischemia, causing secondary injury 82.

Re-bleeding

After the initial rupture of an intracranial aneurysm a plug of fibrin and platelets seals the rupture site and the bleeding ceases. However, this seal is unstable and lysis of the clot results in subsequent bleeding from the aneurysm. Re-bleeding is suspected when a SAH patient experience an additional episode of sudden headache, loss of consciousness, sudden deterioration of reaction level or a sudden increase in ICP. It is a major cause of secondary brain damage in SAH patients and is a considerable contributor to the total death and disability 76-78, 82-87.

The peak incidence of re-bleeding occurs on the same day as the initial bleed, the risk being highest within hours from the initial bleed and then declines over the next few days and weeks 88. The risk of re-bleeding within 24 hours from the initial rupture is 9.6–17.3% 82, 89, 90, with approximately 90% of the re-bleedings occurring within 6 hours 89, 90. The cumulative risk of re-bleeding within 4 weeks is between 22–42% 68, 83, 91. In one study the
re-bleeding was fatal in approximately 50% of the patients and another 30% who re-bled died within 3 months. The risk of re-bleeding is increased in patients with poor neurological grade on admission, hypertension, greater aneurysm diameter, and associated findings such as ICH and IVH on the diagnostic CT. The risk of further re-bleeding is significantly increased in survivors of a first re-bleed.

The dissolution of the clot at the site of the ruptured aneurysm probably results from fibrinolytic activity in the CSF after SAH. In order to reduce the incidence of re-bleeds, treatment protocols using antifibrinolytic therapy, such as tranexamic acid, to prevent clot lysis were suggested. In a meta-analysis of early randomized controlled studies of this therapy, antifibrinolytic therapy was shown to reduce the frequency of re-bleeds, but was associated with a corresponding increase in poor outcome caused by cerebral ischemia. Hence there was no net overall clinical benefit of antifibrinolytic therapy. When the administration of tranexamic acid was restricted to the period before the aneurysm was occluded and maximally until 72 hours after the SAH, the incidence of ultra-early re-bleeds was reduced from 10.8% to 2.4%, without increasing the rate of clinical ischemic manifestations or vasospasm. Subsequently, similar results in reduction of re-bleeding without an increase in ischemic manifestations have been reported with antifibrinolytic therapy, although in this study an increase of deep venous thrombosis was evident.

Aneurysm treatment

Re-bleeding is potentially an avoidable cause of death and disability since the risk of re-bleeding can be effectively diminished by early treatment of the ruptured aneurysm. Two treatment modalities are now available to exclude the aneurysm from the circulation: neurosurgical clipping and endovascular coiling.

Microneurosurgical clipping is the traditional method of aneurysm treatment and is the gold standard in many centers. It requires a craniotomy and open dissection of the cerebral vessels and clipping of the aneurysm neck, excluding the aneurysm from the circulation. The efficacy rate in excluding the aneurysm from the circulation has been reported to 92–96%. The recurrence rate in completely clipped aneurysms is estimated to 0.5% per year. The risk of re-bleeding from a completely clipped aneurysm is estimated to 0–0.14% per year, and from an incompletely clipped aneurysm (broad based or dog-ear residua) approximately 1.5% per year.

To evaluate the risks of mortality and morbidity caused by the procedure per se, figures from studies on surgical clipping of unruptured intracranial aneurysms are scrutinized: The mortality rate from neurosurgical clipping is 1–3.8%, and the morbidity rate 3.5–12%.
The overall mortality in surgically treated SAH patients in the co-operative study on the timing of aneurysm surgery was 14% and the morbidity rate 18% \(^7\).

With the invention of the Guglielmi detachable coil, a detachable platinum coil, an alternative modality of treating intracranial aneurysms was introduced \(^104\). This method allowed exclusion of the aneurysm from the cerebral circulation through an endovascular approach, thus offering protection from re-rupture of the aneurysm without the need for a craniotomy. From 1995 endovascular coiling of both ruptured and unruptured intracranial aneurysms has been extensively used and has become the first therapeutic option in some centers \(^105\). The technical advances in this field has been tremendous with development of soft coils to allow denser packing, balloon re-modeling technique \(^106\), three-dimensional-shaped coils \(^107\), stents for facilitating coil placement in aneurysms with unfavorable geometry \(^108\) and bioactive coils to prevent aneurysm re-canulization \(^109,110\). The idea of offering protection against re-bleeding without the need of craniotomy, thus inflicting less surgical trauma, was early thought to be beneficial in especially elderly and poor grade SAH patients. Questions were raised whether this new alternative method was as effective as standard neurosurgical clipping in terms of aneurysm occlusion and protection against re-bleeding and regarding the safety of the procedure.

With endovascular coiling several series have reported 40–55% complete occlusion, 35–52% near-complete occlusion and 3.5–8% incomplete occlusion of the aneurysms \(^111-113\). The rate of re-canulization has been reported to 21–28% \(^113,114\). However, also progressive thrombosis of initially incompletely occluded aneurysms has been reported \(^114\). Despite the fact that the rate of complete occlusion is lower after endovascular than after neurosurgical treatment, the rate of re-bleeding from incompletely coiled aneurysms are reported in the range of 0.9–1.4% per year \(^111,115\). In completely occluded aneurysms the re-bleeding rate was 0% \(^111,114,115\).

In a meta-analysis of 30 studies of endovascular coiling of unruptured intracranial aneurysms comprising 1379 patients the mortality rate was 0.6% (Range 0–5%) and the morbidity rate 7% (Range 0–20%) \(^115\).

Thus endovascular coiling seems to be safer than neurosurgical clipping in terms of procedure-related mortality and morbidity, but offers a lower rate of complete occlusion of the aneurysm.

The notion that endovascular coiling is safer than surgical clipping was reinforced by the International Subarachnoid Aneurysm Trial (ISAT), which demonstrated an absolute risk reduction of dependence or death of 6.9% at 1 year with a policy of endovascular aneurysm treatment \(^116\). Analyses of the treatment effects in the pre-specified subgroups in ISAT were heterogeneous and difficult to interpret, mainly because of small numbers in the subgroups. There was no indication that neurosurgical aneurysm treatment would be more beneficial in any of the subgroups that would offset the main finding of the study \(^117\).
Cerebral vasospasm

The exact etiology of cerebral vasospasm is not known. Arterial narrowing occurs when free subarachnoid blood encounters the large cerebral vessels in the basal cisterns. The delayed onset of vasospasm points in the direction that degradation products from lysis of the erythrocytes and the release of oxyhemoglobin and breakdown products, such as hemin, iron, bilirubin and globin chains, are necessary for its development. Other compounds have also been implicated in the development of vasospasm, such as platelet contents, leukocytes and inflammatory mediators, products of the coagulation cascade, free radicals, amines, lipids, and endothelin and reduction in nitric oxide 118. A complex interplay of several mechanisms results in prolonged contraction of the smooth muscle cells and intimal and medial thickening of cerebral arteries resulting in arterial narrowing. This may lead to progressively lower cerebral blood flow (CBF) resulting in cerebral ischemia and infarction if CBF is reduced for a significant time.

Different terms are used to describe the different features of this condition. Angiographical (or radiological) vasospasm refers to the arterial narrowing seen on cerebral angiography, most frequently 4–12 days after the SAH. The peak incidence is on day 7 after the SAH, and the onset of angiographical vasospasm more than 14 days after the SAH is rare 118. The incidence of angiographical vasospasm at some point during the first two weeks after the SAH is approximately 70% 119, but is dependent on the timing of the angiography in relation to the SAH 76.

Clinical vasospasm is clinically characterized by delayed onset of confusion or decreased level of consciousness with or without focal neurological signs such as motor deficits or dysphasia. The term delayed ischemic neurological deficit (DIND) is used interchangeable with clinical vasospasm. The diagnosis of clinical vasospasm or DIND is made by exclusion of other possible causes of neurological deterioration, such as cerebral edema, hydrocephalus, infarct, hematoma, and electrolyte and metabolic abnormalities. Approximately 20–35 % of all patients with SAH develop DIND 76, 119-123, and the peak incidence is on day 8 after the SAH 118.

In one multi-center study cerebral vasospasm was identified as the cause of death in 7% and the cause of disability in 6% of the patients 76. In a Swedish study, cerebral vasospasm was the cause of poor outcome (death and disability) in 11% 124.

The amount of subarachnoid blood in the basal cisterns correlates to the incidence of cerebral vasospasm 123, 125-129, and to delayed cerebral infarction 130-132. IVH may have an additive effect on the risk of vasospasm 123, 127. Also the neurological grade on admission correlates with the incidence of vasospasm. Patients in poor neurological grade have a higher incidence of vasospasm 127-129. Furthermore, the duration of unconsciousness after the initial bleed was an important risk factor for the development of DIND in one
study. The patients who were unconscious ≥1 hour after the onset of SAH had a 6-fold increase in the risk of DIND compared to the patients who were awake or were unconscious <1 hour 121.

Treatment of vasospasm
Although, several candidate drugs (tirilazad 133, aspirin 134-136, enoxaparin 137) have been tested for the treatment of cerebral vasospasm over the years, nearly all trials so far have failed to prove efficacy in reducing the mortality and morbidity from cerebral vasospasm. The only drug in clinical use today for the prevention of cerebral vasospasm is nimodipine, a calcium channel blocker, which has been shown to reduce the risk of poor outcome and secondary ischemia after aneurysmal SAH 138, 139.

Ongoing investigations on clazosentan, an endothelin receptor antagonist, have shown reduced angiographical vasospasm 140, 141, but statistical significant reduction in poor clinical outcome could not be proven 141. A larger trial designed to evaluate the effects of clazosentan on vasospasm-related morbidity and mortality (CONSCIOUS-2) is in progress.

A meta-analysis of 3 small randomized studies of statins for the prevention of vasospasm, has shown that statins decrease the incidence of vasospasm and DIND and reduce mortality 142. There is currently an on-going multi-center placebo-controlled double-blinded phase III trial assessing the clinical benefit of simvastatin in aneurysmal SAH (STASH) 143.

Another measure taken when cerebral vasospasm is clinically evident or proven by cerebral angiography is the hypertensive, hypervolemic and hemodilution therapy (triple-H-therapy or hemodynamic therapy). The theoretical rationale for this therapy is to improve the CBF to ischemic areas of the brain by increasing the cerebral perfusion pressure, counteract arterial narrowing and optimize blood rheology, thus improving the delivery of oxygen and glucose to the cerebral tissue. Various protocols for this therapy have been described, using different monitoring devices and target values of physiological variables 144-147. The hypertension, hypervolemia and hemodilution is accomplished by infusing synthetic colloids, such as dextrans, hexastarch or gelatins, or albumin and crystalloids to increase the intravascular volume and reduce the hematocrit to 33–35%. If the effect on blood pressure is inadequate, vasoactive inotropic drugs are administered to increase systolic blood pressure to desired levels. Hemodynamic therapy was shown to achieve prolonged elevation of systemic blood pressure and reversal of ischemic deficits in early uncontrolled studies 148-151. Also, in pseudorandomized and controlled non-randomized studies, triple-H-therapy reduced the risk of vasospasm 152-154 and improved outcome 154. Triple-H-therapy is accompanied with a 10–20% risk for intra- and extracranial complications, such as cerebral edema, hemorrhagic infarction in previous areas of ischemia, aneurysmal re-bleeding of unsecured aneurysms, pulmonary
edema, myocardial infarction, cardiac failure, dilutional hyponatriema and coagulopathy\textsuperscript{144, 146}. Triple-H-therapy has become a widely used therapeutic option to counteract the effects of cerebral vasospasm after SAH, and in some centers triple-H-therapy is given prophylactically to all patients after securing the aneurysm. However, the efficacy of prophylactic triple-H-therapy to reduce the incidence of DIND, improve CBF and improve outcome has not been proven in 2 small randomized controlled trials\textsuperscript{155-157}.

Improvement and refinement of endovascular therapies (balloon angioplasty\textsuperscript{158} and intra-arterial injection of nimodipine\textsuperscript{159} and papaverine\textsuperscript{160}) may prove to be an alternative to medical treatment of vasospasm in patients with severe refractory vasospasm\textsuperscript{161}.

Secondary insult concept

SAH patients who have survived the initial bleed in good clinical condition with little or no neurological impairment are still at risk for a devastating clinical course and poor outcome due to complications causing secondary brain injury. Parallels can be drawn to patients with traumatic brain injury (TBI) who talk and die\textsuperscript{162}, in whom potentially avoidable secondary complications were implicated in the development of secondary brain damage, clinical deterioration and death\textsuperscript{162, 163}. In SAH the major causes for a “talk and die”-scenario are re-bleeding from the ruptured aneurysm and cerebral vasospasm causing secondary cerebral ischemia.

Also other unfavorable events may be implicated in causing secondary cerebral ischemia after SAH. The hypothesis is that cerebral vasospasm is only one of several pathophysiological processes leading to secondary cerebral ischemia after SAH\textsuperscript{164, 165}. Rather several unfavorable factors – secondary insults – interact and augment each other in a complex interplay that ultimately leads to ischemia and poor outcome. A pilot study from our department showed that secondary insults were implicated in cases with poor outcome also in SAH\textsuperscript{164}. Ischemia is the result of insufficient CBF in relation to the metabolic demands, which means that ischemia can be caused by decreased CBF or increased energy metabolism or both. The potential mechanisms leading to secondary ischemia in SAH are schematically shown in figure 1 and discussed below.
In the normal brain CBF is maintained at an adequate level through several regulating mechanisms. Cerebral autoregulation maintains a relatively constant CBF over a wide range of cerebral perfusion pressures (CPP). Decreasing CPP below the normal limits of autoregulation will result in a steep fall in CBF. However, the autoregulation mechanism may be disturbed or even absent after SAH\textsuperscript{166-168}. This may cause the CBF to be directly dependent on the CPP. Reduction in the CBF can be global or regional/local. Reduction of global CBF is caused by inadequate CPP, due to elevated ICP or reduced MAP, or widespread cerebral vasospasm. Regional decreases in CBF can be the result of regional cerebral vasospasm, local mass effect of a hematoma, thrombo-embolic events and/or surgical trauma.

Early after aneurysm rupture elevated ICP is common in SAH patients and may have several causes: 15–23\% of SAH patients have acute hydrocephalus on the diagnostic CT\textsuperscript{76,169-171}. Factors associated with acute hydrocephalus after SAH are IVH, which is present in about 13–17\% of the patients\textsuperscript{75,76}, and the amount of subarachnoid blood in the basal cisterns\textsuperscript{171}. Acute hydrocephalus and its effect on intracranial dynamics can be effectively diminished by placement of a ventriculostomy and CSF drainage\textsuperscript{169}. It has been suggested that this would increase the risk of re-bleeding from the ruptured aneurysm\textsuperscript{172}. However in a controlled study, the risk of re-bleeding from the ruptured aneurysm was not increased after placement of a ventriculostomy\textsuperscript{173}. In 17–25\% of aneurysmal SAH patients an ICH is present\textsuperscript{76,92,174}, and sometimes a subdural hematoma (SDH) may be present concomitantly with the SAH. ICH in SAH patients is associated with poorer clinical grade on admission and worse clinical outcome\textsuperscript{76,92,174}. Expansive ICH and SDH can give rise to elevated ICP, which may necessitate immediate surgical evacuation in order to normalize ICP. Persistent elevated ICP causes global ischemia, but with localized lesions such as ICH and SDH also focal.

**Figure 1** Mechanisms of secondary ischemia in SAH
ischemia can ensue. If untreated, ischemic areas may develop to expansive cerebral infarctions, which in turn may elevate ICP further.

Hypoxemia aggravates cerebral ischemic conditions and is therefore regarded as a secondary insult. PaO$_2$ levels below 8.0 kPa has been shown to dramatically increase CBF and the cerebral blood volume, which may lead to increased ICP $^{175}$. Hypoxemia may ensue from several situations in SAH: obstructed airway and poor ventilation in unconscious patients, aspiration, ventilator-associated pneumonia, pulmonary atelectasis and cardiac failure with pulmonary edema $^{176}$.

In the acute stage after SAH, hyperglycemia is common and may be related to the stress response after aneurysm rupture. Hyperglycemia is associated with worse outcome after SAH $^{177-185}$. Hyperglycemia combined with cerebral ischemia results in glucose utilization via accelerated anaerobic glycolysis leading to lactic acidosis, and in increased oxidative stress, which exacerbates and accelerates brain damage $^{186}$. Hyperglycemia also has pro-vasoconstrictive, pro-thrombotic and pro-inflammatory effects on the cerebral vasculature $^{187}$, which may contribute to the development of brain damage.

Even modest elevations of body temperature have been shown to aggravate ischemic brain damage in experimental brain ischemia and trauma models as well as after acute ischemic stroke $^{188}$. Pyrexia after SAH is associated with worse clinical outcome $^{185, 189, 190}$. In neurointensive care of SAH patients there are several causes for pyrexia: aseptic meningitis due to the subarachnoid blood, and infections, such as meningitis, pneumonia and septicemia. Epileptic seizures in the acute stage after SAH are common $^{191}$. Pyrexia and epileptic seizures increase the cerebral metabolic rate, thus increasing the demand of oxygen and glucose delivery by increased CBF. In a situation where the CBF cannot be further increased to meet the demands of the increased metabolism, ischemia will ensue. Furthermore, pyrexia and seizures increase the cerebral blood volume, which may lead to increased ICP. In turn the elevation of ICP results in a reduction of CBF ultimately leading to further aggravation of ischemia. This illustrates how different secondary insults may lead to and aggravate each other in a complex interplay ultimately leading to cerebral ischemia and worse clinical outcome (Figure 1).

Neurointensive care

The goal of neurointensive care (NIC) is to prevent secondary ischemic damage to the brain and thereby improve the overall clinical outcome. The aim is to control intracranial dynamics and to maintain normal body physiology. Special attention is paid to prevention, early diagnosis and intensive management of factors contributing to secondary ischemic brain damage – secondary insults. The neurosurgical department at the Uppsala University Hospital gradually adopted the principles of NIC from the mid-eighties, and a special neurointensive care unit (NICU) was inaugurated in 1990. Im-
proved survival after TBI \(^{192, 193}\) and SAH in patients of all ages \(^{75}\) has been reported from the department. The principles of neurointensive care has further developed to a standardized protocol system containing written standardized operative procedures regarding both basic nursing and medical treatment of complications of TBI and SAH \(^{165, 194}\).

**Subarachnoid hemorrhage in the elderly**

Elderly patients with SAH have a higher risk of an unfavorable clinical outcome than younger patients \(^{76, 195-205}\). Reasons for worse outcome is thought to be caused by less active management and conservative referral patterns \(^{206, 207}\), poorer clinical grades on admission \(^{197, 200, 204, 208}\), higher frequency of comorbidity \(^{9, 199, 204}\) and increased incidence of severe complications \(^{204}\). Multivariate analysis of overall outcome, adjusted for different prognostic factors, revealed that high age per se was a negative prognostic factor, suggesting that the aging brain have less optimal response to the initial bleeding \(^{204}\).

**Physiological effects of normal aging**

When managing elderly patients with intracranial disease, such as SAH, age-related physiological changes in other vital organ systems must also be considered \(^{176, 209}\).

The effects of aging in the cardiovascular system include a decrease in elasticity and reduced compliance of the vasculature, reduced responsiveness to beta-adrenergic receptor stimulation, decreased reactivity to baro- and chemoreceptors and an increase in circulating catecholamines. This leads to an increased afterload, increased systolic blood pressure and left ventricular hypertrophy \(^{10}\). Alpha-adrenergic effects on the vasculature predominate resulting in vasoconstriction, resting cardiac output declines and cardiovascular performance under stress is reduced.

Age-related changes of the respiratory system include decreased total respiratory system (lung and chest wall) compliance and decline in arterial oxygenation, due to a decreased diffusion capacity caused by increased ventilation/perfusion mismatching and reduced alveolar surface area. Altogether, age-related alterations of the respiratory system cause a reduced pulmonary reserve rendering the elderly patient more susceptible to respiratory complications in situations of positive fluid balance, increased metabolic demands, and prolonged bed rest during intensive care. Increased sensitivity to respiratory depressants and muscle weakness in the elderly further increase the risk of respiratory complications. Elderly patients have an increased risk of respiratory failure requiring mechanical ventilation after surgery and a higher risk of long-term ventilator dependency in intensive care \(^{11}\).
Aging is accompanied by a decline in liver volume but the clinical significance of this alteration is unclear and liver function tests have not shown age-related deficits. The rate of liver regeneration after injury decreases, which may increase the rate of progression of hepatic dysfunction in the elderly.

The renal mass and the renal blood flow decrease with age. The loss of renal volume is attributed to a reduction in the number of functioning glomeruli accompanied by a reduction in the glomerular filtration rate, limitations in sodium conservation, and potassium and acid excretion. Under normal conditions most elderly individuals can maintain normal fluid and electrolyte homeostasis despite these changes. However the reserve to withstand disease-related or iatrogenic stress becomes progressively smaller with age and may lead to disturbance in water and electrolyte homeostasis.

Aging causes a gradual decrease of bone density, decrease in the amount and number of muscle fibers and connective tissue within tendons and ligament become stiffer and more brittle. The resulting decreased muscle strength has implications for the respiratory system in the intensive care setting and may impede rehabilitation after SAH.

All together, the total effects of aging on vital extracranial organ systems render the elderly patient more susceptible to dysfunction of several vital organs and more vulnerable for complications.

With normal aging the functional metabolism of the brain and its blood supply decline. This accounts for the widespread clinical observations that the elderly tolerate disorders of the brain worse than the young do. The decline in CBF may be secondary to the age-related increase in atherosclerosis, which results in increased cerebrovascular resistance, reduced elasticity and contractility of small arteries and arterioles, and the cerebral vasomotor reactivity declines.

In addition to the normal aging processes causing decline in organ function, the incidence of several diseases with systemic involvement increase with age, causing further dysfunction of vital organs.

**Conservative management in the elderly**

The management of SAH in the elderly has changed considerably in the last decades. Thirty years ago, elderly patients were at a rule treated conservatively on the basis of their advanced age alone and inevitably suffered a poor outcome. It was argued that intracranial investigations and surgery was not justifiable in elderly patients, due to poor surgical results compared to conservative treatment in this age group.

**Neurosurgical aneurysm treatment in the elderly**

Some authors argued that selected elderly patients would benefit from surgical repair of their aneurysm. In Hugosson’s series from Uppsala in
1973, 43 SAH patients aged 60–68 years were surgically treated. The surgical mortality was 9% and 66% were symptom-free and 13% had minor disabilities after 9 years. He argued that even elderly patients with ruptured intracranial aneurysms could be surgically treated with good results if some contraindications were observed. These were prolonged initial unconsciousness in association with the SAH, prior clinical signs of arteriosclerosis and angiographically verified arteriosclerosis in the cerebral vessels.

The early studies showing that surgical aneurysm treatment was feasible in the elderly, were followed by others supporting that good grade elderly SAH patients should be actively treated. In one study it was demonstrated that the difference in total outcome between elderly and younger patients could to a certain extent be explained by significantly poorer condition on admission in the elderly patients. The demonstration of the benefit of surgical treatment in elderly patients resulted in the view that elderly should not be withheld surgery based on their advanced age alone.

Improved management outcome in elderly patients was demonstrated when more elderly patients were actively treated. The outcome results in good grade elderly SAH patients are approaching those in younger patients, and surgery has been considered even in the patients older than 80 years with variable results. Despite the improved management of selected elderly SAH patients, overall outcome is still worse in the elderly, especially in the higher age groups and worse clinical grades. Thus, the possibility to treat more elderly SAH patients needs to be studied further.

Endovascular aneurysm treatment in the elderly

In the prospect of reducing the risk of re-bleeding without the need for craniotomy, thus inflicting less surgical trauma, endovascular coiling was conceived as a promising alternative to neurosurgery, especially in elderly and poor grade patients.

In two relatively small studies of elderly patients in good clinical grade, endovascular coiling was found to be a safe way of securing ruptured and unruptured aneurysms with good technical and functional outcome. Endovascular coiling was suggested to be the treatment of choice for acutely ruptured aneurysms in the elderly. In another series, clinical outcome after endovascular coiling in elderly SAH patients of all clinical grades was compared with a younger age group. The outcome results after endovascular coiling in elderly patients were comparable to those obtained in the best surgical series of elderly SAH patients but worse than in the younger patients. Endovascular coiling was found to be an effective means of preventing re-bleeding and represent an alternative to surgical aneurysm treatment in the elderly. However, the risk of intraprocedural complications during endovascular coiling, especially thrombo-embolic, was higher in the elderly age group than in the younger patients.
Although technical feasibility and favorable outcome results of endovascular coiling in selected elderly SAH patients have been shown in small series the results of endovascular coiling in elderly patients remain to be evaluated in a larger series of patients. Also direct comparison between endovascular and neurosurgical aneurysm treatment in the elderly needs to be evaluated in a randomized trial.

Possible advantage of neurointensive care in the elderly

The introduction of NIC has contributed to the improved management results of SAH in patients of all ages. The improved outcome can be attributed to the early detection and treatment of secondary complications of SAH, thus avoiding secondary brain damage, which is the fundamental principle of NIC. With the introduction of endovascular aneurysm procedures as a standard treatment, even elderly patients in poor neurological grade could be subjected to early aneurysm treatment. Thus, elderly patients in poor neurological grade can be admitted early and receive full neurointensive care treatment. Therefore, it is important to investigate if modern neurosurgical management principles with early aneurysm treatment and neurointensive care are meaningful also in elderly patients with severe SAH.

It is possible that neurointensive care has an even more important role in the elderly than in younger patients, since elderly patients are more vulnerable and more prone to develop complications. It is therefore desirable to learn more about secondary insults and neurointensive care specifically for elderly SAH patients.

Cerebral vasospasm in the elderly

Some studies have suggested that age is inversely related to the risk of vasospasm, while others have shown no effect of age. The reported lower incidence of vasospasm in older patients may be secondary to the age-related increase in atherosclerosis, which results in impairment of contractility and elasticity of the muscle wall of small arteries and arterioles. This seems to be a reasonable explanation for the lower risk of DIND in the elderly, however data are conflicting. The definition of vasospasm and the method of proving vasospasm are not uniform in different studies. Also most previous reports are retrospective studies, which makes interpretation difficult. It would therefore be valuable to study the effect of age on the risk for cerebral vasospasm, using several definitions of vasospasm in the same prospective cohort of patients.
Aims of the investigations

General aim
The general aim of this thesis was to explore different aspects of the management of subarachnoid hemorrhage specifically in elderly patients.

Specific aims
To evaluate if the population of elderly SAH patients admitted to a neurosurgical unit had changed over time, and whether altered management principles had improved functional outcome in this age group. (Paper I)

To evaluate clinical outcome, complication frequency and occlusion degree of the ruptured aneurysm after endovascular coiling in elderly SAH patients. (Paper II)

To compare endovascular coiling with neurosurgical aneurysm treatment in elderly SAH patients in regard to functional outcome, procedural complication rates and frequency of adverse events. (Paper III)

To investigate the occurrence of secondary insults during neurointensive care and their association with admission characteristics and outcome of SAH patients, using a computerized multi-modality monitoring system, as a basis for subsequent studies specifically in elderly patients. (Paper IV)

To investigate the functional outcome and describe the occurrence of secondary insults in elderly patients with severe SAH compared to younger patients, and to explore which clinical characteristics and treatment variables that may explain possible age-dependent differences. (Paper V)

To investigate age-dependent differences in the incidence of radiological vasospasm, clinical vasospasm and abnormal transcranial Doppler (TCD) measurements indicative of cerebral vasospasm. (Paper VI)
Materials and Methods

Paper I

Patients

All patients with aneurysmal SAH, 65 years or older, admitted to the neurosurgical department in Uppsala with an intention to treat between January 1, 1981 and December 31, 1998 were included in the study.

Data collection

Patient characteristics, such as sex, age, neurological grade on admission, the amount of blood on the diagnostic CT and treatment data were retrospectively recorded from the patients’ medical records according to a pre-defined protocol. Neurological grade on admission was classified according to Hunt and Hess (H&H) (Table 2, page 37) and the amount and distribution of subarachnoid blood was assessed according to Fisher’s scale (Table 4, page 38).

Follow-up was conducted 1–10 years after SAH (Mean 3.6 years), according to the Glasgow Outcome Scale (GOS) (Table 5, page 39). The clinical outcome in the patients alive at follow-up was based on written interviews with the patients or their relatives. Mortality figures were gathered from the Swedish National Death Register. SAH was considered the cause of death in all patients dying within 3 months after the hemorrhage, and in those who died later when death was related to the SAH. In the patients who were considered to have died of unrelated causes, the clinical outcome was based on their pre-existing physical and neurological status.

Statistical analyses

The 18-year period was divided into three periods of 6 years, Period A 1981–86, period B 1987–92, and period C 1993–98. Univariate analyses of changes over time were made comparing period A and period C. GOS scores were grouped as favorable (good recovery and moderate disability), severe disability, and poor (vegetative state and dead). Non-parametric methods were used, and a p-value <0.05 was considered statistically significant.

A multivariate logistic regression model was fitted for each of the two outcomes: poor and favorable outcome. The method implemented in S-Plus
(Insightful corp.) was used. The initial model fit contained admission variables (sex, age and Hunt and Hess grade), time period and treatment variables (use of ventriculostomy and timing of aneurysm treatment) as explanatory variables. The final model included all admission variables, time period and treatment variables that were significant.

Paper II

Patients

All SAH patients, 65 years or older, admitted to the neurosurgical department in Uppsala between September 1, 1996 and December 31, 2000, in whom endovascular coiling was chosen as the first line of treatment for the ruptured aneurysm were included in the study.

Data collection

Patient characteristics, such as sex, age, time of SAH, time of admission, Hunt and Hess grade \(^{230}\) (Table 2, page 37), Fisher grade \(^{125}\) (Table 4, page 38) and treatment variables were collected from the neurovascular database established at the NICU.

Procedural reports from the endovascular treatment were reviewed for information about aneurysm(s) treated, technical success, timing of treatment, angiographic occlusion degree, and procedural complications. The angiographic occlusion degree was based on the final angiogram during the endovascular procedure and categorized into 5 groups based on location of possible remnant: complete occlusion, neck remnant, residual filling, and other remnant and not treated. The term neck remnant was used when the neck of the aneurysm could not be packed with coils, and residual filling refers to the aneurysm not being densely packed. Other remnant refers to an aneurysm remnant that could not be otherwise classified.

Procedural complications during endovascular treatment were registered as aneurysm rupture, unintentional parent artery occlusion, other artery occlusion due to thrombo-embolism, coil migration and intraluminal coil protrusion.

Data on clinical outcome at 6 months after SAH were obtained from written structured interviews with the patients or their close relatives, and classified according to GOS \(^{231}\) (Table 5, page 39).

Statistical analyses

Univariate analysis of admission and treatment variables effect on outcome was performed using a chi-square test. All variables were categorical. GOS scores were grouped as favorable (good recovery and moderate disability),
severe disability, and poor (vegetative state and dead). A p-value <0.05 was considered statistically significant.

A multivariate logistic regression model was fitted with favorable outcome as the dependent variable. The initial model fit contained admission variables (Hunt and Hess grade, age and Fisher grade) and treatment variables (use of ventriculostomy, treatment day, aneurysm location and occurrence of any procedural complication) as explanatory variables. All variables were categorical except age and treatment day, which were continuous. Variables were removed in a backward elimination manner based on the p-value. The final model included admission and treatment variables that were considered statistically significant (p<0.05), or were marginally significant (0.05<p<0.10). All statistical analyses were performed using commercially available software (StatSoft, Inc. (2001). STATISTICA (data analysis software system), version 6. www.statsoft.com.).

**Paper III**

**Patients**

The patients included in paper III were a subgroup of all patients who were 65 years or older at the time of hemorrhage included in the International Subarachnoidal Aneurysm Trial. The ISAT study protocol including randomization procedures is previously published\(^{116}\). In summary, eligible patients had SAH due to a ruptured aneurysm, which was suitable for both neurosurgical clipping and endovascular coiling, and there was uncertainty as to whether the aneurysm should be treated by neurosurgical or endovascular means.

**Data collection**

Key baseline characteristics were recorded before the treatment allocation was issued. These were age, sex, clinical grade on the World Federation of Neurological Surgeons (WFNS) scale\(^{232}\) (Table 3, page 38), size and location of the target aneurysm, and Fisher grade\(^{125}\) (Table 4, page 38). Randomization to endovascular or neurosurgical treatment was done through a 24-hours telephone randomization service, provided by the Clinical Trial Unit at the University of Oxford. A minimization algorithm based on the baseline characteristics was used to ensure balance between the two groups.

Data were collected and reported on specific case record forms, regarding technical success and procedural complications for endovascular and neurosurgical procedures as well as any adverse events and additional procedures after the time of randomization during the first admission.

Procedural complications recorded during endovascular treatment were aneurysm rupture, parent artery occlusion, the use of thrombolytic agent and
coil migration. During neurosurgical clipping the following procedural complications were recorded: aneurysm rupture, parent artery occlusion and the use of temporary clips. Upon waking the patient after anesthesia from either treatment, neurological deterioration was defined as the patient’s WFNS grade being lower after than before the procedure or if a neurological deficit was present. If the deficit was thought to be of thrombo-embolic nature this was specifically recorded.

The recorded adverse events were pre- and post-procedural re-bleeding, delayed ischemic neurological deficit, hydrocephalus, epilepsy, infection, cerebral hematoma, pulmonary complications, serious groin hematoma and severe headache. The main outcome measure was a modified Rankin scale 233 assessed at 1 year after the hemorrhage (Table 6, page 39).

The data were extracted from the ISAT database on November 9, 2005, and include some selected data on all 278 randomized patients aged 65 or older.

Statistical analyses
Comparisons between the endovascular and the neurosurgical group were made on an intention to treat basis. If a patient crossed over from one treatment modality to the other, they were analyzed in the group in which they were allocated based on the randomization result. However, comparison of procedural complications was made between the actual treatment groups.

In the outcome analyses modified Rankin scores were dichotomized into Rankin 0–2 (Independent survival) and Rankin 3–6 (Dependency or death) (Table 6, page 39). Categorical data were examined by chi-square statistics. The Mann-Whitney U test was used to compare the non-normally distributed data, and Student’s t test was used to compare normally distributed data. All analyses were done with commercially available software (StatSoft, Inc. (2005). STATISTICA (data analysis software system), version 7.1. www.statsoft.com).

Papers IV and V
Patients
The patients eligible for inclusion in the papers IV and V were admitted to the NICU at the Uppsala University Hospital between January 1999 and December 2002 with SAH caused by a ruptured aneurysm. For inclusion, treatment with ventriculostomy was required. Further, the patients had to have a minimum of 120 hours (5 days) of valid multi-modality monitoring data for ICP, CPP, MAP and systolic blood pressure (BPs) within the first 240 hours (10 days) following the SAH. Furthermore, two subgroups were created, in which patients with a minimum of 120 hours of valid monitoring
data for arterial oxygen saturation (SpO₂) and body temperature (T°), respectively, within the first 240 hours after the initial bleed was added to the initial inclusion criteria. In paper V patients ≥65 years were analyzed specifically. The general policy during this period was to admit elderly patients who were previously relatively healthy and conscious at the primary evaluation at the referring hospital.

Data collection
Patient characteristics, such as sex, age, time of SAH, time of admission, Hunt and Hess grade (Table 2, page 37) and Fisher grade (Table 4, page 38) on the diagnostic CT and various treatment variables were collected from the neurovascular database established at the NICU.

At the NICU in Uppsala a computerized multi-modality monitoring system to collect and store physiological data has been in use and developed since 1998. Specialized software saves one value per minute for each monitored physiological parameter and patient in a database. The minute by minute value is an average of the values received by the system for that minute. The data collection is interrupted when patients leave the NICU for radiology examinations or surgical procedures. Data collection could also be discontinued due to software, network or system failures. Subtracting these gaps in the data collection and the data judged to be artifacts from the total monitoring time yields the good monitoring time (GMT).

All monitoring data was screened manually to disclose artifacts. The patients’ records were used to confirm or reject questionable values. If the records could not verify abnormal values as true or false, the policy was to leave the data as valid. In the patients who were declared brain dead in the NICU all data was marked invalid from the time point when the patient was no longer receiving active treatment against secondary insults. This was done to avoid including insult values from a period when a patient was no longer receiving active treatment.

Thresholds for secondary insults in SAH were derived based on the treatment goal for ICP, MAP, BPs, CPP, T° and SpO₂, and previous work at our department in TBI (Table 1). The amount of secondary insult was calculated as the time spent within an insult level divided by the GMT for each parameter and patient and is presented as percent of GMT.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment goal</th>
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<th>Severe insult</th>
</tr>
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<td>&lt;15–20</td>
<td>≥20</td>
<td>≥25</td>
</tr>
<tr>
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<td>&gt;60</td>
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<td>≤55</td>
</tr>
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</tr>
<tr>
<td>Individual</td>
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</tr>
<tr>
<td>SpO2 (%)</td>
<td>&gt;95</td>
<td>&lt;95</td>
<td>&lt;90</td>
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**Table 1** Secondary insult definitions
ICP, intracranial pressure; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; BPs, systolic blood pressure; T°, body temperature; SpO2, arterial oxygen saturation

Functional outcome 6 months after the SAH was obtained by written structured interviews with the patients or their close relatives, and classified according to GOS 231 (Table 5, page 39). In paper IV, an additional dichotomized outcome measure, “Clinical course outcome”, was constructed based on the clinical course of each patient in analogy to the “talk and die” concept 162. Patients who were awake (GCS-M 6) on admission but deteriorated clinically and were unconscious (GCS-M ≤5) at discharge, and all patients who died in the NICU were assigned to the “deteriorated” group. Patients who were unchanged or improved neurologically were assigned to the “Improved or unchanged” group.

**Statistical analyses (Paper IV)**
Logistic regression modeling was used to analyze the effect of each admission and treatment and secondary insult variable on both of the two outcome measures, functional outcome and clinical course outcome. All admission and treatment variables and all secondary insult variables were analyzed with univariate logistic regression with the functional outcome “independent” or the clinical course outcome “deteriorated” as the dependent variable, respectively. Admission and treatment variables were categorical and secondary insult variables were continuous. The admission and treatment variables and secondary insult variables that were significant in the univariate analyses were included as explanatory variables in a multivariate logistic regression model. Explanatory variables were removed in backward elimination manner based on the p-value. The final model included explanatory variables that were considered significant (p<0.05).
Statistical analyses (Paper V)

A chi-square test was used to compare functional outcome between younger (<65 years) and elderly patients (≥65 years) and for comparisons of clinical and treatment variables between different age groups: <55 years, 55–64 years and ≥65 years. The occurrence of secondary insults, expressed as percent of GMT, was compared between three age groups (<55 years, 55–64 years and ≥65 years) with the Mann-Whitney U test and Kruskal-Wallis ANOVA.

Logistic regression modeling was used to analyze the effect of clinical and treatment variables on each of the secondary insult variables. For this purpose each secondary insult variable was dichotomized based on the median percent of GMT with insult of all patients. In this manner half of the patients were considered to have had the secondary insult in larger quantity and half of the patients were considered to have had the secondary insult in smaller quantity. The median percent of GMT for each secondary insult – and the basis for this dichotomization – is shown in Table 19 (page 56). This dichotomized secondary insult variable was used as the dependent variable and clinical and treatment variables as explanatory variables in the logistic regression modeling. All clinical and treatment variables were categorical except age, which was continuous. Factors that were significant (p<0.05) or marginally significant (0.05<p<0.10) in the univariate analyses were included in the initial multivariate logistic regression model for each of the secondary insult variables. Factors were removed in a backward elimination manner based on the p-value. The final model included explanatory variables that were considered significant (p<0.05).

Paper VI

Patients

The patients included in paper VI were enrolled in the CONSCIOUS-1 study, which was an international, multi-center, double-blind, randomized, placebo-controlled study, designed to evaluate the efficacy of three dose levels of clazosentan (1, 5 and 15 mg/hour) in preventing vasospasm assessed by angiography after SAH. The patients were recruited between January 2005 and March 2006 from 52 centers in Israel, Europe and North America.

The patients eligible for inclusion in the trial were 18 to 70 years old. All patients had SAH with a diffuse or localized thick subarachnoid clot on baseline CT scan within 48 hours of SAH, from a ruptured saccular aneurysm confirmed by digital subtraction angiography (DSA), and for which clipping or endovascular coiling was possible. Admission neurological grade were WFNS Grades I–IV, and those Grade V patients who improved to Grade IV or better after ventriculostomy (Table 3, page 38). Drug or ve-
Vehicle treatment had to begin within 56 hours of SAH. If there were presence of any degree of cerebral vasospasm on the baseline DSA, the patients were excluded from the study.

Data collection

Baseline characteristics recorded were gender, age, WFNS grade, subarachnoid clot size on the diagnostic CT, size and location of the ruptured aneurysm, history of hypertension and IVH and/or ICH in addition to the SAH.

Recorded treatment variables were type of aneurysm treatment (clipping or coiling), clazosentan treatment group (placebo, 1 mg/h, 5 mg/h or 15 mg/h) and use of ventriculostomy, rescue therapy, hemodynamic therapy (hypertension, hypervolemia and/or hemodilution), calcium channel blocker, antiepileptic drugs and phenytoin. Rescue therapy was defined as the start of either hemodynamic therapy or angioplasty in the presence of vasospasm on DSA or TCD. Fever above 38 °C for 8 days was also registered.

The outcome measures were radiological vasospasm, DIND and TCD measurements indicative of vasospasm.

Statistical analyses

Patient age was considered in two ways. First as a dichotomized variable with a cut point of < or ≥65 years and second as a categorical variable based on age by decade. Decades were collapsed into 4 groups (≤40 years, 41–50 years, 51–60 years and ≥61 years). The reason for creating the categorical age variable was to achieve a reasonable distribution of patients between the groups, which was not seen with the dichotomized age variable. The age variables were investigated as the main variable while other possible confounding variables were adjusted for in the multivariate logistic regression modeling. The dichotomized dependent outcome measures were:

1. Radiological vasospasm on DSA on day 9±2 or at any time later, compared to the baseline DSA based on blinded, adjudicated central review. None or mild (0–33% reduction of arterial diameter) vasospasm was grouped as absence of radiological vasospasm and moderate (34–66% reduction of arterial diameter) or severe (67–100% reduction of the arterial diameter) vasospasm as presence of radiological vasospasm. Two classes of the presence or absence of radiological vasospasm have been considered: one with missing values and the other with imputed values. The imputation was based on the substitution rules outlined in the protocol, which stipulated that missing data would be classified as severe vasospasm.

2. DIND defined as neurological worsening (decrease in 2 points on the modified Glasgow Coma Scale or an increase in 2 points on the abbreviated NIH Stroke Scale for at least two hours).
3. Abnormal TCD measurements at any time during patient’s stay in the ICU. Abnormal TCD measurements indicative of vasospasm was defined as either Lindegaard ratio $\geq 3^{238}$, absolute mean flow velocity $>200$ cm/s or an increase of mean flow velocity in the middle cerebral artery or anterior cerebral artery of $>50$ cm/s in 24 hours.

During the data preparation stage some categorical variables had very low numbers in some levels of the measured scales and these have been collapsed into fewer levels. The measured clot thickness was re-coded into thin and thick clot while admission WFNS grades were re-coded from 5 to 3 grade levels.

Chi-square and Fisher exact tests were performed to test the association of admission and treatment variables with the dependent dichotomized outcome measures. The variables which were statistically significant at <10% level were considered for further predictive modeling in multivariate logistic regression. A stepwise selection applied to these models was used to eliminate those variables not significant at the desired significance level (<5%) to build the final predictive models.

**Grading scales**

**Neurological grading scales**

In this thesis two scales for grading the neurological condition of the patients are used. The Hunt and Hess (H&H) scale $^{230}$ is a five level ordinal scale that not only considers level of consciousness but also headache, neck stiffness, focal neurological deficits and hemiparesis (Table 2).

<table>
<thead>
<tr>
<th>Hunt and Hess</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic, or minimal headache and slight nuchal rigidity</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>III</td>
<td>Drowsiness, confusion, or mild focal deficit</td>
</tr>
<tr>
<td>IV</td>
<td>Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances</td>
</tr>
<tr>
<td>V</td>
<td>Deep coma, decerebrate rigidity, moribund appearance</td>
</tr>
</tbody>
</table>

*Table 2* Hunt and Hess grading scale $^{230}$
The neurological grading scale proposed by the World Federation of Neurological Surgeons (WFNS)\(^{232}\) is essentially based on the patients’ score on the Glasgow Coma Scale (GCS)\(^{239}\) and on the presence of major focal motor deficit, cranial nerve palsies excluded (Table 3).

<table>
<thead>
<tr>
<th>WFNS</th>
<th>GCS (sum score)</th>
<th>Motor deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>13 or 14</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>13 or 14</td>
<td>+</td>
</tr>
<tr>
<td>IV</td>
<td>7 to 12</td>
<td>+/-</td>
</tr>
<tr>
<td>V</td>
<td>3 to 6</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Table 3 World Federation of Neurological Surgeons scale (WFNS)\(^{232}\)

Radiological grading scale

Fisher’s scale is a four level scale, where level 1 represents no visible blood on the CT and level 2 represents a thin layer of subarachnoid blood less than 1 mm, corresponding to a low risk of cerebral vasospasm. Level 3 represents a layer of subarachnoid blood thicker than 1 mm in vertical cisterns or fissures or a localized clot, which is correlated with a high risk of developing cerebral vasospasm\(^{125}\). Level 4 on Fisher’s scale represent either presence of intraventricular hemorrhage or intracerebral hematoma or both.

<table>
<thead>
<tr>
<th>Fisher grade</th>
<th>CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No visible blood</td>
</tr>
<tr>
<td>2</td>
<td>Subarachnoid blood &lt;1 mm</td>
</tr>
<tr>
<td>3</td>
<td>Subarachnoid blood &gt;1 mm or localized clot</td>
</tr>
<tr>
<td>4</td>
<td>Intraventricular hemorrhage, intracerebral hematoma or both</td>
</tr>
</tbody>
</table>

Table 4 Fisher’s scale for grading of subarachnoid hemorrhage\(^{125}\)
Outcome grading scales

Two different functional outcome grading scales were used: the Glasgow Outcome Scale and a modified Rankin scale. The Glasgow Outcome Scale (GOS) \(^{231}\) is an ordinal five-point scale (Table 5): dead (D), persistent vegetative state (VS), severe disability (SD), moderate disability (MD) and good recovery (GR). This scale is aimed at measuring disability and handicap rather than impairment \(^{240}\) and it has been tested for reliability, sensitivity and validity \(^{241,242}\).

<table>
<thead>
<tr>
<th>GOS category</th>
<th>Summary</th>
<th>Paper I–II</th>
<th>Paper III–IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead (D)</td>
<td>Poor</td>
<td>Dependent</td>
<td>or dead</td>
</tr>
<tr>
<td>Vegetative state (VS)</td>
<td>Sleep/awake, non-sentient</td>
<td>Poor</td>
<td>Dependent or dead</td>
</tr>
<tr>
<td>Severe disability (SD)</td>
<td>Conscious but dependent</td>
<td>SD</td>
<td>Dependent or dead</td>
</tr>
<tr>
<td>Moderate disability (MD)</td>
<td>Disabled but independent</td>
<td>Favorable</td>
<td>Independent</td>
</tr>
<tr>
<td>Good recovery (GR)</td>
<td>None or minor symptoms</td>
<td>Favorable</td>
<td>Independent</td>
</tr>
</tbody>
</table>

Table 5 Glasgow Outcome Scale (GOS) \(^{231}\)

Description of outcome categories and outline of grouping of outcome used in the papers

The modification of the original Rankin \(^{233}\) scale was that the original category 1 was split into two grades – 0 and 1. Deceased patients were given a Rankin score of 6 (Table 6).

<table>
<thead>
<tr>
<th>Description</th>
<th>Rankin</th>
<th>GOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no symptoms at all and cope well with life</td>
<td>0</td>
<td>GR</td>
</tr>
<tr>
<td>I have a few symptoms but they do not interfere with my everyday life</td>
<td>1</td>
<td>GR</td>
</tr>
<tr>
<td>I have symptoms which have caused some changes in my life but I am still</td>
<td>2</td>
<td>MD</td>
</tr>
<tr>
<td>able to look after myself</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have symptoms which have significantly changed my life and prevent me</td>
<td>3</td>
<td>SD</td>
</tr>
<tr>
<td>from coping fully, and I need some help looking after myself</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have quite severe symptoms which mean I need to have help from other</td>
<td>4</td>
<td>SD</td>
</tr>
<tr>
<td>people but I am not so bad as to need attention day and night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have major symptoms which severely handicap me and I need constant</td>
<td>5</td>
<td>VS</td>
</tr>
<tr>
<td>attention day and night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>6</td>
<td>D</td>
</tr>
</tbody>
</table>

Table 6 Modified Rankin scale \(^{233}\)

Description of outcome categories and comparison to the Glasgow Outcome Scale (GOS). Modified Rankin score 0–2 (GOS: GR and MD) denotes independent survival, and modified Rankin score 3–6 (GOS: SD, VS and D) denotes dependency or death.
Results

Paper I

The management of elderly SAH patients was compared for different time periods in paper I. The volume of elderly SAH patients admitted for treatment increased over time: 44 elderly patients in period A, 92 in period B and 145 in period C. The proportion of patients aged 70–74 and ≥75 years increased markedly (70–74 years: A: 11%, B: 23%, C: 47%, p<0.001; ≥75 years: A: 0%, B: 4%, C: 14%, p<0.01) (Figure 2).

![Figure 2](image.png)

**Figure 2** Number of elderly patients by age category and treatment period. *Black*, 65–69 years; *Hatched*, 70–74 years and *White*, 75 years and older.

Also the proportion of elderly SAH patients in Hunt and Hess grade IV–V increased over time (H&H IV–V: A: 11%, B: 18%, C: 26%; p<0.05), and the proportion of Hunt and Hess grade I–II decreased (H&H I–II: A: 50%, B: 43%, C: 33%; p<0.05) (Figure 3).

![Figure 3](image.png)

With time the proportion of patients with posterior circulation aneurysms increased (Posterior circulation: A: 0%, B: 9%, C: 12%; p<0.05). More patients were admitted within 24 hours after hemorrhage in period C than in period A (Admission day 0: A: 23%, B: 47%, C: 61%; p<0.001). The use of mechanical ventilation during transport to the neurosurgical department became more frequent with time (Mechanical ventilation: A: 7%, B: 20%, C: 29%; p<0.01).
Moreover, the use of ventriculostomy for continuous ICP registration and CSF drainage increased (Ventriculostomy: A: 9%, B: 50%, C: 61%; p<0.001).

![Figure 3](image)

**Figure 3** Proportion of elderly patients by H&H grade and treatment period  
*Black*, H&H I–II; *Hatched*, H&H III and *White*, H&H IV–V.

Treatment to obliterate the ruptured aneurysm was performed in 247 of 281 patients (88%); 215 underwent neurosurgical treatment and 32 endovascular coiling (all in period C). Although all patients were admitted with an intention to treat, 34 patients were managed conservatively. Reasons for conservative management were re-bleeding in 15 patients, delayed neurological deterioration in 6, complications from other organ systems in 7, technical impossibility to treat in 5 and non-consent in 1 patient. In period A, 30% of the patients were managed conservatively compared with 9% in period C (p<0.01). Early aneurysm treatment (within 3 days of aneurysm rupture) was more frequent in later years (Aneurysm treatment day 0–3: A: 39%, B: 56%, C: 62%; p<0.05). Likewise, aneurysm treatment in the “vasospasm phase” (day 4–10), became less frequent (Aneurysm treatment day 4–10: A: 26%, B: 18%, C: 11%; p<0.05).

A reliable neurological outcome could not be determined in 3 patients in period C, because they were deceased more than three months after SAH, and the cause of death could not be established. The outcome figures are based on of the remaining 278 patients (99%). Twenty-four patients died of unrelated causes, such as cardiovascular disease (11), malignancy (10) and other (3). Despite the fact that the patients were older and in worse neurological grade in the latter periods, there was a trend toward better outcome over time. The proportion of patients with severe disability did not change over time (Table 7).
Table 7 Functional outcome by time period and clinical grade
GOS, Glasgow Outcome Scale; GR, good recovery; MD, moderate disability; VS, vegetative state; D, dead

In the multivariate logistic regression model, independent predictors of favorable outcome were good Hunt and Hess grade on admission, no use of ventriculostomy and later time period of treatment (Table 8).

Table 8 Multivariate logistic regression with favorable outcome as dependent variable
OR, odds ratio; OR >1, increased chance of favorable outcome; OR <1, decreased chance of favorable outcome; A, 1981–86; B, 1987–92; C, 1993–98
The technical feasibility and clinical outcome after endovascular aneurysm treatment of elderly SAH patients was evaluated in this study, comprising 62 elderly patients, in whom endovascular coiling was the first line of treatment for the ruptured aneurysm. Twenty-two patients (35%) were aged 65–69 years, 26 (42%) were aged 70–74 years and 14 (23%) were ≥75 years. Twenty-four patients (39%) were in good neurological grade (H&H I–II) on admission, 17 (27%) were drowsy or confused (H&H III), and 21 (34%) were in poor neurological grade (H&H IV–V). The amount of subarachnoid blood on the diagnostic CT according to Fisher’s scale was grade 1 in 3 patients (5%), grade 2 in 6 (10%), grade 3 in 18 (29%), and grade 4 in 35 (56%). The distribution of ruptured aneurysms was 26 (42%) on the anterior cerebral (ACA) or anterior communicating artery (AComA), 15 (24%) on the internal carotid (ICA) and posterior communicating artery (PComA), 6 (10%) on the middle cerebral artery (MCA) and 15 (24%) in the posterior cerebral circulation. Endovascular coiling was completed as intended in 58 of 62 patients (94%). In 3 cases, the target aneurysm was not successfully catheterized and, in 1 case, the target aneurysm anatomy was re-evaluated during the procedure and found unsuitable for endovascular treatment and the procedures were discontinued. These 4 patients were later neurosurgically treated for their ruptured aneurysms and were not included in the outcome analysis. Aneurysm occlusion degree and procedural complications are shown in table 9.

<table>
<thead>
<tr>
<th>Occlusion degree</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>35</td>
<td>(56)</td>
</tr>
<tr>
<td>Neck remnant</td>
<td>13</td>
<td>(21)</td>
</tr>
<tr>
<td>Residual filling</td>
<td>7</td>
<td>(11)</td>
</tr>
<tr>
<td>Other *</td>
<td>3</td>
<td>(5 )</td>
</tr>
<tr>
<td>Not treated</td>
<td>4</td>
<td>(6 )</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm rupture</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Parent artery occlusion</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Other artery occlusion</td>
<td>4</td>
<td>(6 )</td>
</tr>
<tr>
<td>Coil migration</td>
<td>0</td>
<td>(0 )</td>
</tr>
<tr>
<td>Intraluminal coil</td>
<td>1</td>
<td>(2 )</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>(11)</td>
</tr>
</tbody>
</table>

Table 9 Aneurysm occlusion and procedural complication rates
* Other, therapeutic occlusion of vertebral artery (2), and posterior inferior cerebellar artery (1)
Outcome in the endovascularly treated patients (n=58) stratified by Hunt and Hess and Fisher grades, age group, aneurysm location and procedural complication is shown in Table 10.

<table>
<thead>
<tr>
<th>GOS</th>
<th>Favorable N (%)</th>
<th>Severe disability N (%)</th>
<th>Poor N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hunt and Hess</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>13 (57)</td>
<td>7 (30)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>III</td>
<td>8 (47)</td>
<td>5 (29)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>IV–V</td>
<td>3 (17)</td>
<td>9 (50)</td>
<td>6 (33) †</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td>8 (42)</td>
<td>7 (37)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>70–74</td>
<td>9 (36)</td>
<td>11 (44)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>≥75</td>
<td>7 (50)</td>
<td>3 (21)</td>
<td>4 (29)</td>
</tr>
<tr>
<td><strong>Fisher grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>6 (75)</td>
<td>2 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3–4</td>
<td>18 (36)</td>
<td>19 (38)</td>
<td>13 (26)</td>
</tr>
<tr>
<td><strong>Aneurysm location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA-AComA</td>
<td>8 (35)</td>
<td>13 (57)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>ICA-PComA</td>
<td>9 (64)</td>
<td>1 (7)</td>
<td>4 (29) ‡</td>
</tr>
<tr>
<td>MCA</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>6 (40)</td>
<td>5 (33)</td>
<td>4 (27)</td>
</tr>
<tr>
<td><strong>Procedural complication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.84</td>
<td>2.31</td>
<td>0.074</td>
</tr>
<tr>
<td><em>Treatment day</em></td>
<td>per day</td>
<td>0.16</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Table 10 Outcome for 58 patients in whom endovascular treatment was completed. GOS, Glasgow Outcome Scale; Favorable, good recovery and moderate disability; Poor, vegetative state and dead; ACA, anterior cerebral artery; AComA, anterior communicating artery; ICA, internal carotid artery; PComA, posterior communicating artery; MCA, middle cerebral artery; † p<0.05 (H&H IV–V vs. H&H I–II); ‡ p<0.01 (ICA-PComA vs. ACA-AComA)

The patients who were treated for aneurysms in the ICA-PComA territory had more favorable outcome and less severe disability than the patients treated for aneurysms in the ACA-AComA territory (Table 10).

In the multivariate logistic regression analysis, a low Fisher grade was associated with an increased probability of favorable outcome (p=0.021); as were later treatment day and the occurrence of a procedural complication, but these findings were not statistically significant (Table 11).

<table>
<thead>
<tr>
<th>Estimate</th>
<th>OR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher grade</td>
<td>1–2</td>
<td>1.03</td>
<td>2.80</td>
</tr>
<tr>
<td>Procedural complication</td>
<td>Yes</td>
<td>0.84</td>
<td>0.92–5.79</td>
</tr>
<tr>
<td>Treatment day</td>
<td>per day</td>
<td>0.16</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Table 11 Multivariate logistic regression with favorable outcome as dependent variable. OR, odds ratio; CI, confidence interval; OR >1, increased chance of favorable outcome; OR <1, decreased chance of favorable outcome.
Paper III

This was a subgroup analysis of all elderly SAH patients in the ISAT study comparing endovascular coiling with neurosurgical clipping in regard to clinical outcome, procedural complications and adverse events. Of the 2143 patients entered in the ISAT cohort, 278 (13%) were 65 years or older at the time of the SAH and included in paper III. Based on the randomization procedure, 138 patients were allocated endovascular treatment and 140 patients were allocated neurosurgery. There were no significant differences between the two groups in terms of the baseline characteristics (Table 12).

<table>
<thead>
<tr>
<th></th>
<th>Endovascular (N=138)</th>
<th>Neurosurgery (N=140)</th>
<th>N.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>43 (31.2)</td>
<td>36 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td>77 (55.8)</td>
<td>75 (53.6)</td>
<td>N.S.</td>
</tr>
<tr>
<td>70–74</td>
<td>47 (34.1)</td>
<td>50 (35.7)</td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>12 (8.7)</td>
<td>13 (9.2)</td>
<td></td>
</tr>
<tr>
<td>80–86</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td></td>
</tr>
<tr>
<td>WFNS grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>73 (52.9)</td>
<td>82 (58.6)</td>
<td>N.S.</td>
</tr>
<tr>
<td>2</td>
<td>40 (29.0)</td>
<td>37 (26.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (8.0)</td>
<td>11 (7.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8 (5.8)</td>
<td>6 (4.3)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (2.2)</td>
<td>3 (2.1)</td>
<td></td>
</tr>
<tr>
<td>6 (not assessable)</td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Fisher grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (3.6)</td>
<td>12 (8.6)</td>
<td>N.S.</td>
</tr>
<tr>
<td>2</td>
<td>14 (10.1)</td>
<td>17 (12.2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>56 (40.6)</td>
<td>60 (42.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>63 (45.7)</td>
<td>51 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Number of aneurysms detected</td>
<td>112 (81.2)</td>
<td>118 (84.3)</td>
<td>N.S.</td>
</tr>
<tr>
<td>2</td>
<td>18 (13.0)</td>
<td>18 (12.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (2.9)</td>
<td>4 (2.9)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>4 (2.9)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Maximum target aneurysm lumen (mm)</td>
<td>76 (55.1)</td>
<td>76 (54.3)</td>
<td>N.S.</td>
</tr>
<tr>
<td>≤5</td>
<td>49 (35.5)</td>
<td>54 (38.6)</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>13 (9.4)</td>
<td>10 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 12 Baseline characteristics of 278 elderly patients in ISAT
WFNS, World Federation of Neurological Surgeons

Almost all ruptured aneurysms were in the anterior circulation (98.6%), with the most common sites being the ACA-AComA (48.9%), the ICA (23.7%), the PComA (12.6%) and the MCA (13.3%). There were no significant imbalance regarding the target aneurysm location between the two groups.
Most patients – 263 (94.6%) – received the treatment they were allocated. However, 5 patients allocated neurosurgery received endovascular treatment, whereas none crossed over from endovascular treatment to neurosurgery. Two patients in the endovascular group and 8 patients in the neurosurgery group were not treated for their ruptured aneurysms, due to re-bleeding and deterioration, systemic complications and patient’s refusal. Thus, 141 patients underwent endovascular aneurysm treatment and 127 neurosurgery. One-hundred-and-twenty-nine (91.5%) of the endovascular procedures were completed as intended compared to 119 (93.7%) of the neurosurgical procedures. Reasons for not completing the treatment procedures were failure to catheterize target aneurysm, unsuitable anatomy, partial clipping or wrapping and not attempted.

There was no difference between the two treatment groups in regard to time interval from SAH to randomization, from randomization to treatment procedure, or in the length of stay in the intensive care unit. Patients allocated endovascular treatment stayed for a significantly shorter time in hospital (Mean: 19.4 days, Median: 15 days, Range: 1–84 days), than the patients allocated neurosurgery (Mean: 23.3 days, Median: 18 days, Range: 3–181 days)(p<0.05).

Data on functional outcome at 1 year after the hemorrhage was available for 277 patients (99.6%). For 1 patient allocated neurosurgery the 1-year outcome data was missing. Eighty-three (60.1%) of the 138 patients allocated endovascular treatment were independent at 1 year, compared with 78 (56.1%) of the 139 patients allocated neurosurgery (N.S.). The 1-year mortality rates were 18.1% for the endovascular group and 21.6% for the neurosurgery group (N.S.).

There was no significant difference in outcome between endovascular treatment and neurosurgery for patients with ACA or AComA aneurysms. The patients that underwent endovascular treatment for an ICA or PComA aneurysm had better outcomes than patients who were neurosurgically treated. Conversely, the patients with ruptured MCA aneurysms that underwent neurosurgery had better outcomes than the endovascularly treated (Table 13). There was no significant difference in outcome between patients with left-sided or right-sided MCA aneurysms in either treatment group (data not shown).
Table 13 Aneurysm location and outcome at 1 year by randomized treatment
ACA, anterior cerebral artery; AComA, anterior communicating artery; MCA, middle cerebral artery; ICA, internal carotid artery; PComA, posterior communicating artery; * 138 randomized to endovascular, 1 basilar artery aneurysm; † 140 randomized to neurosurgery, 3 posterior inferior cerebellar artery aneurysms; ‡ 1 patient lost to follow-up: 1 PComA aneurysm

The rates of procedural complications are shown in table 14. Aneurysm rupture occurred more frequently during neurosurgical procedures than during endovascular procedures. Aneurysm rupture during either procedure did not have any impact on the functional outcome. In the endovascularly treated patients, parent artery occlusion, thrombo-embolic problems, neurological deterioration and the use of thrombolytic agents were associated with a greater risk of dependency or death 1 year after SAH. Procedural complications during neurosurgical treatment did not have a marked influence on the functional outcome (data not shown).

Table 14 Procedural complications by actual treatment
There was a lower rate of epilepsy, infectious and pulmonary complications in the patients allocated endovascular therapy than in the patients allocated neurosurgery (Table 15). Adverse events that had a significant negative influence in functional outcome were delayed neurological deficit, hydrocephalus, epilepsy, infection, cerebral hematoma, pulmonary complications and other adverse event (data not shown).

<table>
<thead>
<tr>
<th></th>
<th>Endovascular (N=138)</th>
<th>Neurosurgery (N=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Delayed neurological deficit</td>
<td>48 (34.8)</td>
<td>51 (36.4)</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>35 (25.4)</td>
<td>43 (30.7)</td>
</tr>
<tr>
<td>Thrombo-embolic comp.</td>
<td>13 (9.4)</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>35 (25.4)</td>
<td>38 (27.1)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1 (0.7)</td>
<td>18 (12.9)</td>
</tr>
<tr>
<td>Infection</td>
<td>16 (11.6)</td>
<td>29 (20.7)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 (1.5)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Other infection</td>
<td>14 (10.1)</td>
<td>26 (18.6)</td>
</tr>
<tr>
<td>Cerebral hematoma *</td>
<td>14 (10.2)</td>
<td>16 (11.4)</td>
</tr>
<tr>
<td>ICH</td>
<td>6 (4.4)</td>
<td>11 (7.9)</td>
</tr>
<tr>
<td>ECH</td>
<td>4 (2.9)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Both ICH and ECH</td>
<td>4 (2.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>26 (18.8)</td>
<td>44 (31.4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7 (5.1)</td>
<td>21 (15.0)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>8 (5.8)</td>
<td>11 (7.9)</td>
</tr>
<tr>
<td>Other pulmonary comp.</td>
<td>11 (8.0)</td>
<td>12 (8.6)</td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Severe headache</td>
<td>5 (3.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other adverse event</td>
<td>38 (27.7)</td>
<td>43 (30.7)</td>
</tr>
</tbody>
</table>

* Missing data for 1 patient; ICH, intracerebral hematoma; ECH, extracerebral hematoma

**Paper IV**

The occurrence and severity of secondary insults in SAH patients during neurointensive care was investigated in 99 patients of all ages (67.7% females), who fulfilled the minimum monitoring data requirement for ICP, CPP, MAP and BPs. Of these, 4 patients did not meet the minimum requirement for SpO2 data, and in 43 patients less than required temperature data was available. All statistical analyses of SpO2 and T° data was done on the remaining 95 and 56 patients who fulfilled the minimum requirement for SpO2 and T°, respectively. The Hunt and Hess grade on admission was grade I in 3 (3.0%), grade II in 4 (4.0%), grade III in 24 (24.2%), grade IV in 65 (65.7%) and grade V in 3 (3.0%) patients. The amount of subarachnoid
blood on the diagnostic CT according to Fisher was grade 1 in 0, grade 2 in 1, grade 3 in 23 (23.2%) and grade 4 in 75 (75.8%) patients. The location of the ruptured aneurysm was the ACA or AComA in 39, the ICA in 11, the PComA in 11, the MCA in 21 and in the posterior circulation in 17 patients. The ruptured aneurysm was treated with endovascular therapy in 62 patients and with surgical clipping or trapping in 34 patients. 3 patients deteriorated clinically and were not deemed suitable for either treatment and were therefore not treated for their ruptured aneurysms. The mean time from SAH to aneurysm treatment was 1.6 days (Median 0.2 days, Range 0–18 days). 38 patients developed DIND, of whom 32 patients (32.3%) received triple-H-therapy. 12 patients (12.1%) re-bleed after admission before (n=7) or during aneurysm coiling (n=5).

Figure 4 Distribution of high ICP insults
Number of patients by percent of good monitoring time (GMT) in 5%-intervals.

The occurrence of secondary insults was low and non-normally distributed. Three quarters of all patients spent less than 5–10% of GMT at standard insult levels for high ICP (Figure 4), low CPP, high MAP and low BPs, and less than 20% of GMT at standard insults levels for high CPP (Figure 5) and high BPs. Only a small number of patients exceeded the limit for severe insult levels for high ICP, low CPP, high CPP, low MAP, high MAP, low BPs and high BPs. Ninety percent of the patients with SpO₂ data spent less than 5% of GMT at the standard insult level for SpO₂ and only one patient had more than 1% of GMT at the severe insult level for SpO₂ (Table 19, page 56).
Figure 5 Distribution of high CPP insults
Number of patients by percent of good monitoring time (GMT) in 5%-intervals

The distribution of pyrexia insults was different from the other secondary insults. Patients ranged from close to no time to more than 80% of GMT at standard insult level in a normally distributed pattern (Figure 6).

Figure 6 Distribution of pyrexia insults
Number of patients by percent of good monitoring time (GMT) in 5%-intervals.
Male patients had less low BPs insults and more high BPs insults than female patients (Median %GMT: BPs ≤110: Male 1.54, Female 3.10, P <0.01; BPs ≤100: Male 0.28, Female 0.66, P<0.001; BPs >180: Male 14.89, Female 5.58, P<0.05; BPs >200 Male 1.45, Female 0.19, P<0.05).

Patients 65 years or older (“Elderly”) had less ICP insults than patients younger than 65 (“Younger”) (Median %GMT: ICP ≥20: Elderly 1.83, Younger 4.38, P<0.01; ICP ≥25: Elderly 0.53, Younger 1.34, P<0.01). The elderly group had less low BPs standard insults, than the younger group (Median %GMT: BPs ≤110: Elderly 1.64, Younger 2.48, P<0.05). Furthermore, the elderly group had more high BPs standard insults, than the younger group (Median %GMT: BPs >180: Elderly 13.34, Younger 4.90, P<0.05). Elderly patients spent more time at standard insult levels for SpO2 than younger patients (Median %GMT: SpO2 <95: Elderly 2.22, Younger 1.05, P<0.05).

Patients who were awake or drowsy on admission (H&H I–III) had less high BPs standard insults than patients who were comatose (H&H IV–V) (Median %GMT: BPs >180: H&H I–III 1.38, H&H IV–V 9.29, P<0.05).

Patients with the presence of an ICH on the diagnostic CT scan had a higher percentage of GMT with ICP ≥20 than patients without an ICH (Median %GMT: ICP ≥20: ICH 5.44, No ICH 2.69, P<0.05).

Patients with the ruptured aneurysm in the anterior circulation (Ant.) had a higher proportion of ICP insults than patients with the ruptured aneurysm in the posterior circulation (Post.) (Median %GMT: ICP ≥20: Ant. 4.21, Post. 2.26, P<0.05; ICP ≥25: Ant. 1.31, Post. 0.56, P<0.05).

There were no differences in the occurrence of any secondary insults depending on re-bleeding, aneurysm treatment modality or Fisher grade on the diagnostic CT scan.

Overall, 13 patients (13.1%) made a good recovery (GR), 24 (24.2%) had a moderate disability (MD), 38 (38.4%) had a severe disability (SD), 3 (3.0%) were in a persistent vegetative state (VS) and 21 patients (21.2%) were dead (D) at the 6 months functional outcome follow-up. Thus, 37 patients (37.4%) had an independent outcome (GR and MD) and 62 (62.4%) were dependent or dead (SD, VS and D).

A univariate logistic regression model with independent functional outcome as dependent variable was fitted with each admission and treatment variable and percentage of GMT for each secondary insult level as explanatory variables. Patients in good clinical grade on admission (Hunt and Hess I–III) had a greater chance of an independent outcome than patients in poor clinical grade (Hunt and Hess IV–V) (OR 1.71, CI 95%: 1.10–2.65, p<0.05). Other admission and treatment variables, such as sex, age, Fisher grade, aneurysm location and triple-H-therapy did not have a significant impact on the functional outcome. Neither did the occurrences of any secondary insults have a significant impact on the functional outcome at 6 months after SAH.

At the time of discharge from NICU 83 patients (83.83%) had improved clinically or were in an unchanged neurological grade and 16 patients
(16.16%) had deteriorated or died. This clinical course outcome was used as the dependent variable in the logistic regression modeling.

In the univariate analyses, no admission or treatment variable had a statistically significant effect on clinical deterioration. ICP ≥20, ICP ≥25, CPP ≤60 and CPP ≤55 was associated with an increased risk of clinical deterioration, while CPP >100 and BPs >180 was associated with a decreased risk of clinical deterioration. MAP, SpO₂ and T° insults did not have a significant impact on clinical deterioration.

A multivariate logistic regression model was fitted with ICP ≥20, ICP ≥25, CPP ≤60, CPP ≤55, CPP >100 and BPs >180 as explanatory variables and clinical deterioration as the dependent variable. The final model included ICP ≥25 and CPP >100 which had an independent significant effect on clinical deterioration. ICP ≥25 increased the risk of clinical deterioration, whereas CPP >100 reduced the risk of clinical deterioration (Table 16).

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>OR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP ≥25</td>
<td>per 5 % ↑ GMT*</td>
<td>1.50</td>
<td>4.47</td>
<td>1.08–18.52</td>
</tr>
<tr>
<td>CPP &gt;100</td>
<td>per 5 % ↑ GMT*</td>
<td>-0.51</td>
<td>0.60</td>
<td>0.36–1.00</td>
</tr>
</tbody>
</table>

Table 16 Multivariate logistic regression with clinical deterioration as dependent variable and secondary insults as explanatory variables

OR, odds ratio; CI, confidence interval; ICP, intracranial pressure; CPP, cerebral perfusion pressure; OR >1 increased risk of clinical deterioration; OR <1 decreased risk of clinical deterioration; * per 5 % increase of GMT at secondary insult level

Paper V

In order to investigate age-dependent differences in functional outcome and occurrence of secondary insults in patients with severe SAH, the same patient cohort as in paper IV was divided into three age groups. Of the 99 patients with severe SAH, 35 patients were <55 years, 35 were 55–64 years and 29 patients were ≥65 years. The clinical characteristics and treatment variables of the patients by age group are shown in table 17. There were no significant imbalances between the groups in terms of gender, Hunt and Hess grade, Fisher grade, presence of ICH and/or IVH or in the distribution of aneurysm location.

There was a significantly higher frequency of re-bleeding before admission in the ≥65 years group and in the <55 years group than in the 55–64 years group (Table 17). The patients who were ≥65 years had a lower rate of clinical vasospasm (DIND) and received triple-H-therapy to a lesser extent than the patients aged 55–64 years. There was no significant difference in the proportion of patients receiving endovascular versus neurosurgical aneurysm treatment between the age groups (Table 17).
| Table 17 Clinical characteristics and treatment variables for three age groups |
|---------------------------------|-----------------|-----------------|-----------------|
| ICH, intracerebral hematoma; IVH, intraventricular hematoma; ACA, anterior cerebral artery; AComA, anterior communicating artery; ICA, internal carotid artery; PComA, posterior communicating artery; MCA, middle cerebral artery; DIND, delayed ischemic neurological deficit; HHH, triple-H-therapy |

Six months after the SAH, 42.9% of the younger patients and 24.1% of the elderly patients had an independent outcome (good recovery and moderate disability) (P=0.062). The mortality rate was 15.7% of the younger and 34.5% of the elderly patients (P<0.05). There was no significant difference in the frequency of severe disability (SD) between elderly and younger patients (Table 18).

Of the patients who were in a poor neurological grade on admission, 32.6% of the younger and 22.7% of the elderly patients made a good recovery or had a moderate disability (N.S.). The frequency of severe disability in poor grade patients was similar in the younger and elderly age groups. There was a trend...
indicating a higher mortality rate in the poor grade elderly patients compared to younger patients, however not statistically significant (Table 18).

<table>
<thead>
<tr>
<th>All Hunt and Hess grades</th>
<th>&lt;65 years</th>
<th>≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Good recovery</td>
<td>10.0</td>
<td>20.7</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>32.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Severe disability</td>
<td>37.1</td>
<td>41.4</td>
</tr>
<tr>
<td>Vegetative state</td>
<td>4.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Dead</td>
<td>15.7</td>
<td>34.5</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>29</td>
</tr>
</tbody>
</table>

| Hunt and Hess I–II       | N.S.      |           |
| Good recovery            | 25.0      | 33.3      |
| Moderate disability      | 75.0      | 0.0       |
| Severe disability        | 0.0       | 0.0       |
| Vegetative state         | 0.0       | 0.0       |
| Dead                     | 0.0       | 66.7      |
| Total                    | 4         | 3         |

| Hunt and Hess III        | N.S.      |           |
| Good recovery            | 10.0      | 25.0      |
| Moderate disability      | 45.0      | 0.0       |
| Severe disability        | 30.0      | 50.0      |
| Vegetative state         | 0.0       | 0.0       |
| Dead                     | 15.0      | 25.0      |
| Total                    | 20        | 4         |

| Hunt and Hess IV–V       | N.S.      |           |
| Good recovery            | 8.7       | 18.2      |
| Moderate disability      | 23.9      | 4.5       |
| Severe disability        | 43.5      | 45.5      |
| Vegetative state         | 6.5       | 0.0       |
| Dead                     | 17.4      | 31.8      |
| Total                    | 46        | 22        |

Table 18 Outcome 6 months after SAH by age group

* P<0.01 for difference between “<65 years” vs. “≥65 years”; † P<0.05 for difference between “<65 years” vs. “≥65 years” in proportion of “Dead” (Chi-square test)

The percent of GMT spent at insult levels for intracranial hypertension (ICP ≥20 and ICP ≥25) decreased with age, whereas the percent of GMT spent at insult levels for hypertensive (BPs >180) and hypoxemic insults (SpO₂ <95%) increased with age (Figure 7) (Table 19).
Figure 7 Intracranial hypertension, hypertensive and hypoxemic insults by age group
Upper: Squares: ICP ≥20 mmHg, Triangles: ICP ≥25 mmHg; Middle: Squares: BPs >180 mmHg, Triangles: BPs >200 mmHg; Lower: Squares: SpO2 <95%, Triangles: SpO2 <90%: Median values of good monitoring time (GMT); Whiskers: 25%–75% range; * ICP ≥20 mmHg: KW-H(2;99)=11.145, p=0.0038; † ICP ≥25 mmHg: KW-H(2;99)=9.9775, p=0.0068; ‡ BPs >180 mmHg: KW-H(2;99)=7.3347, p=0.0255; § BPs >200 mmHg: KW-H(2;99)=5.1369, p=0.0767; ¶ SpO2 <95%: KW-H(2;95)=7.476, p=0.0238; # SpO2 <90%: KW-H(2;95)=2.8564, p=0.2397 (Kruskal-Wallis ANOVA)
Elderly patients (≥65 years) had a greater percent of GMT with BPs >200 than patients younger than 55 years. The patients aged ≥65 years spent a greater percent of GMT at insult levels for MAP ≤70 than the patients aged <55 years. However, elderly patients (≥65 years) spent lesser percent of GMT at insult level for BPs ≤110 than younger patients (<55 years and 55–64 years). There were no differences between the age groups in the percent of GMT spent at insult levels for low CPP and high CPP insults, high MAP insults and pyrexia insults (Table 19).

<table>
<thead>
<tr>
<th>Secondary insult variable</th>
<th>All patients</th>
<th>&lt;55 years</th>
<th>55–64 years</th>
<th>≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP ≥20</td>
<td>3.52</td>
<td>4.90</td>
<td>1.83</td>
<td>* §</td>
</tr>
<tr>
<td>ICP ≥25</td>
<td>1.16</td>
<td>1.37</td>
<td>0.53</td>
<td>† §</td>
</tr>
<tr>
<td>CPP ≤60</td>
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<td>4.52</td>
<td>3.95</td>
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</tr>
<tr>
<td>CPP ≤55</td>
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<td>1.50</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>CPP &gt;100</td>
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<td>7.68</td>
<td>9.04</td>
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</tr>
<tr>
<td>CPP &gt;110</td>
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<td>2.06</td>
<td>1.93</td>
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</tr>
<tr>
<td>MAP ≤80</td>
<td>12.94</td>
<td>9.53</td>
<td>19.22</td>
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</tr>
<tr>
<td>MAP ≤70</td>
<td>1.58</td>
<td>1.07</td>
<td>2.31</td>
<td>‡</td>
</tr>
<tr>
<td>MAP &gt;120</td>
<td>2.70</td>
<td>3.00</td>
<td>3.30</td>
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</tr>
<tr>
<td>MAP &gt;130</td>
<td>0.38</td>
<td>0.41</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>BPs ≤110</td>
<td>2.21</td>
<td>2.27</td>
<td>1.64</td>
<td>* ‡</td>
</tr>
<tr>
<td>BPs ≤100</td>
<td>0.43</td>
<td>0.54</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>BPs &gt;180</td>
<td>8.10</td>
<td>3.03</td>
<td>13.34</td>
<td>§</td>
</tr>
<tr>
<td>BPs &gt;200</td>
<td>0.65</td>
<td>0.17</td>
<td>1.34</td>
<td>‡</td>
</tr>
<tr>
<td>T° ≥38</td>
<td>48.05</td>
<td>41.90</td>
<td>55.49</td>
<td></td>
</tr>
<tr>
<td>T° ≥39</td>
<td>1.24</td>
<td>1.18</td>
<td>1.64</td>
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</tr>
<tr>
<td>SpO2 &lt;95</td>
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<td>0.97</td>
<td>2.22</td>
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<tr>
<td>SpO2 &lt;90</td>
<td>0.05</td>
<td>0.04</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

Table 19 Occurrence of secondary insults by age group
Occurrence of secondary insults expressed as percent of good monitoring time (%GMT) by age group; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; BPs, systolic blood pressure; T°, body temperature; SpO2, arterial oxygen saturation; IQR, interquartile range; * P<0.05 “≥65 years” vs. “55–64 years”; † P<0.01 “≥65 years” vs. “55–64 years”; ‡ P<0.05 “≥65 years” vs. “<55 years”; § P<0.01 “≥65 years” vs. “<55 years” (Mann-Whitney U test)

In the univariate logistic regression analyses, increasing age was negatively associated with ICP ≥20 and ICP ≥25, and positively associated with MAP ≤80, MAP ≤70, BPs >180 and BPs >200. Presence of an ICH in addition to the SAH was positively associated with ICP ≥20 and CPP ≤55. Triple-H-therapy (HHH) was negatively associated with CPP ≤60, CPP ≤55, MAP ≤80 and MAP ≤70. Clinical vasospasm (DIND) was negatively associated with MAP ≤80 and MAP ≤70. Female gender was positively associated with BPs ≤110 and BPs ≤100 and negatively associated with BPs >180, BPs >200 and MAP >130.
In the multivariate logistic regression analyses, increased patient age was an independent factor associated with decreased risk of ICP ≥20 and ICP ≥25, and increased risk of MAP ≤70, BPs >180, BPs >200 and SpO2 <95. Presence of an ICH was associated with increased risk of ICP ≥20 and CPP ≤55. Triple-H-therapy was independently associated with decreased risk of CPP ≤60, CPP ≤55, MAP ≤80 and MAP ≤70. Female gender was an independent factor associated with increased risk of BPs ≤110, BPs ≤100, and decreased risk of MAP >130, BPs >180 and BPs >200 (Table 20).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>OR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>ICP ≥20</td>
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<td></td>
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</tr>
<tr>
<td>Age</td>
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<td>0.89–0.98</td>
<td>0.0039</td>
</tr>
<tr>
<td>ICH</td>
<td>0.47</td>
<td>1.61</td>
<td>1.04–2.49</td>
<td>0.0336</td>
</tr>
<tr>
<td>ICP ≥25</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.04</td>
<td>0.96</td>
<td>0.92–1.00</td>
<td>0.0411</td>
</tr>
<tr>
<td>CPP ≤60</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HHH</td>
<td>-0.49</td>
<td>0.61</td>
<td>0.40–0.95</td>
<td>0.0287</td>
</tr>
<tr>
<td>CPP ≤55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>0.47</td>
<td>1.60</td>
<td>1.04–2.45</td>
<td>0.0314</td>
</tr>
<tr>
<td>HHH</td>
<td>-0.50</td>
<td>0.61</td>
<td>0.39–0.95</td>
<td>0.0292</td>
</tr>
<tr>
<td>MAP ≤80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHH</td>
<td>-0.49</td>
<td>0.61</td>
<td>0.40–0.95</td>
<td>0.0287</td>
</tr>
<tr>
<td>MAP ≤70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.04</td>
<td>1.05</td>
<td>1.00–1.09</td>
<td>0.0440</td>
</tr>
<tr>
<td>HHH</td>
<td>-0.47</td>
<td>0.63</td>
<td>0.40–0.98</td>
<td>0.0400</td>
</tr>
<tr>
<td>MAP &gt;130</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>-0.56</td>
<td>0.57</td>
<td>0.37–0.89</td>
<td>0.0138</td>
</tr>
<tr>
<td>BP ≤110</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.70</td>
<td>2.01</td>
<td>1.27–3.17</td>
<td>0.0028</td>
</tr>
<tr>
<td>BP ≤100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.93</td>
<td>2.53</td>
<td>1.55–4.12</td>
<td>0.0002</td>
</tr>
<tr>
<td>BP &gt;180</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.08</td>
<td>1.08</td>
<td>1.03–1.13</td>
<td>0.0015</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.47</td>
<td>0.63</td>
<td>0.39–1.00</td>
<td>0.0502</td>
</tr>
<tr>
<td>BP &gt;200</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.06</td>
<td>1.07</td>
<td>1.02–1.12</td>
<td>0.0055</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.46</td>
<td>0.63</td>
<td>0.40–1.00</td>
<td>0.0492</td>
</tr>
<tr>
<td>SpO2 &lt;95</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>1.05</td>
<td>1.00–1.10</td>
<td>0.0303</td>
</tr>
</tbody>
</table>

Table 20: Multivariate logistic regression with secondary insult variables as dependent variable and clinical and treatment variables as explanatory variables. OR, odds ratio; OR <1, decreased risk of secondary insult occurrence; OR >1, increased risk of secondary insult occurrence; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; BPs, systolic blood pressure; T°, body temperature; SpO2, arterial oxygen saturation; CI, Confidence interval; ICH, intracerebral hematoma; HHH, triple-H-therapy.
Age-dependent differences in the incidence of cerebral vasospasm were investigated in paper VI on 413 patients, who fulfilled the inclusion criteria for this study. There were 368 patients (89.1%) who were <65 years and 45 patients (10.9%) were ≥65 years (Table 21).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients mean age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51 ± 11</td>
<td></td>
</tr>
<tr>
<td><strong>Patients age, dichotomized</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>368</td>
<td>(89.1)</td>
</tr>
<tr>
<td>≥65</td>
<td>45</td>
<td>(10.9)</td>
</tr>
<tr>
<td><strong>Patients age, categorized</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>00–40</td>
<td>70</td>
<td>(17.0)</td>
</tr>
<tr>
<td>41–50</td>
<td>128</td>
<td>(31.0)</td>
</tr>
<tr>
<td>51–60</td>
<td>124</td>
<td>(30.0)</td>
</tr>
<tr>
<td>≥61</td>
<td>91</td>
<td>(22.0)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>121</td>
<td>(29.3)</td>
</tr>
<tr>
<td>Female</td>
<td>292</td>
<td>(70.7)</td>
</tr>
<tr>
<td><strong>Admission WFNS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>184</td>
<td>(44.6)</td>
</tr>
<tr>
<td>Grade II</td>
<td>117</td>
<td>(28.3)</td>
</tr>
<tr>
<td>Grade III</td>
<td>12</td>
<td>(2.9)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>97</td>
<td>(23.5)</td>
</tr>
<tr>
<td>Grade V</td>
<td>3</td>
<td>(0.7)</td>
</tr>
<tr>
<td><strong>Subarachnoid clot size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diffuse thick</td>
<td>280</td>
<td>(68.8)</td>
</tr>
<tr>
<td>diffuse thin</td>
<td>88</td>
<td>(21.6)</td>
</tr>
<tr>
<td>local thick</td>
<td>34</td>
<td>(8.4)</td>
</tr>
<tr>
<td>local thin</td>
<td>5</td>
<td>(1.2)</td>
</tr>
<tr>
<td><strong>IVH</strong></td>
<td>322</td>
<td>(78.0)</td>
</tr>
<tr>
<td><strong>IVH/ICH</strong></td>
<td>331</td>
<td>(80.1)</td>
</tr>
<tr>
<td><strong>History of hypertension</strong></td>
<td>172</td>
<td>(41.7)</td>
</tr>
<tr>
<td><strong>Aneurysm sizes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 mm</td>
<td>153</td>
<td>(38.2)</td>
</tr>
<tr>
<td>6–15 mm</td>
<td>238</td>
<td>(59.4)</td>
</tr>
<tr>
<td>16–25 mm</td>
<td>5</td>
<td>(1.2)</td>
</tr>
<tr>
<td>&gt; 25 mm</td>
<td>5</td>
<td>(1.2)</td>
</tr>
<tr>
<td><strong>Aneurysm location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>181</td>
<td>(45.0)</td>
</tr>
<tr>
<td>ICA</td>
<td>116</td>
<td>(28.9)</td>
</tr>
<tr>
<td>MCA</td>
<td>73</td>
<td>(18.1)</td>
</tr>
<tr>
<td>Posterior</td>
<td>32</td>
<td>(8.0)</td>
</tr>
</tbody>
</table>

Table 21 Baseline characteristics in 413 patients
WFNS, World Federation of Neurological Surgeons; IVH, intraventricular hemorrhage; ICH, intracerebral hematoma; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; Posterior, posterior cerebral circulation
The distribution of clinical characteristics and treatment in the different age groups are shown in table 22.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (% )</td>
<td>N (% )</td>
</tr>
<tr>
<td>Male</td>
<td>112 (30.4)</td>
<td>9 (20.0)</td>
</tr>
<tr>
<td>Female</td>
<td>256 (69.6)</td>
<td>36 (80.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WFNS grade, collapsed</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>171 (46.5)</td>
<td>13 (28.9)</td>
</tr>
<tr>
<td>Grade II</td>
<td>101 (27.4)</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>Grade III–V</td>
<td>96 (26.1)</td>
<td>16 (35.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clot size, collapsed</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin</td>
<td>89 (24.5)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Thick</td>
<td>274 (75.5)</td>
<td>40 (90.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of aneurysm treatment</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clipping</td>
<td>180 (48.9)</td>
<td>19 (42.2)</td>
</tr>
<tr>
<td>Coiling</td>
<td>188 (51.1)</td>
<td>26 (57.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clazosentan treatment group</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>84 (22.8)</td>
<td>12 (26.7)</td>
</tr>
<tr>
<td>1 mg/h</td>
<td>98 (26.6)</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>5 mg/h</td>
<td>97 (26.4)</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>15 mg/h</td>
<td>89 (24.2)</td>
<td>9 (20.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rescue therapy, all</th>
<th>Age &lt;65 years</th>
<th>Age ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>66 (17.9)</td>
<td>8 (17.8)</td>
</tr>
</tbody>
</table>

Table 22 Admission and treatment variables by age groups
WFNS, World Federation of Neurological Surgeons

The ruptured aneurysm was treated with neurosurgical clipping in 199 (48.2%) patients and with endovascular coiling in 214 (51.8%). The patients were randomized to one of four study drug treatment groups. There were 96 patients (23.2%) in the placebo group, 108 (26.2%) in the clazosentan 1 mg/h group, 111 (26.9%) in the clazosentan 5 mg/h group, and 98 (23.7%) patients were allocated to the clazosentan 15 mg/h group. Rescue therapy was performed in 74 (17.9%) patients, of whom 68 (16.5%) patients received hemodynamic therapy. In 186 (45.0%) patients a ventriculostomy was placed for ICP monitoring and CSF drainage. 366 (88.6%) patients received a calcium channel blocker. In 155 (37.5%) patients an anti-epileptic drug was given, of whom 128 (31.0%) patients received phenytoin. In 62 patients (15.0%) a temperature ≥38 °C was recorded for 8 days.

The rate of radiological vasospasm was 45.1% and when severe vasospasm was imputed for missing values, the rate was 47.0%. The rate of DIND was 18.9%. The analysis on abnormal TCD and the reported results are based on the 75 patients with TCD data only. Abnormal TCD measurements indicative of cerebral vasospasm were recorded at some point in 61 of 75 patients (81.3%).
Radiological VSP | Radiological VSP* | DIND | TCD VSP
--- | --- | --- | ---
N=381 | N=413 | N=413 | N=75

**Gender**  
- Male: 34.82 (39/112) 37.19 (45/121) 14.88 (18/121) 66.67 (10/15)  
- Female: 49.44 (133/269) 51.03 (149/292) 20.55 (60/292) 85.00 (51/60)

**Age, dichotomized**  
- ≤65: 45.91 (157/342) 47.28 (174/368) 19.02 (70/368) 84.06 (58/69)  
- ≥65: 38.46 (15/39) 44.44 (20/45) 17.78 (8/45) 50.00 (3/6)

**Age, categorized**  
- <65: 45.91 (157/342) 47.28 (174/368) 19.02 (70/368) 84.06 (58/69)  
- ≥65: 38.46 (15/39) 44.44 (20/45) 17.78 (8/45) 50.00 (3/6)

**WFNS, collapsed**  
- Grade I: 38.37 (66/172) 40.22 (74/184) 10.87 (20/184) 86.21 (25/29)  
- Grade II: 40.00 (44/110) 41.88 (49/117) 18.80 (22/117) 84.21 (16/19)  
- Grade III–V: 62.63 (62/99) 63.39 (71/112) 32.14 (36/112) 74.07 (20/27)

**Clot size, collapsed**  
- Thin: 33.33 (30/90) 35.35 (35/99) 9.68 (9/93) 84.62 (11/13)  
- Thick: 48.77 (139/285) 50.65 (156/314) 21.97 (69/314) 80.65 (50/62)

**Aneurysm treatment**  
- Clipping: 55.14 (102/185) 55.78 (111/199) 23.12 (46/199) 88.89 (32/36)  
- Coiling: 35.71 (70/196) 38.79 (83/214) 14.95 (32/214) 74.36 (29/39)

**Clazosentan group**  
- Placebo: 67.74 (63/93) 66.67 (64/96) 22.92 (22/96) 75.00 (18/24)  
- 1mg/h: 46.08 (47/102) 48.15 (52/108) 20.37 (22/108) 90.48 (19/21)  
- 5mg/h: 40.59 (41/101) 41.44 (46/111) 15.32 (17/111) 91.67 (11/12)  
- 15mg/h: 24.71 (21/85) 32.65 (32/98) 17.35 (17/98) 72.22 (13/18)

**Ventriculostomy**  
- Yes: 56.47 (96/170) 56.45 (105/186) 27.96 (52/186) 82.86 (29/35)  
- Rescue therapy, all: 88.57 (62/70) 87.84 (65/74) 68.92 (51/74) 97.14 (34/35)  
- Hemodynamic therapy: 87.69 (57/65) 86.76 (59/68) 66.18 (45/68) 93.10 (27/29)  
- Calcium channel blocker: 43.07 (146/339) 44.81 (164/366) 19.13 (70/366) 80.28 (57/71)  
- Phenytoin: 56.64 (64/113) 56.25 (72/128) 21.09 (27/128) 86.96 (20/23)

**Table 23** Patient characteristics and treatments by vasospasm outcomes measures p, difference between categories (chi-square)/(Fisher exact test); sample size in brackets. VSP, vasospasm; *“Severe vasospasm” imputed for missing values; TCD, transcranial Doppler; WFNS, World Federation of Neurological Surgeons; Variables not significantly associated with the outcomes at p<0.10 and not considered in further analyses included: History of hypertension, IVH, IVH/ICH, use of antiepileptics, aneurysm sizes, aneurysm locations, and body temperature ≥38 °C for 8 days.

The associations of admission and treatment variables with the three dependent dichotomized vasospasm outcome measures are shown in table 23. Gender, WFNS grade, clot size, type of aneurysm treatment, clazosentan treatment group, and use of ventriculostomy, rescue therapy, hemodynamic therapy, calcium channel blocker and phenytoin were associated with radiological vasospasm in the univariate analysis. Factors associated with DIND in the univariate analysis were WFNS grade, clot size, type of aneurysm treatment, use of ventriculostomy, rescue therapy and hemodynamic therapy. In the 75 patients with
TCD data, age and the use of rescue therapy and hemodynamic therapy were associated with TCD abnormalities in the univariate analysis (Table 23).

These variables were modeled as potential predictors of each of the outcome measures in the multivariate logistic regression with age forced into the model as the initial independent predictor variable.

Multivariate logistic regression with age as a dichotomous variable (Table 24A) or as a categorical variable (Table 24B) showed that there was no significant relationship of age with any of the vasospasm outcome measures.

Significant predictors of radiological vasospasm were gender, subarachnoid clot size, aneurysm treatment modality, clazosentan treatment group, and use of ventriculostomy, rescue therapy, hemodynamic therapy and phenytoin. The imputation of ‘severe’ for the missing data in radiological vasospasm did impact the relationship of certain clinical characteristics like WFNS grade, use of ventriculostomy, calcium channel blocker and hemodynamic therapy in the resulting model. The factors that were associated with an increased rate of radiological vasospasm were female gender, higher WFNS grade, thick clot size, neurosurgical clipping, use of ventriculostomy, rescue therapy, hemodynamic therapy and phenytoin and not using a calcium channel blocker. A higher WFNS grade, neurosurgical clipping, use of ventriculostomy and rescue therapy were significant predictors associated with a higher rate of DIND. The only significant relationship in the final model for TCD abnormalities was the use of rescue therapy, which was associated with a higher rate of TCD abnormalities (Table 24A and 24B).
<table>
<thead>
<tr>
<th>Vasospasm outcomes</th>
<th>Adjusted OR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
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<td><strong>Radiological Vasospasm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients age, dichotomized</td>
<td>0.468</td>
<td>0.181–1.207</td>
<td>0.1163</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>1.965</td>
<td>1.092–3.536</td>
<td>0.0242</td>
</tr>
<tr>
<td>WFNS, collapsed</td>
<td>1.371</td>
<td>0.974–1.931</td>
<td>0.0708</td>
</tr>
<tr>
<td>Clot size, collapsed</td>
<td>1.961</td>
<td>1.023–3.759</td>
<td>0.0427</td>
</tr>
<tr>
<td>Type of aneurysm treatment</td>
<td>0.292</td>
<td>0.169–0.502</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clazosentan treatment group</td>
<td>0.431</td>
<td>0.329–0.565</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of ventriculostomy</td>
<td>1.979</td>
<td>1.136–3.448</td>
<td>0.0159</td>
</tr>
<tr>
<td>Use of rescue therapy, all</td>
<td>7.953</td>
<td>2.766–22.87</td>
<td>0.0001</td>
</tr>
<tr>
<td>Use of hemodynamic therapy</td>
<td>3.534</td>
<td>1.160–10.76</td>
<td>0.0263</td>
</tr>
<tr>
<td>Use of phenytoin</td>
<td>2.074</td>
<td>1.173–3.666</td>
<td>0.0121</td>
</tr>
<tr>
<td><strong>Radiological Vasospasm - Imputed</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients age, dichotomized</td>
<td>0.892</td>
<td>0.416–1.913</td>
<td>0.7686</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>1.797</td>
<td>1.067–3.026</td>
<td>0.0276</td>
</tr>
<tr>
<td>WFNS, collapsed</td>
<td>1.431</td>
<td>1.070–1.914</td>
<td>0.0156</td>
</tr>
<tr>
<td>Clot size, collapsed</td>
<td>1.894</td>
<td>1.075–3.336</td>
<td>0.0271</td>
</tr>
<tr>
<td>Type of aneurysm treatment</td>
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<td>0.259–0.684</td>
<td>0.0005</td>
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<tr>
<td>Clazosentan treatment group</td>
<td>0.552</td>
<td>0.441–0.691</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of rescue therapy, all</td>
<td>12.02</td>
<td>5.544–26.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of calcium channel blocker</td>
<td>0.444</td>
<td>0.211–0.935</td>
<td>0.0326</td>
</tr>
<tr>
<td>Use of phenytoin</td>
<td>1.968</td>
<td>1.184–3.273</td>
<td>0.0091</td>
</tr>
<tr>
<td><strong>DIND</strong></td>
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<td></td>
</tr>
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<td>0.939</td>
<td>0.339–2.605</td>
<td>0.9045</td>
</tr>
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<td>1.056–2.371</td>
<td>0.0263</td>
</tr>
<tr>
<td>Type of aneurysm treatment</td>
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<td>0.0291</td>
</tr>
<tr>
<td>Use of ventriculostomy</td>
<td>2.722</td>
<td>1.338–5.538</td>
<td>0.0057</td>
</tr>
<tr>
<td>Use of rescue therapy, all</td>
<td>29.19</td>
<td>14.41–59.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Abnormal TCD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients age, dichotomized</td>
<td>0.290</td>
<td>0.045–1.860</td>
<td>0.1917</td>
</tr>
<tr>
<td>Use of rescue therapy, all</td>
<td>14.67</td>
<td>1.784–120.7</td>
<td>0.0125</td>
</tr>
</tbody>
</table>

Table 24A Multivariate logistic regression with vasospasm outcomes as dependent variables and patients age dichotomized at age 65 as the main explanatory variable. Adjusted odds ratios for the vasospasm outcomes with significant predictors at <10% level and back selected at <5% level. Odds ratio >1, increased risk for vasospasm outcomes; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurological Surgeons; DIND, delayed ischemic neurological deficit; TCD, transcranial Doppler.
<table>
<thead>
<tr>
<th>Vasospasm outcomes</th>
<th>Adjusted OR</th>
<th>CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiological Vasospasm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients age, categorized</td>
<td>0.954</td>
<td>0.734–1.239</td>
<td>0.7254</td>
</tr>
<tr>
<td>Gender</td>
<td>1.906</td>
<td>1.063–3.417</td>
<td>0.0304</td>
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<tr>
<td>WFNS, collapsed</td>
<td>1.357</td>
<td>0.963–1.912</td>
<td>0.0814</td>
</tr>
<tr>
<td>Clot size, collapsed</td>
<td>2.005</td>
<td>1.047–3.841</td>
<td>0.0359</td>
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<tr>
<td>Type of aneurysm treatment</td>
<td>0.291</td>
<td>0.169–0.499</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clazosentan treatment group</td>
<td>0.432</td>
<td>0.330–0.565</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of ventriculostomy</td>
<td>1.846</td>
<td>1.070–3.184</td>
<td>0.0276</td>
</tr>
<tr>
<td>Use of rescue therapy, all</td>
<td>8.213</td>
<td>2.882–23.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of hemodynamic therapy</td>
<td>3.397</td>
<td>1.128–10.24</td>
<td>0.0297</td>
</tr>
<tr>
<td>Use of phenytoin</td>
<td>2.111</td>
<td>1.196–3.724</td>
<td>0.0099</td>
</tr>
<tr>
<td><strong>Radiological Vasospasm - Imputed</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Patients age, categorized</td>
<td>1.028</td>
<td>0.814–1.301</td>
<td>0.8151</td>
</tr>
<tr>
<td>Gender</td>
<td>1.785</td>
<td>1.062–3.001</td>
<td>0.0287</td>
</tr>
<tr>
<td>WFNS, collapsed</td>
<td>1.419</td>
<td>1.060–1.899</td>
<td>0.0187</td>
</tr>
<tr>
<td>Clot size, collapsed</td>
<td>1.876</td>
<td>1.061–3.314</td>
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</tr>
<tr>
<td>Type of aneurysm treatment</td>
<td>0.421</td>
<td>0.259–0.683</td>
<td>0.0005</td>
</tr>
<tr>
<td>Clazosentan treatment group</td>
<td>0.553</td>
<td>0.442–0.692</td>
<td>&lt;0.0001</td>
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<td>Use of rescue therapy, all</td>
<td>12.18</td>
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<td>Use of calcium channel blocker</td>
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<td>Use of phenytoin</td>
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<td>1.193–3.304</td>
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</tr>
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<td><strong>DIND</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients age, categorized</td>
<td>1.103</td>
<td>0.804–2.354</td>
<td>0.5541</td>
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<td>Use of ventriculostomy</td>
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<td>Use of rescue therapy, all</td>
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<td>14.73–61.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Abnormal TCD</strong></td>
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<td>Patients age, categorized</td>
<td>0.589</td>
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<tr>
<td>Use of rescue therapy, all</td>
<td>17.16</td>
<td>2.074–141.9</td>
<td>0.0084</td>
</tr>
</tbody>
</table>

Table 24B Multivariate logistic regression with vasospasm outcomes as dependent variables and patients age categorized by decade as the main explanatory variable. Adjusted odds ratios for the vasospasm outcomes with significant predictors at <10% level and back selected at <5% level. Odds ratio >1, increased risk for dependent variable; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurological Surgeons; DIND, delayed ischemic neurological deficit; TCD, transcranial Doppler.
Discussion

Changes in management and outcome over time

The volume of elderly SAH patients admitted for treatment at the department of Neurosurgery in Uppsala increased over an 18-year period. In part this increase has a mere demographic cause, since during the same time the total elderly population in the referral area of the clinic increased with 18%. However, most of the increase reflects an increasing propensity to refer and admit these patients due to changes in attitude towards active treatment in this group of patients over time. One explanation for this gradual change towards more active treatment of elderly SAH patients may be that it became obvious that the general treatment results had improved, and that positive experiences of individual cases catalyzed the evolution towards a more active treatment policy of the elderly. Subsequently, the management also changed at the referral hospitals, which can be illustrated by the finding that with time more patients were referred earlier, and artificial ventilation during transport was more widely used. With time, elderly patients in more advanced ages and in worse neurological grade were admitted for active treatment. Improved or unchanged clinical outcome would therefore reflect better management, and not an effect of selection of patients with better chances.

With time, trends toward more favorable outcome and a lower mortality rate were seen, but the difference between the periods was not significant in the univariate analysis. The rate of severe disability was unchanged. However, the improvement in outcome may be underestimated because of the patients being older and in worse neurological grade with time. Considering this it is reasonable to believe that the management of elderly patients had actually improved. This was supported in the multivariate logistic regression analysis, which revealed that the outcome results had improved substantially.

The improved results may be explained by several factors. An important contribution is the establishment of a NICU, and that elderly patients were also treated according to NIC principles, e.g. intensive monitoring and secondary insult prevention. It is difficult to evaluate which specific parts of the management approach have had the most important impact. The use of ventriculostomy was related to less favorable results according to the multivariate logistic regression analysis. The clinical impression is that poor grade patients improve and qualify for early aneurysm treatment after CSF drainage without an increased risk of re-bleeding. The unexpected finding may be
explained by the fact that the indication for ventriculostomy was neurological deterioration or re-bleeding in many cases. The timing of aneurysm treatment did not influence the outcome significantly. However in the last 2 periods, more patients underwent treatment of the ruptured aneurysm, which most likely has contributed to the improved outcome. The more efficient initial management and early referral have probably also had a positive effect on the results. The introduction of endovascular aneurysm treatment during the last period improved the management of patients with aneurysms in the posterior circulation in absolute terms, since most elderly patients with posterior circulation aneurysm were treated conservatively prior to this. The impact of endovascular aneurysm treatment in the elderly SAH patients overall was evaluated in a separate investigation, which will be discussed in the following section.

**Introduction of coiling in elderly SAH patients**

Shortly after endovascular coiling was established as a routine therapy at our department, it became the first line of aneurysm treatment. A particularly quick change in treatment policy occurred for the elderly SAH patients after reports of successful endovascular treatment in this age group. The patients included in paper II was a consecutive series of 62 elderly SAH patients who were treated for ruptured intracranial aneurysms during the first four years this treatment modality was the first line of aneurysm treatment. During this period 56% of the elderly patients underwent endovascular coiling, while neurosurgical aneurysm treatment was preferred in 33% and 11% were managed conservatively due to clinical deterioration.

**Technical feasibility and aneurysm occlusion rate**

The technical success of endovascular coiling in elderly patients in paper II was 94%. Only 4 procedures were terminated because of technical inaccessibility. Fifty-six percent of the target aneurysms were completely occluded on the end-procedural angiogram. Neck remnants were present in 21% of the cases and 11% were not densely packed with coils, which may seem disappointing. The main reason was probably that the goal in this age group was to prevent the ruptured aneurysm from re-bleeding without running too great a complication risk. It is reasonable to believe that a partly occluded aneurysm may be sufficient for the remainder of a patient’s expected life span, but a neurological deficit may substantially decrease the quality of life in this age group. The rate of total occlusion in patients of all ages is reported from 50% to 57.5% and in elderly patients from 39% to 69%, which is in accordance with our data. In the ISAT study, the total oc-
clusion rate on the first angiographic follow up was 66%, 26% had neck remnants and 8% had incomplete occlusion in the endovascular group. 

Procedural complications

The procedural complication rate was 11%, most of which were potentially serious complications such as aneurysm rupture, parent vessel occlusion and occlusion of other vessels due to thrombo-embolism. Procedural complication rates of this magnitude has been reported before in patients of all ages. The total procedural complication rate in elderly patients has been reported between 4.2% and 21% . The rate of procedural aneurysm rupture was 2%, which is slightly greater than the 1.4% risk of aneurysm rupture during endovascular treatment reported from a high volume center. The rate of parent artery occlusion was 2% and the rate of occlusion of arteries other than the parent artery due to thrombosis from coils and catheters and embolism was 6%. Thrombo-embolic complications at a rate of 5.7% have been reported before. However, there was no increased morbidity or mortality related to procedural complications. Of the 7 patients, who had a procedural complication, 5 enjoyed a favorable outcome, 1 had a severe disability and 1 patient died. It is generally accepted that the seriousness of a disease determines the level of risk, involved with the treatment, one finds acceptable. The natural course of SAH is truly grim, with a high risk of fatal re-bleeding and delayed neurological deterioration due to vasospasm. Occlusion of the ruptured aneurysm is crucial for the further management of the patient, so an 11% risk of a procedural complication in treating high-risk elderly patients with this devastating disease may therefore be considered acceptable.

Outcome

In the crude outcome analysis, 41% of all patients and 57% of the Hunt & Hess I–II patients had a favorable outcome. The mortality rate was 22% and 36% were severely disabled at 6 months after SAH. These outcome figures are comparable to other series of endovascularly treated aneurysms in elderly SAH patients. In a small series of 9 endovascularly treated elderly SAH patients in good neurological grade by Rowe and colleagues, 6 had a favorable outcome, 1 had a severe disability, 1 patient died and 1 patient was lost to follow-up. In a study by Birchall et al, 12 of 14 good grade elderly SAH patients made a full recovery, 1 had a moderate disability and 1 patient died. In a series by Sedat and colleagues of 52 endovascularly treated patients ≥65 years, 48% had a favorable outcome, 27% were severely disabled and the mortality rate was 23% at 1 year after the SAH. Lubicz et al reported good or excellent outcome in 59% of 68 elderly SAH patients treated with endovascular coiling. However, these series enclosed a
greater proportion of good grade patients and a greater proportion of patients with a low Fisher grade compared to the patients in paper II. In a series by Mont’alverne et al 52% of endovascularly treated SAH patients over 60 years had a favorable outcome and the mortality rate was 36% 248. In a series by Cai et al of 41 SAH patients over 70 years, 89% of Hunt and Hess I–II patients had a favorable outcome, whereas 77% of Hunt and Hess III–V patients were severely disabled or died 247. Jain et al reported 38% favorable outcome in Hunt and Hess IV–V patients over 70 years 246. In paper II, 65% of the patients were >70 years and 34% of the patients were in poor neurological grade on admission. Furthermore, 24% of the patients had posterior circulation aneurysms, which before the introduction of endovascular coiling largely would have been managed conservatively due to the high surgical risks in this age group. The clinical outcome of the patients with posterior circulation aneurysms was similar to the patients with anterior circulation aneurysms. The results of this series should be viewed against this background, thus the outcomes in paper II may be considered fair.

Patients with a low Fisher grade had better outcomes and there was a trend towards better outcome in patients treated on days 4–10 and >10 days after SAH. This is illustrated in the multivariate logistic regression analysis where a later day of treatment was associated with favorable outcome; however, not statistically significant (p=0.060). This may reflect that the patients who underwent endovascular coiling at a later stage after the SAH were subjected to a selection process, in which only patients retaining a good clinical grade at this stage were considered for treatment. The optimal timing of endovascular coil embolization of ruptured aneurysms in the elderly requires further investigation in larger series. However, it is notable that as many as 40% of the patients treated before and during the “vasospasm phase” had a favorable outcome.

The aneurysm location seems to be an important determining factor for clinical outcome in endovascularly treated elderly SAH patients. In spite of small numbers, differences in outcome depending on aneurysm location were seen; however, interpretation should be made with caution. The highest proportion of favorable outcomes and lowest proportion of severe disabilities were seen in patients with ICA and PComA aneurysms, whereas the most severe disability was seen in patients with aneurysms on the ACA and the AComA. Half of the patients (3/6) with MCA aneurysms had a poor outcome and only one enjoyed a favorable outcome, which implies that the endovascular aneurysm treatment of MCA aneurysms is associated with higher risks (further discussed below).

Due to differences in the patient populations, comparison of the outcome results of this endovascular series to previous surgical series at the department was problematic. A comparison of neurosurgical clipping and endovascular coiling was also beyond the scope of paper II, but was done in
paper III on a subset of elderly patients randomized to endovascular coiling or neurosurgical clipping within the ISAT study.

Coiling versus clipping in elderly SAH patients

The patients in paper III were a subset of all patients 65 years or older in the ISAT study. They were predominately good grade patients with a single small anterior circulation aneurysm, which reflects a selection bias due to the eligibility criteria for entering the trial. Less than 10% of the patients were in poor neurological grade (WFNS IV–V) on admission. This probably reflects the view in many centers that early neurosurgical aneurysm treatment was deemed inappropriate in a poor grade elderly patient and early endovascular treatment was therefore preferred in these patients \(^{256}\). The proportion of posterior circulation aneurysms was 1.4%; a low figure compared to other surgical and particularly endovascular series. Most centers probably considered endovascular treatment the favored modality for these aneurysms \(^{257}\). The findings in paper III can be generalized to elderly patients similar to those enrolled, i.e. good grade elderly patients with a ruptured anterior circulation aneurysm with a suitable anatomy for either endovascular or neurosurgical treatment.

Outcome

In paper III there was no statistically significant difference in independent survival between endovascular and neurosurgical treatment, although there was a trend towards a greater proportion of independent survival after endovascular treatment (60%) than after neurosurgery (56%). The number of elderly patients in the ISAT study were relatively few (278), encompassing only 13% of the whole study population, thus not enough to reach the goal of the statistical power calculations set out in the ISAT study protocol for the whole study cohort. However, there is no reason to doubt that the reduction of dependent survival or death after endovascular treatment seen in all patients in the ISAT cohort shouldn’t be valid even in the elderly.

The location of the ruptured aneurysm had an important impact on the functional outcome in paper III, as in paper II. Moreover, the aneurysm occlusion technique – endovascular coiling or neurosurgical clipping – influenced the functional outcome depending on the aneurysm location.

ACA and AComA aneurysm – Patients with ruptured ACA and AComA aneurysms had 55% independent survival in the endovascular and 51% independent survival in the neurosurgical group. Because of the proximity to the frontal lobes it would be expected that these patients could develop cognitive impairment, deficits in executive functions, personality changes and speech impairment. These impairments may be caused by the disease itself,
i.e. the aneurysm rupture or by regional cerebral vasospasm, but also by the
treatment of the ruptured aneurysm. Previous studies focusing on the cogni-
tive result after surgical treatment of AComA aneurysms have shown defi-
cits in verbal fluency, pattern recognition and spatial working memory
as well as increased risk-taking behavior. In a comparative study of en-
dovascular and neurosurgical treatment of AComA aneurysms and controls
have indicated worse cognitive performance in the surgically treated group.
There has also been reported a greater structural damage, MRI detected
focal encephalomalacia and multiple small infarcts, after neurosurgery com-
pared with endovascular treatment.

ICA and PComA aneurysms – Endovascular treatment of ICA and
PComA aneurysms achieved 72% independent survival compared to 52% in
the neurosurgically treated group. In the pre-specified subgroup analysis of
all patients in ISAT, the point estimate for patients with ICA aneurysms
favored endovascular treatment. These results suggest that endovascular
coiling should be the treatment of choice in elderly SAH patients with a rup-
tured aneurysm in the ICA and PComA territory.

MCA aneurysms – 87% of the patients who underwent neurosurgery for a
ruptured MCA aneurysm had an independent outcome at 1 year compared
with 46% of the endovascularly treated patients. There was no indication
that the difference in outcome between neurosurgery and endovascular
treatment was the effect of imbalance between the treatment groups in terms
of right- or left-sided aneurysms, WFNS grade, Fisher grade, patient age,
aneurysm lumen diameter, or aneurysm neck size. Difficulty in endovascular
treatment of MCA aneurysms due to morphological characteristics have
been described before and is a challenge for the interventional radiologist.
The often-encountered configuration with multiple branches arising
adjacent to the aneurysm neck in MCA aneurysms predisposes to incomplete
aneurysm occlusion and increased risk for vessel occlusion. This implies that
endovascular aneurysm treatment of MCA aneurysms is associated with
higher risks and careful selection of suitable MCA aneurysms for endovas-
cular treatment seems to be fundamental for good results. These results sug-
gest that neurosurgical clipping appear to be the favored treatment for most
ruptured MCA aneurysms in elderly SAH patients, presupposed that other
clinical factors does not contraindicate surgery.

Posterior circulation aneurysms – In paper III only 4 patients with poste-
rior circulation aneurysms were included, due to the inclusion criteria of
clinical equipoise. Most centers probably considered endovascular therapy to
be the treatment of choice for these surgically challenging aneurysms in
elderly SAH patients. Previous studies have reported excellent results with
endovascular treatment of ruptured and unruptured posterior circulation an-
eurysms.
Procedural complications

One objective in paper III was to analyze the rates of procedural complications of endovascular coiling versus neurosurgical clipping of elderly SAH patients. Since the procedural complications to a certain extent are procedure-specific, the comparison of procedural complications was made by the actual treatment performed and not by the randomized treatment allocation.

Aneurysm rupture is a feared intra-procedural complication during both endovascular coiling and neurosurgical clipping of an intracranial aneurysm. Aneurysm rupture during aneurysm surgery has been reported at a rate of 17–19% and is associated with less favorable outcome. During endovascular coiling the risk of aneurysm rupture has been reported to 1.4%. In paper III the rate of aneurysmal rupture during treatment was significantly higher in the neurosurgically treated group (16.7%) than in the endovascular group (6.4%). However, aneurysm rupture did not have a significant impact on functional outcome in either treatment group.

The rate of thrombo-embolic problems after the procedure was higher in the endovascularly treated group (7.1%) compared to the neurosurgically treated group (1.6%). The rate of parent artery occlusion was similar in the endovascular group (5%) compared to the neurosurgical group (3.2%). However, in the neurosurgically treated patients the occurrence of a procedural complication did not have any effect on the functional outcome, whilst procedural complications (other than aneurysm rupture) in the endovascularly treated patients had a detrimental effect on the functional outcome. Only 1 patient with thrombo-embolic problems and none with parent artery occlusion had an independent survival. Of the 7 patients in whom a thrombolytic agent was used only 1 had an independent outcome. Further development of methods for avoiding inappropriate intraluminal thrombus formation during endovascular coiling is likely to improve outcome in these patients.

Adverse events

The frequency of epilepsy was greater after neurosurgery than after endovascular aneurysm treatment of the elderly SAH patients in paper III. It is reasonable to believe that the craniotomy, aneurysm dissection and the use of self-retaining retractors contribute to the development of epilepsy. The frequency of epilepsy in the neurosurgically treated patients in paper III was higher than in recently published series, but lower or at the same level as several earlier studies. The results suggest that the less invasive nature of endovascular aneurysm treatment can prevent morbidity in elderly SAH patients by reducing the risk of epilepsy.

Infectious and pulmonary complications, particularly pneumonia was found to be more prevalent in the patients allocated neurosurgery than in the patients allocated endovascular coiling. These complications are well known
in patients with prolonged artificial ventilation \textsuperscript{176, 273}, increased length of stay in an intensive care unit and prolonged bed rest. Accordingly we found that neurosurgically treated patients were admitted to hospital for a significantly longer period of time than endovascularly treated patients, but there was no difference in the length of stay in the intensive care unit. The difference in the frequency of infections and pulmonary complications between the two groups may be that endovascular treatment allowed quicker mobilization in these patients and therefore prolonged bed rest could be avoided and earlier discharge from hospital was possible.

Concern has been raised that endovascular aneurysm treatment does not allow irrigation of the basal cisterns and subarachnoid clot removal inherently to the nature of the treatment modality. It has been proposed that this would expose the patient to a greater risk of vasospasm and communicating hydrocephalus in the long term. Previous non-randomized studies comparing endovascular coiling and neurosurgical clipping have shown less vasospasm in the endovascular group \textsuperscript{244, 274-276}, less vasospasm in the neurosurgical group \textsuperscript{277}, as well as no difference between the two treatment modalities \textsuperscript{129, 177, 278, 279}. One small randomized study showed no difference in the rate of symptomatic vasospasm between endovascular and neurosurgical treatment \textsuperscript{280}. In a recent meta-analysis there were no difference in the rate of vasospasm after neurosurgical compared to endovascular treatment in patients of all ages \textsuperscript{281}.

Moreover, shunt dependent chronic hydrocephalus was unrelated to the aneurysm treatment modality in previous non-randomized studies of patients in all ages \textsuperscript{244, 282, 283}. One study found more shunt dependent hydrocephalus after endovascular aneurysm treatment, but the patients treated with endovascular coiling in this study were in worse neurological grade on admission compared to the neurosurgically treated, which may have biased the result \textsuperscript{284}.

In paper III there were no difference between the two treatment modalities in the frequency of delayed ischemic neurological deficits due to vasospasm or in the frequency of hydrocephalus necessitating a later shunting procedure. Thus, the importance of subarachnoid clot removal during craniotomy for aneurysm surgery may be overestimated in the elderly.

The shorter length of hospital stay and lesser frequency of pulmonary and infectious complications and epilepsy with endovascular aneurysm treatment compared with neurosurgical clipping in elderly patients may have implications for the net cost to the health care sector associated with each procedure. Also, a lower frequency of complications and a shorter length of hospital stay reduce suffering and are beneficial to the well-being and quality of life for the individual patient.
Secondary insults in severe subarachnoid hemorrhage

Although studied extensively in traumatic brain injury, few studies have reported the occurrence of secondary insults and its impact on outcome in SAH. A pilot study from our center showed that the number of secondary complications was an independent negative prognostic factor for favorable outcome \(^{164}\). However, the secondary insults were retrospectively recorded manually from surveillance charts and treated as categorical data. Heuer et al. reported increased risk for poor outcome in patients with elevated ICP, in particular when ICP did not respond to treatment \(^{285}\). The measure was the mean of a daily maximal ICP. Wartenberg et al. studied medical complications after SAH and their impact on outcome and found that fever, anemia and hyperglycemia were independent significant predictors of poor outcome \(^{286}\). Each complication in this study was coded as present if it occurred once during the hospital stay. As described by Jones et al., a large proportion of the secondary insults in TBI patients may be missed when using a manual recording method compared to a computerized monitoring system \(^{287}\). Paper IV is the first prospective study using computerized multi-modality monitoring for continuous registration of secondary insults and their impact on outcome in SAH. In paper V the outcome and impact of secondary insults after severe SAH in relation to age was studied.

All patients in this cohort had severe SAH requiring a ventriculostomy, for ICP monitoring and CSF drainage, and neurointensive care. The majority of patients were in poor neurological grade on admission (in some patients due to secondary deterioration before admission) and with high Fisher grades. Also the rates of re-bleeding and clinical vasospasm were higher than what is usually reported in consecutive series. The inclusion criteria requiring a substantial amount of multi-modality monitoring data during the first 10 days after SAH has further skewed the selection of patients toward increased severity of the SAH and patients with more complicated course of the disease requiring longer stay in the neurointensive care unit. Thus, the study population in papers IV and V differs from the general SAH patient population but could be quite representative for severe SAH patients admitted to neurointensive care units. The results and interpretations of this patient cohort should be viewed accordingly.

The minimum amount of monitoring data per patient for inclusion in paper IV and V was 5 days of data within the first 10 days after the SAH. The actual median monitoring time was approximately 7 to 8 days. Most patients had much more monitoring data than the minimum requirements. Thus, the amount of monitoring data collected was substantial. The median time from the SAH to the start of collection of multi-modality monitoring data was approximately 20 hours. Within this time interval one must account for the patient to seek medical attention, diagnosis of the SAH, referral time from
the referring hospital to our center, and time for intra-hospital transport to and from the operation theatre for placement of a ventriculostomy.

Definitions of secondary insults
The definitions of secondary insult levels in this study were based on previous studies of secondary insults in TBI and on clinical tradition and experiences. For high ICP, low CPP, low BPs, low SpO₂ and pyrexia the secondary insult levels were at or close to the treatment goal for each clinical parameter. Some secondary insult levels, for instance high CPP and high blood pressure, were arbitrarily chosen at the other extreme than the treatment goal for these parameters. This was done to explore the effects of physiological derangement in the opposite direction of what is intuitively associated with increased risk for secondary cerebral injury. Further, the same definitions of secondary insult levels were used in all patients regardless of age, gender and presenting clinical condition. It may be that the vulnerability for secondary brain injury differs depending on the patient characteristics and therefore differentiated secondary insult levels should be applied. However, it was not possible to foresee how such differentiated insult level definitions should be constructed, since there were no prior knowledge of the occurrence of secondary insults in different patient groups.

Occurrence and distribution of secondary insults
The occurrences of high ICP and low CPP insults were low and unevenly distributed. Only a few patients had large proportions of insults. This finding was especially distinct for the severe insults (Fig 4 and 5, pages 49–50). These findings are consistent with earlier reports on secondary insults in TBI from our center.

Previous experience indicates that the occurrence of secondary insults depend on the treatment protocol. Our treatment protocol for SAH stipulates continuous CSF drainage if the ICP is elevated above 20 mm Hg due to acute hydrocephalus. Most patients with high ICP due to this reason would therefore have drained CSF and ICP would have normalized, which explains the low occurrence of ICP insults. Patients with high ICP due to other reasons than acute hydrocephalus, such as ICH, large IVH or large ischemic lesions, in which the elevation in ICP would not be amenable to treat with CSF drainage may have spent a greater proportion of monitoring time above insult levels.

Further, our treatment protocol includes a standard lower limit for CPP (60 mm Hg), and action is taken to avoid lower CPP than 60 mm Hg. An upper limit for CPP has not been implemented, which explains the low occurrence of low CPP insults while high CPP insults were more common.

The distributions of blood pressure insults (MAP and BPs) show a similar pattern, although not so marked for MAP ≤80 and BPs >180. Our treatment
protocol is mainly ICP and CPP oriented and no strict limits for MAP are implemented as long as the treatment goals for ICP and CPP are met.

The occurrence of SpO\textsubscript{2} insults was very rare, all patients spent less than 5\% of monitoring time below the severe insults level. Pyrexia was the only commonly occurring secondary insult. The goal was to keep body temperature $<38$ °C, but this was not achieved in many patients. Efforts must be made to find better methods to avoid hyperthermia during neurointensive care of SAH patients.

Occurrence of secondary insults related to base characteristics

There was no difference between female and male patients in the distribution of CPP and ICP insults but female patients sustained more low BPs insults and less high BPs insults. Somewhat surprisingly the patient neurological grade on admission was not found to be a strong predictor of the subsequent occurrence of secondary insults, except for high BPs insult, where patients in a poor neurological grade on admission spent more monitoring time above the insult levels. As expected, patients with an ICH in addition to the SAH on the diagnostic CT had more ICP insults than patients without an ICH. Ruptured aneurysms in the anterior cerebral circulation seem to be a factor associated with more ICP insults. The patients with anterior circulation aneurysms spent more time at insult levels than patients with posterior circulation aneurysms. This may reflect a tendency that the patients with ruptured aneurysms in the anterior circulation to a greater extent also have ICH and IVH than patients with ruptured aneurysms in the posterior circulation\textsuperscript{92}.

Age and occurrence of secondary insults

In the elderly patients there was a lower occurrence of ICP insults and a higher occurrence of hypertensive, as well as hypotensive, and hypoxemic insults. The baseline characteristics on admission such as gender, Hunt and Hess grade, Fisher grade, presence of ICH and IVH and location of the ruptured aneurysm were similar in all age groups. Therefore it is unlikely that the observed difference in the occurrence of secondary insults in different age groups is caused by selection bias of patients in the elderly group with lower risk of secondary insults. To control for other possible causal factors contributing to the occurrence of secondary insults, multivariate logistic regression was performed with each secondary insult as dependent variable and admission and treatment variables as explanatory variables.

Age and presence of an ICH were independent factors for decreasing and increasing the risk for high ICP insults, respectively. The lower occurrence of ICP insults in the elderly SAH patients may be attributed to that the relative size of the brain to the intracranial compartment decreases with age, due to age-related brain atrophy. This has implications for the intracranial dy-
namics, yielding a greater tolerance for conditions that may lead to increased ICP, such as an ICH or disturbed CSF circulation, before the pressure within the intracranial compartment increases above insult levels.

Elderly patients spent a larger percent of GMT above insult levels for high BPs. This may be explained by the greater prevalence of hypertension in the elderly in the population, which is reflected also in the elderly patients admitted with SAH. The association between age and hypotension was ambiguous and may be difficult to interpret. In the univariate analysis the elderly group had a greater percent of GMT at insult level for MAP ≤70 but a lower percent of GMT at insult levels for BPs ≤110 than the younger patients. In the multivariate analysis age was independently associated with an increase in the percent of GMT at insult levels for hypotensive insults (MAP ≤70). The effects of aging on the cardiovascular system include a decrease in elasticity and a reduced compliance of the vasculature, which leads to an increased afterload and increased systolic blood pressure. The finding that elderly patients had less hypotensive insults if defined as BPs ≤110 is probably explained by the greater prevalence of hypertension in the elderly population, especially high systolic blood pressure, in accordance with the increased occurrence of hypertensive insults (above). With increasing age there is also a decreased reactivity to baro- and chemoreceptors, and cardiovascular performance under stress is reduced, which may explain the association between age and the increased risk for MAP ≤70. When in a situation of hypovolemia elderly patients may have a lower capacity to compensate with vasoconstriction and increased cardiac output than younger patients and hence are more prone to hypotensive insults.

The percent of GMT spent at insult levels for low oxygen saturation increased in the elderly age group and increased age was an independent predictor of increased hypoxemic insults in the multivariate analysis. This may be explained by the age-related decline in arterial oxygenation and the reduced pulmonary reserve rendering the elderly patient more susceptible to respiratory complications during prolonged bed rest in intensive care. Increased sensitivity to respiratory depressants and muscle weakness in the elderly patient further increase the risk of respiratory complications.

It is obvious in paper V that the physiological monitoring data collected during neurointensive care are different in the elderly. This was demonstrated by applying defined criteria for the secondary insults. For methodological reasons, the criteria were the same for all ages. This may be reasonably adequate for ICP but regarding e.g. hypertension and hypotension the critical threshold for secondary brain injury is probably different depending on age. In order to optimize the neurointensive care management of the elderly SAH patients, it is important to identify critical threshold levels in this age group. High resolution monitoring data from larger patient series may provide a possibility to study the impact of different threshold levels on functional outcome and clinical deterioration in different age groups. Fur-
thermore, multi-modality monitoring, including e.g. intracerebral microdialysis, may be helpful. Extensive monitoring may also be beneficial in the elderly concerning the complicated situation observed where both low MAP and high systolic BP were common.

Secondary insults and functional outcome

It could not be demonstrated in paper IV that any of the secondary insult at any level had impact on functional outcome at 6 months after SAH. At most tendencies for numerical differences could be seen where the patients with an independent outcome had less high ICP and less low CPP insults. However this should not be interpreted as that secondary insults does not have an effect on functional outcome. The standard regimen to early detect and treat secondary insults in the NICU has resulted in a low occurrence of secondary insults. This may indicate that secondary insults that were avoidable were reduced to a minimum, while the insults still present were not amenable to treatment and may be coupled to the primary injury. This may explain the lack of correlation to long term functional outcome. It is reasonable to believe that there would have been a stronger correlation between secondary insults and outcome in another setting where secondary insults would not have been monitored and actively treated. The general experience is that the significance of an established prognostic factor disappears if the factor can be treated effectively. In this setting, when secondary insults are actively avoided, it may be needed a larger patient cohort to prove an effect of secondary insults on outcome. Furthermore, rehabilitation efforts may restore and/or alleviate lost functions, which will impact the long-term functional outcome. Thus the impact of secondary insults may be overshadowed by the impact of the primary injury or rehabilitation efforts. To study the specific effects of secondary insults during neurointensive care we used an alternative outcome measure, based on the clinical course.

Secondary insults and clinical deterioration

The patients who deteriorated during stay in NICU spent more time at insult levels for high ICP and low CPP, and spent significantly less time at insult levels for high CPP, high MAP and high BPs.

The patients who deteriorated probably reflect a group where the elevation in ICP was intractable to treatment. Whether the patients deteriorated because of the intractable elevated ICP, or ICP was elevated because of some factor causing the deterioration is not clear. In the multivariate logistic regression analysis, intracranial hypertension (ICP ≥25) was an independent predictor of clinical deterioration. This implies that raised ICP that does not respond to standard treatment for a significant amount of time results in clinical deterioration, which was an expected result and consis-
tent with result from other centers. Heuer and colleagues used mean daily maximum ICP as explanatory variable and found that elevated ICP was associated with worse patient outcome in particular if ICP did not respond to treatment. However, it could not be shown that this association was independent from neurological grade and severity of the SAH in the multivariate analysis in their study 285.

High CPP insults (CPP >100) were independently associated with improvement or unchanged clinical status. Most management protocols (including our own) focus on detecting and avoiding high ICP and low CPP, but less focus is put on targeting the optimal CPP and MAP. In some treatment protocols for TBI much attention is given to avoid high CPP because of the risk of inducing cerebral edema causing additional ICP elevation 289, 290. In SAH, induction of hypervolemia, hypertension and hemodilution (triple-H-therapy) is widely accepted for treatment of symptomatic cerebral vasospasm. Managing all patients with triple-H-therapy, regardless of symptoms of delayed ischemic deficits has also been proposed, but its prophylactic efficacy has not been confirmed in randomized controlled trials 155, 156, and it is not recommended 291. The finding in paper IV, that CPP over 100 mm Hg independently decreased the risk for clinical deterioration may reflect the positive effect of high cerebral perfusion pressure in patients with severe SAH on lowering the risk for secondary ischemic injury. Conclusions regarding the mechanism can not be drawn from this data. Hypothetically the effect could be mediated either directly by increased CBF to areas of the brain at risk for ischemia or indirectly by decreasing the risk for cerebral vasospasm. The threshold at which high CPP was defined as an insult in this study was arbitrarily chosen based on clinical impression of the ordinary occurrence and supposed clinical impact. The optimal CPP levels for decreasing the risk of clinical deterioration in SAH patients should be evaluated in future prospective studies. Furthermore, one must also bear in mind that spontaneous high CPP due to hypertension and normalized ICP may not have the same effect on the risk for clinical deterioration as induced high CPP by means of vasopressors and/or volume expansion. Therefore it can not be recommended to induce high CPP in all patients based on these results. However, it may be beneficial not to lower spontaneous high CPP in SAH patients.

Outcome in elderly patients with severe SAH

The chance of an independent outcome in the elderly patients with severe SAH was 24%, compared to 43% in the younger patients. It can always be argued that this figure is too low to justify aggressive neurointensive care in this group of patients. However, one must consider the natural history of poor grade SAH patients; if untreated, the mortality rate approaches 100% 292, 293. The number of elderly patients with severe SAH needed to treat to save one patient to an independent life is approximately four to one. The most important
issue in this age group is probably the risk of surviving with a severe disability as opposed to dying from the hemorrhage. In this perspective the risk of severe disability was not increased in the elderly population, but rather on the same level as for the younger patients. Thus, the gradually increasing active management of elderly patients with severe SAH seems to be justified.

Against these experiences and the increasing proportion of elderly patients in the population, it is reasonable to expect that the trend towards treating more and more elderly patients with severe SAH will continue. The clue to successful treatment is to avoid secondary insults leading to secondary ischemia. Neurointensive care is dedicated to that purpose. The occurrence and consequences of secondary insults are probably different in elderly patients and it is therefore desirable to increase the knowledge in this field in order to be able to offer elderly patients with severe SAH a tailored neurointensive care.

**Age and cerebral vasospasm**

In paper VI, possible predictors of vasospasm including age were analyzed with multivariate logistic regression to discern which factors had an independent effect on the development of radiological vasospasm, DIND and abnormal TCD measurements indicative of vasospasm.

The data used in paper VI was collected for the CONSCIOUS-1 trial, a dose-finding study to evaluate the efficacy of three levels of clazosentan in preventing vasospasm following SAH. Patients with no or thin subarachnoid clot on CT were excluded, thus skewing the studied population towards more severe SAH. However the distributions of remaining baseline characteristics were similar to most previous studies and well reflect the typical patient population at neurosurgical centers managing SAH patients.

In some previous studies a reduced risk of radiological vasospasm with age have been shown 129, 225, 226, 294, 295, but in other studies age had no effect on the rate of radiological vasospasm 229, 296. Likewise the rate of clinical vasospasm or DIND has been reported to decrease with age in some studies 128, 177, 228, while in others the rate of DIND in the elderly patients was similar to that of younger patients 129, 229.

In a retrospective series of Artiola i Fortuny et al the rate of generalized radiological vasospasm declined in patients ≥60 years 225. Oka et al demonstrated 23% radiological vasospasm in patients ≥65 years compared to 44% in patients <65 years 294. In these early series the effect of age on vasospasm was not controlled for other factors associated with vasospasm, such as clinical grade or severity of SAH. Inagawa analyzed the radiological vasospasm grade in three age groups: <60 years, 61–69 years and ≥70 years in relation to the severity of SAH. The radiological vasospasm grade declined with age, which was consistent in all subgroups 226. In a later study by Inagawa the grade of radiological vasospasm was analyzed in patients <60 years compared to pa-
tients ≥60 years in relation to severity of the SAH and clinical grade. In that study strong correlation of the SAH grades to the radiological vasospasm grade and to the incidence of symptomatic vasospasm were found, but there were no significant differences between older and younger patients.

The observed reduced risk of cerebral vasospasm with age in some previous studies may be explained by imbalances in clinical grade and severity of SAH in the selection of patients in the older and younger age groups. In most series predominately elderly patients in good neurological grade were selected for treatment. The neurological grade is correlated to the amount of subarachnoid blood, which is a strong predictor of cerebral vasospasm. It is therefore important to control for other known factors predictive of cerebral vasospasm with multivariate analysis, to avoid confounding of the age effect on the risk for vasospasm.

In a retrospective study by Macdonald et al the degree of radiological vasospasm was analyzed using multiple regression with severity of radiological vasospasm as the dependent variable and preoperative angiographical arterial diameter ratio, clinical grade and age as independent variables. Increased age was associated with less radiological vasospasm. In a study by Hoh et al, age over 50 years was negatively related to total vasospasm (combined TCD abnormalities, radiological vasospasm and symptomatic vasospasm), but not associated with symptomatic vasospasm alone, when other predictors for vasospasm were controlled for in multivariate logistic regression. Rabb et al analyzed admission and treatment variables as to their relation to symptomatic vasospasm using multivariate logistic regression. Clinical grade, amount of SAH and younger age (less than 35 years) was found to be independent predictors of symptomatic vasospasm. In a study by Charpentier et al, age >50 years was an independent factor associated with reduced risk of symptomatic vasospasm, when other predictors for symptomatic vasospasm were controlled for with multivariate logistic regression. Torbay et al demonstrated that the rate of symptomatic vasospasm and TCD defined vasospasm was significantly lower in patients ≥68 years than in patients <68 years, but no statistically significant difference between the age groups could be detected in the rate of radiological vasospasm.

When TCD has been used for detection of vasospasm according to defined criteria, elderly patients have a lower rate of cerebral blood flow velocities (CBFV) indicative of vasospasm. The sensitivity of high CBFV for detecting vasospasm in elderly SAH patients was low when using the same criteria as in younger patients. Symptomatic vasospasm occurred at lower CBFV in elderly patients necessitating an age-dependent CBFV nomogram for detecting vasospasm. Reasons for lower CBFV in older individuals may be explained by the greater prevalence of atherosclerosis, but also by age-dependent changes in the anatomical course of the MCA changing the insonation angle when performing the TCD measurements.
Thus, even when other predictive factors for vasospasm are controlled for with multivariate analyses, the effect of age on the risk for vasospasm is inconsistent. Differences in the used measure and definition of vasospasm and the used cut-off age for the elderly group in different studies complicate comparison and influence the interpretation. It was therefore desirable to investigate the independent effect of age on radiological vasospasm, DIND and TCD abnormalities in the same prospective cohort of patients in paper VI. Multivariate logistic regression was used to control for admission and treatment variables that may be associated with vasospasm. The outcome measures, radiological vasospasm, DIND and TCD abnormalities, were clearly defined in the protocol and data was meticulously recorded prospectively.

Age is not a predictor of cerebral vasospasm

In the univariate analysis in paper VI, a trend towards less radiological vasospasm and less TCD abnormalities in the elderly age group was seen when age was considered dichotomized at age 65. However the proportion of patients \( \geq 65 \) years was only 11% of the total study population, creating an imbalance between the age groups. This was the reason for categorizing age by decade to get a more even distribution of patients in the different age groups. When age was considered categorized by decade it was obvious that there was no difference in the rate of radiological vasospasm and DIND between the age groups. There was a numerical difference with less TCD abnormalities in the patients over 60 years compared to the younger patients, however not statistically significant.

In the multivariate analysis, age, whether considered as a dichotomous or a categorical variable, was not significantly associated with radiological vasospasm, DIND or TCD abnormalities.

The size of the patient cohort was chosen based on power calculations for demonstrating a reduction in radiological vasospasm in the clazosentan treatment groups, and not for the question in the present study. It can therefore be argued that the sample size may be too small for rejecting the null hypothesis, that there is no difference between elderly and younger patients in the rate of vasospasm, i.e. supporting that there is an actual difference. However, the present study population is larger than or has approximately the same size as previous studies that have shown an age-dependent difference in the rate of vasospasm.

Thus, the main finding in paper VI that the patient age does not seem to be a predictor for cerebral vasospasm after SAH, does not appear to be an effect of selection bias, inaccurate detection rate of vasospasm or too small study population.
Conclusions

Elderly patients with SAH can be treated successfully and the results are improving and a defeatist attitude towards elderly patients with this otherwise devastating disease is not justified.

Endovascular aneurysm treatment can be performed in elderly SAH patients with a high level of technical success, with acceptable aneurysm occlusion results, with an acceptable rate of procedural complications, and with fair outcome results.

There was no clear evidence that early endovascular coil embolization in elderly SAH patients should be avoided.

Middle cerebral artery aneurysms may be less suitable for endovascular coiling and elderly SAH patients with middle cerebral artery aneurysms appear to benefit from neurosurgical clipping.

Endovascular coiling may be the treatment of choice for ruptured internal carotid artery and posterior communicating artery aneurysms in elderly SAH patients.

Endovascular coiling reduced the risk of infectious and pulmonary complications and the frequency of epilepsy compared to neurosurgical clipping in elderly SAH patients.

Endovascular coiling reduced the length of stay in hospital compared to neurosurgical clipping in elderly SAH patients.

A neurointensive care unit with strict management protocols and standard treatment regimens for detecting and treating secondary insults has resulted in a low occurrence of secondary insults in SAH patients.

The occurrence of secondary insults was not predictive of poor functional outcome in this study.
Elevated ICP not responding to treatment is predictive of clinical deterioration whereas high CPP is associated with decreased risk of clinical deterioration.

It may be beneficial not to lower spontaneous high CPP in SAH patients.

Elderly patients with severe SAH have less intracranial hypertension insults and more hypertensive, hypotensive and hypoxemic insults than younger patients.

An independent outcome was achieved in a substantial proportion of the elderly patients with severe SAH and the proportion of elderly patients with severe disability was at the same level as for younger patients. Thus, neuro-intensive care is justified also in elderly patients with severe SAH.

Further studies of multi-modality monitoring may provide insights on age-specific secondary insult levels necessary for a tailored neurointensive care specific for elderly patients with severe SAH.

Patient age is not a significant independent predictor for radiological vasospasm, clinical vasospasm and transcranial Doppler abnormalities indicative of vasospasm after SAH.
Subaraknoidalblödning (SAB) till följd av ett brustet intrakraniellt aneurysm är en allvarlig sjukdom med hög dödlighet och stor risk för betydande neurologiska handikapp. Äldre patienter med SAB har en sämre prognos än yngre, och historiskt har aktiv behandling av äldre SAB-patienter inte bedömts vara meningsfullt. Nya behandlingsstrategier har dock möjliggjort aktiv behandling av allt fler och allt äldre SAB-patienter. Idag är 17% av befolkningen över 65 år och andelen äldre fortsätter öka. Incidensen av SAB tilltar med åldern och i takt med den ökande andelen äldre i befolkningen kommer antalet äldre SAB-patienter att stiga. Således är det nödvändigt att öka kunskapen om behandling av SAB specifikt i den äldre åldersgruppen.


Volymen äldre patienter som behandlades ökade med tiden och framför allt ökade antalet patienter ≥70 år och andelen medvetandepåverkade och medvetslösa äldre patienter. Andelen äldre patienter som levde ett självständigt liv utan eller med endast ringa neurologiska handikapp vid uppföljningen ökade med tiden (A: 45%, B: 61% and C: 58%). Däremot ökade inte andelen patienter med svåra neurologiska handikapp och stort vårdbehov. Således räddades de flesta inte bara till livet, utan också till en självständig tillvaro.

Resultaten talar för att man bör ha en aktiv och icke defaitistisk attityd vid behandling av äldre patienter med SAB.


Det tekniska och kliniska behandlingsresultatet av 62 äldre SAB-patienter (≥65 år), som behandlades med endovaskulär coiling under de första fyra år denna nya behandlingsteknik användes i Uppsala, studerades.
Endovaskulär coiling var tekniskt möjligt i 94% av patienterna. Ocklusionsgraden av det behandlade aneurysmet var helt ockluderat i 56%, halsrest i 21% och kvarvarande minimal fyllnad av aneurysmet i 11%. Procedurrelaterade komplikationer inträffade i 11% av patienterna, men dessa komplikationer påverkade inte det kliniska behandlingsresultatet negativt. Andelen patienter som återgick till ett självständigt liv var 57% av de vakna patienterna, 47% av patienterna med grumlat medvetande och 17% av de medvetslösa patienterna.

Endovaskulär coiling av intrakraniella aneurysm hos äldre SAB patienter kan genomföras med en hög grad av teknisk framgång, med acceptabel ocklusionsgrad av aneurysmen, acceptabel komplikationsfrekvens och med rimliga behandlingsresultat.

International Subarachnoid Aneurysm Trial (ISAT) är en internationell randomiserad multicenterstudie som jämför behandlingsresultatet mellan öppen neurokirurgisk behandling och endovaskulär coiling för behandling av intrakraniella aneurysm efter SAB.

En subgrupp av 278 äldre (≥65 år) SAB-patienter som deltog i ISAT-studien studerades med avseende på kliniskt behandlingsresultat 1 år efter SAB, procedurrelaterade komplikationer och övriga komplikationer i de två behandlingsgrupperna.

Av de 138 patienter som randomiserades till endovaskulär behandling återgick 60% till ett självständigt liv jämfört med 56% av de 140 patienter som randomiserades till öppen neurokirurgisk behandling. Andelen patienter med aneurysm på a. carotis interna och a. communicans posterior som återgick till ett självständigt liv var 72% i den endovaskulärt behandlade gruppen jämfört med 52% i gruppen som genomgått öppen neurokirurgisk behandling. Av patienterna med aneurysm på a. cerebri media återgick 46% av patienterna i den endovaskulära gruppen till ett självständigt liv jämfört med 87% i den neurokirurgiska gruppen. Frekvensen av epilepsi och lungkomplikationer var högre och vårdtiden längre i gruppen som genomgått neurokirurgisk behandling jämfört med den endovaskulärt behandlade gruppen.

Vid behandling av äldre patienter med SAB bör endovaskulär behandling vara förstahandsmetod, då det brustna aneurysmet utgår från a. carotis interna eller a. communicans posterior. Öppen neurokirurgisk behandling bör kanske föredras då aneurysmet utgår från a. cerebri media.

Ogynnsamma sekundära händelser under neurointensivvården – sekundära insulter – antas bidra till ytterligare hjärnskada utöver den primära hjärnskadan efter SAB.

Ett datoriserat multimodalt övervakningsverktyg användes för att kontinuerligt samla in monitoreringsdata med ett mätvärde per minut för intrakraniellt tryck (ICP), cerebralt perfusionstryck (CPP), medelartärbloftryck (MAP), systoliskt blodtryck (BPs), syrgasmättnad i blodet (SpO2) och
Kroppstemperatur ($T^\circ$). Nivåer för varje sekundär insult definierades och förekomsten av sekundära insulter kvantifierades som procent av den totala monitoreringstiden över den definierade insultnivån.

99 patienter med svår SAB som behandlades med ventrikeldränage och neurointensivvård och med tillräcklig mängd monitoreringsdata inkluderas. Förekomsten av sekundära insulter var låg och ojämnt fördelad; merparten av patienterna hade mindre än 5–10% av monitoreringstiden ovan insultnivå, medan ett fåtal patienter hade en stor andel av monitoreringstiden ovan insultnivå. Kön, ålder, grad av neurologisk påverkan, förekomst av intracerebralt hematom och plats för aneurysmet inverkade på förekomsten av sekundära insulter.

Förekomsten av varje enskild sekundär insults inverkan på kliniskt behandlingsresultat och risk för neurologisk försämring under vården under söktes med multipel logistisk regression. Ingen av de studerade sekundära insulterna kunde påvisas ha inverkan på det kliniska behandlingsresultatet vid 6 månader efter SAB. En större proportion av monitoreringstiden med ICP $\geq$25 och en mindre proportion av monitoreringstiden med CPP $>$100 var oberoende prognostiska faktorer för neurologisk försämring.

Det är troligt att neurointensivvård och prevention av sekundära insulter har en mer framträdande betydelse vid behandling av äldre SAB-patienter, eftersom de är känsligare och mer sårbara för komplikationer. De goda erfarenheterna av behandling av äldre SAB-patienter ledde till en relativt hastig förändring av attityden till aktiv behandling av allt äldre patienter och äldre patienter med svår SAB.

Förekomsten av höga ICP-insulter var lägre medan förekomsten av hypotensiva, hypotemiska och hypoxemiska insulter var högre bland äldre patienter med svår SAB. Med multipel logistisk regression analyserades vilka epidemiologiska och kliniska behandlingsfaktorer som hade inverkan på förekomsten av varje enskild sekundär insult. Stigande ålder var associerad med minskad risk för ICP $\geq$20 och ICP $\geq$25 och ökad risk för MAP $\leq$70, BPs $>$180, BPs $>$200 och SpO2 $<$95. Av de äldre patienterna med svår SAB återgick 24% till ett självständigt liv 6 månader efter blödningen jämfört med 43% av de yngre, medan andelen överlevande med svåra neurologiska hinder var likartad mellan yngre och äldre patienter.

Således är neurointensivvård meningssäker även för äldre patienter med svår SAB. Mönstret av sekundära insulter skiljer sig mellan äldre och yngre patienter. Fortsatta monitoreringsstudier kan leda till åldersdifferentierade gränser för sekundära insulter, nödvändiga för att utveckla en skräddarsydd neurointensivvård specifik för äldre SAB-patienter.

Cerebral vasospasm är en fruktad komplikation och en bidragande orsak till neurologiska bortfall och död efter SAB. Flera tidigare studier tyder på att äldre patienter med SAB drabbas av denna komplikation i mindre utsträck-
ning än yngre patienter, men i flera studier kontrollerades inte för effekten av andra faktorer som har betydelse för risken att utveckla vasospasm.

413 patienter som ingick in en läkemedelsstudie (CONSCIOUS-1), varav 45 patienter ≥65 år, studerades med syftet att bestämma om ålder är en obe-
roende prediktiv faktor för risken att utveckla vasospasm. Multipel logistisk
regression användes för att kontrollera för effekten av andra möjliga predik-
tiva faktorer för vasospasm, såsom kön, grad av neurologisk påverkan,
mängd subaraknoidalt blod, aneurysmbehandlingsmetod och användningen
av olika läkemedel och vätsketerapier.

Patientåldern kunde inte påvisas vara en oberoende prediktiv faktor för ris-
ken att utveckla radiologisk vasospasm, klinisk vasospasm respektive ökad
blodflödes hastighet mätt med transkraniell Doppler talande för vasospasm.
Således är risken att utveckla vasospasm är inte avhängig patientens ålder.
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