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Aneurysmal subarachnoid hemorrhage, adverse events and outcome

Adverse events and outcome

Baldvinsdóttir, Bryndís

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PO Box 117
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Adverse events and outcome

BRYNDÍS BALDVINSDÓTTIR
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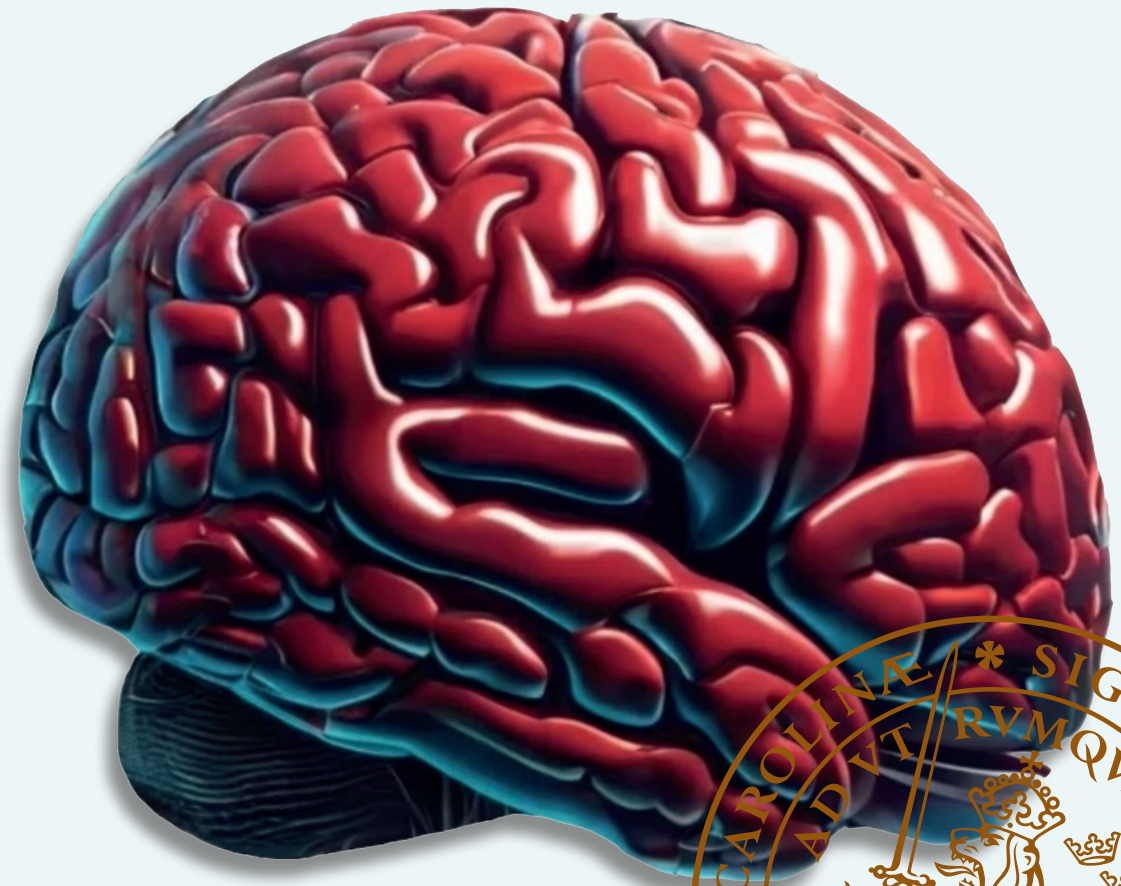

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Bryndís Baldvinsdóttir

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Abstract:

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening disease and one of the most complicated diseases neurosurgeons treat, with many factors having impact on outcome. It is of clinical interest for every neurosurgeon treating these patients to know how different factors can affect the outcome. The outcome measure in this thesis is strictly clinical, with patients either having favorable functional outcome (able to live independently) or unfavorable functional outcome (deceased or dependent on others). The aim of this thesis is to analyse factors related to treatment of aSAH patients in Sweden, with focus on adverse events (AEs) related to the treatment.

Paper I: The study cohort consists of 322 patients treated with microsurgery for a ruptured intracerebral aneurysm. AEs associated with the operations are analysed as well as their effect on outcome. Temporary parent artery occlusion > 5 minutes is significantly associated with increased risk of unfavorable outcome.

Paper II: In this study, 715 patients treated with endovascular aneurysm occlusion are analysed. Aneurysmal re-rupture during endovascular treatment is strongly correlated to increased risk of unfavorable outcome.

Paper III: Thirty-five patients operated with decompressive craniectomy (DC) following aSAH are in focus in this study. Overall, 3.4% of patients with aSAH were operated with DC. The strongest risk factors of having DC being poor clinical grade, aneurysm location on the middle cerebral artery (MCA), cerebral edema, and AEs during aneurysm treatment.

Paper IV: Patients that were in a good clinical condition before aneurysm treatment but had unfavorable outcome are analysed in this study. Factors significantly related to unfavorable outcome being noted in patients initially in a good clinical condition are increased age, hydrocephalus, delayed ischemic neurological deficit (DIND), and AEs during aneurysm treatment.

Patients treated for aSAH are in risk of AEs occurring, both related to the bleeding itself but also associated with the treatment. Treatment-related AEs have impact on patients' outcome and should by all measures possible sought to be avoided. This thesis reveals the impact these AEs have on patient outcome.

Key words: Aneurysm, subarachnoid hemorrhage, adverse event, microsurgery, endovascular treatment, decompressive craniectomy, outcome

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Aneurysmal subarachnoid hemorrhage

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Bryndís Baldvinsdóttir

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“To avoid complications,
she never kept the same address”
– Freddie Mercury

Table of Contents

Popular scientific summary
(English)

A brain-bleeding can occur due to different reasons. One such is when aneurysm, which is an out-pouch like a balloon, has formed on a vessel in the brain. This aneurysm can rupture and cause a bleeding which can differ a lot in its magnitude, with varying effects on the patient.

Risk factors for this kind of bleeding are, among others, cigarette smoking, hypertension, older age, and they are more common in females. The most common symptom of this type of bleeding is a sudden, severe headache which the patients often describe as the most intense pain they have ever suffered. Other symptoms are a seizure, paresis, speech impairment, and loss of consciousness. Death can occur immediately at the time of bleeding.

Patients with a ruptured brain aneurysm are treated at a neurosurgical clinic. With occlusion of the ruptured aneurysm being one of the most important factors of the treatment. This can be performed by open surgery where a clip is applied on the aneurysm to close it off. During these operations, a so-called temporary clip is sometimes used. This is applied on the vessel which supplies blood to the aneurysm. Another method of occluding the aneurysm is by endovascular approach. Where the aneurysm is closed off by filling it on its inside with a metal, which is mostly made of platinum. Sometimes the brain gets very swollen as a reaction to the bleeding, necessitating an operation where part of the skull is opened up. This type of operation is called “decompressive craniectomy”.

Unwanted and unexpected events can occur during the treatment; these are generally called “complications” or “adverse events”. It can be difficult to avoid these events, and they can have major impact on the patients’ wellness.

In this PhD thesis I use a nationwide database that involves patients that were treated at the neurosurgical clinics in Sweden during a period of 3.5 years, in the years 2014 – 2018. The goal of this thesis was to analyse adverse events related to the treatment, which factors are related to increased risk of adverse events and if these events have impact on patient outcome. The thesis is made up of four different papers, each of which has its own focus area.

Paper I describes patients treated with open surgery. Comprising 322 patients. The focus is on adverse events occurring during the operation and how they affect patient

outcome. The main results of the article are that an increased bleeding severity and a brain swelling are related to increased risk of adverse events during the operation. Also, the use of a temporary clip for more than five minutes is associated with increased risk of negative outcome (dead or unable to live independently).

In Paper II, 715 patients treated by endovascular approach are in focus. The primary results are that adverse events with the treatment are related to several factors. Among others; aneurysm location, size and type, as well as brain swelling. The results also reveal that the adverse event where the aneurysm re-ruptures during aneurysm treatment is related to a highly increased risk of the patient having a negative outcome at one year follow-up.

With Paper III, brain swelling is in focus where thirty-five patients treated with decompressive craniectomy are analysed. The results show that few patients are operated with this kind of operation in Sweden. Risk factors for the need of this kind of operation are poor clinical condition when the aneurysm is treated, aneurysm located at a certain vessel (middle cerebral artery), a swelling of the brain, and adverse events during aneurysm treatment. One in every three-patient operated with decompressive craniectomy had a positive outcome at clinical follow-up one year after the bleeding.

In Paper IV the emphasis is on patients that were in a good clinical condition before treatment of the aneurysm but had a negative outcome at one year follow-up. Twenty percent of these patients that were doing quite well before the aneurysm treatment were either dead or unable to live independently when followed up one year after the bleeding. Several factors are related to this, one of them being an adverse event during the aneurysm treatment.

The results of the four different articles can be summarised to say that the examined adverse events during treatment can have major effects on the patients' wellness. The results describe how different factors can be related to risks of different adverse events and how these impact the patients' outcome. The results can hopefully be used in clinical practice, helping neurosurgeons during treatment selection and patient care.

Popular scientific summary
(Swedish/Svenska)

Hjärnblödning kan förekomma av olika anledningar. En orsak är när pulsåderbråck som är en utbuktning, liknande en ballong, har bildats på ett blodkärl i hjärnan. Ett sådant pulsåderbråck kan rupturera och orsaka blödning. Mängden av blod och effekten på patienten varierar. Risk-faktorer för en sådan blödning är till exempel rökning, hypertoni, ålder och kvinnligt kön. Det vanligaste symtomet av den här typen av blödning är plötslig besvärlig huvudvärk som patienterna beskriver ofta som absolut värsta smärta dem har någonsin upplevt. Andra symtom är krampanfall, svaghet i extremiterna, talsvårigheter och medvetandeförlust. Ett visst antal avlider direkt när blödningen tillkommer.

Patienterna behandlas på neurokirurgisk klinik, där ocklusion av pulsåderbråcket är en av viktigaste komponenterna av behandlingen. Detta kan utföras med öppen kirurgi varvid en klämma sätts på pulsåderbråcket och stänger således av det. Ibland under en sådan operation appliceras en temporär klämma på blodkärlet var pulsåderbråcket befinner sig.

Annan metod för att ockludera pulsåderbråcket är endovaskular behandling, där pulsåderbråcket stängs av igenom att via en kateter sätta material gjort av metall in i pulsåderbråcket. Detta material är för det mesta gjort av platina. Det kan förekomma att hjärnan blir svullen till följd av blödningen. Det kan leda till att en operation utförs där en del av skallbenet tas bort, denna typ av operation kallas för dekompressiv kraniektomi.

Oönskade och oväntade händelser (komplikationer) kan förekomma under tiden patienten behandlas. Det kan vara svårt att undvika vissa sådana komplikationer och de kan ha betydlig effekt på patientens mående.

I denna avhandling använder jag en nationell databas med insamlad information om patienter som behandlades på någon av de neurokirurgiska klinikerna i Sverige för hjärnblödning orsakat av brustet pulsåderbråck under åren 2014 – 2018, 3,5 år. Målsättningen med avhandlingen är att analysera komplikationer relaterada till behandlingen, vilka faktorer ökar risken för komplikationerne och om de har effekt på hur patienten mår ett år efter blödningen. Avhandlingen består av fyra olika artiklar.

Artikel I beskriver patienter som blev behandlade med öppen kirurgi, totalt 322 patienter. Artikeln fokuserar på komplikationer i samband med öppen kirurgi och hur de kan ha effekt på utfallet. Huvudresultaten är att kraftig blödning och svullnad i hjärnan kopplas till ökat risk för komplikationer i samband med operationen. Användning av temporär klämma i mer än 5 minuter visade sig vara associared med ökat risk för dåligt utfall.

I artikel II är 715 patienter behandlada med endovaskular metod i fokus. Resultaten är att komplikationer i samband med behandlingen relateras till några olika faktorer, bland annat lokalisation, storlek och typ av pulsåderbråcket, samt svullnad i hjärnan. Resultaten visar också att komplikationer var pulsåderbråcket brister igen under tiden det behandlas kopplas till ökat risk för dåligt utfall vid ett-årsuppföljning.

Artikel III fokuserar på patienter som blev opererade med dekompressiv kraniektomi, totalt 35 patienter. Resultaten är att ett begränsat antal genomgick en sådan operation i Sverige. Risk-faktorer för att en sådan operation behövde utföras var dålig klinisk status när pulsåderbråcket behandlades, pulsåderbråck lokaliserad på ett visst blodkärl (mellersta hjärnartären), svullnad i hjärnan, samt komplikationer när pulsåderbråcket behandlades. En tredjedel av patienterna som opererades med dekompressiv kraniektomi hade positivt utfall, i meningen att de överlevde och klarade sig utan stöttning i hemmet ett år efter blödningen.

I artikel IV läggs vikten på patienter som mådde bra innan behandlingen men hade dåligt utfall vid ett-årsuppföljning. Alltså om de hade avlidit eller inte klarade sig utan stöttning med dagliga aktiviteter. Tjugo procent av de som mådde rätt bra innan pulsåderbråcket behandlades hade dåligt utfall. Några faktorer kunde kopplas till detta, en var komplikationer i samband med behandlingen av pulsåderbråcket.

Resultaten av de fyra artiklarna kan sammanfattas till att säga att komplikationerne som granskades och kan förekomma i samband med behandlingen kan ha stor effekt på patientens mående. Resultaten beskriver hur olika faktorer kan associeras till komplikationerne och att utfallet blir påverkat av detta. Resultaten kan förhoppningsvis användas kliniskt och vara av nytta för neurokirurger som behandlar patienter med brustet pulsåderbråck.

Popular scientific summary
(Icelandic/Íslenska)

Heilablæðing getur orðið af mismunandi orsökum, ein ástæða er rof á æðagúl. Æðagúl má líkja við blöðru sem hefur myndast á æð í heilanum. Slíkur æðagúll getur rofnað og orsakað blæðingu. Þessar blæðingar eru misalvarlegar. Áhættuþættir eru meðal annars reykingar, háþrýstingur, öldrun og þessi tegund heilablæðingar er algengari í konum.

Skyndilegur, kröftugur höfuðverkur er algengasta einkennið. Einstaklingar sem hafa fengið þessa gerð heilablæðingar lýsa verknum oft sem þeim versta þeir hafa nokkru sinni upplifað. Önnur einkenni geta verið flogakast, máttleysi í hendi eða fæti, málhelti eða jafnvel meðvitundarleysi. Þá getur blæðingin orsakað skyndilegt andlát.

Heila- og taugaskurðlæknar sjá um meðferð þessara sjúklinga og er lokun æðagúlsins einn af meginþáttum meðferðarinnar. Er þetta gert til að fyrirbyggja að það verði önnur blæðing. Ein leið er að gera opna heilaskurðaðgerð þar sem klemma er sett á æðagúlinn. Önnur aðferð er að fara inn í æð í náranum, þræða upp í æðagúlinn, leggja inn málmþræði sem eru að mestu gerðir úr platínum og loka þannig æðagúlnum. Þess háttar meðferð kallast innanæðahnoðrun. Sem hluti af viðbrögðum líkamans við blæðingunni getur heilinn bólgnað mikið. Getur þá þurft að gera aðgerð þar sem hluti höfuðkúpunnar er sagaður burt, þetta er gert til að skapa meira pláss fyrir heilann.

Við meðferð sjúklinganna geta fylgikvillar átt sér stað. Það getur verið erfitt að koma í veg fyrir þá og þeir geta haft mikil áhrif á hvernig sjúklingnum reiðir af.

Í þessu doktorsverkefni notast ég við gagnagrunn með upplýsingum um sjúklinga sem fengu meðferð við rofnum æðagúl í heila á heila- og taugaskurðdeildunum í Svíþjóð yfir þriggja og hálfs árs tímabil, á árunum 2014 – 2018. Markmiðið með doktorsverkefninu er að greina fylgikvilla sem áttu sér stað þegar sjúklingarnir voru meðhöndlaðir. Skoða hvaða þættir voru tengdir þessum atburðum og hvort þeir höfðu áhrif á hvernig sjúklingunum reiddi af. Doktorsverkefnið samanstendur af fjórum greinum sem hver og ein einblínir á mismunandi atriði.

Fyrsta greinin lýsir sjúklingum þar sem æðagúlnum var lokað í opinni heilaskurðaðgerð. Samtals voru þetta 322 sjúklingar. Áherslan er á fylgikvilla sem urðu á meðan aðgerðinni stóð. Meginniðurstöður greinarinnar eru að kröftug

blæðing og bjúgur í heilanum voru áhættuþættir fyrir að fylgikvillar ættu sér stað í aðgerðinni. Einnig að tímabundin lokun á æðinni sem flutti blóð síðasta spölinn í æðagúlinn í meira en fimm mínútur var tengt aukinni hættu á að sjúklingnum reiddi illa af þegar honum var fylgt eftir einu ári eftir blæðinguna.

Í annarri greininni er einblítt á 715 sjúklinga þar sem æðagúlnum var lokað með innanæðahnoðrun. Helstu niðurstöður eru að fylgikvillar við meðferðina voru tengdir nokkrum þáttum, þar á meðal staðsetningu, stærð og tegund æðagúlsins. Bólga í heilanum hafði einnig neikvæð áhrif í þessu samhengi. Þá hafði það einnig meðal annars töluverð neikvæð áhrif á hvernig sjúklingnum reiddi af ef það varð blæðing frá æðagúlnum á meðan innanæðahnoðruninni stóð.

Í þriðju greininni er einblítt á brottnám á hluta höfuðkúpunnar. Niðurstöðurnar gefa til kynna að það eru ekki gerðar margar svona aðgerðir í Svíþjóð. Þeir sem þurfa á þess konar aðgerð að halda eru oft í slæmu ástandi þegar æðagúllinn er meðhöndlaður og þá er æðagúllinn oft staðsettur á æð sem kallast mið-hjarnaslagæð. Þá kemur einnig í ljós að fylgikvillar þegar æðagúllinn er meðhöndlaður auka líkurnar á að taka þurfi hluta höfuðkúpunnar. Einn af hverjum þremur sjúklingum sem fór í slíka aðgerð hafði engu að síður náð sér nokkuð vel við eins árs eftirfylgd.

Í fjórðu greininni er áhersla lögð á sjúklinga sem voru í góðu ástandi fyrir meðferð en við eins árs eftirfylgd voru annað hvort látnir eða þurftu markvissa aðstoð í daglegu lífi. Einn af hverjum fimm sem voru í góðu ástandi áður en æðagúlnum var lokað höfðu slíka neikvæða útkomu eftir eitt ár. Nokkrir þættir voru tengdir þessu, þar á meðal fylgikvillar er æðagúllinn var meðhöndlaður.

Segja má að helstu niðurstöður þessara fjögurra greina sé að fylgikvillar við meðferðina geta haft gríðarlega mikil áhrif á hvernig sjúklingunum reiðir af. Greinarnar lýsa hvernig mismunandi þættir geta verið tengdir hættunni á mismunandi fylgikvillum og hvernig þeir geta haft áhrif á hvernig sjúklingnum reiðir af.

List of original papers

This PhD thesis is based on the following studies.

Paper I

Baldvinsdóttir B, Kronvall E, Ronne-Engström E, Enblad P, Lindvall P, Aineskog H, Friðriksson S, Klurfan P, Svensson M, Alpkvist P, Hillman J, Eneling J, Nilsson OG. Adverse events associated with microsurgial treatment for ruptured intracerebral aneurysms: a prospective nationwide study on subarachnoid haemorrhage in Sweden. *J Neurol Neurosurg Psychiatry*. Jul 2023;94(7):575-580. doi:10.1136/jnnp-2022-330982

Paper II

Baldvinsdóttir B, Klurfan P, Eneling J, Ronne-Engström E, Enblad P, Lindvall P, Aineskog H, Friðriksson S, Svensson M, Alpkvist P, Hillman J, Kronvall E, Nilsson OG. Adverse events during endovascular treatment of ruptured aneurysms: A prospective nationwide study on subarachnoid hemorrhage in Sweden. *Brain Spine*. 2023;3:102708. doi:10.1016/j.bas.2023.102708

Paper III

Baldvinsdóttir B, Kronvall E, Ronne-Engström E, Enblad P, Klurfan P, Eneling J, Lindvall P, Aineskog H, Friðriksson S, Svensson M, Alpkvist P, Hillman J, Nilsson OG. Decompressive craniectomy following subarachnoid hemorrhage: A prospective Swedish multicenter study.
Brain Spine. 2025; 5:104218. doi:10.1016/j.bas.2025.104218

Paper IV

Baldvinsdóttir B, Kronvall E, Aineskog H, Klurfan P, Alpkvist P, Eneling J, Enblad P, Jakola AS, Svensson M, Lindvall P, Ronne-Engström E, Hillman J, Nilsson OG. Causes of unfavorable outcome in patients with good grade subarachnoid hemorrhage prior to aneurysm treatment: impact of adverse events Manuscript.

Author’s contribution to the papers

Papers I - III

Data collection. Visualization. Data analysis and interpretation. Writing the article. Re-writing after comments from supervisors and co-authors. Final approval of the manuscript. Responsible for the publishing process. Corresponding author.

Paper IV

Data collection. Visualization. Data analysis and interpretation. Writing the article. Re-writing after comments from supervisors and co-authors. Final approval of the manuscript.

Abbreviations

ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
aSAH	Aneurysmal subarachnoid hemorrhage
BRAT	Barrow Ruptured Aneurysm Trial
BA	Basilar artery
CPP	Cerebral perfusion pressure
CT	Computed tomography
CTA	Computed tomography angiography
DC	Decompressive craniectomy
DCI	Delayed cerebral ischemia
DIND	Delayed ischemic neurological deficit
DSA	Digital subtraction angiography
EVD	External ventricular drain
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
GOSE	Glasgow outcome scale extended
ICA	Internal carotid artery
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ISAT	International Subarachnoid Aneurysm Trial
IVH	Intraventricular hemorrhage
MCA	Middle cerebral artery
mRS	Modified Rankin scale
PCA	Posterior cerebral artery

PComm	Posterior communicating artery
SAH	Subarachnoid hemorrhage
TCD	Transcranial doppler
TNF-α	Tumor necrosis factor-alpha
VA	Vertebral artery
VP	Ventriculo-peritoneal
WEB	Woven-EndoBridge
WFNS	World Federation of Neurosurgical Societies

Preface

Aneurysmal subarachnoid hemorrhage is a life-threatening disease. The treatment is complicated where many factors can impact how well the patients recover. When I started my clinical rotations as a medical student in the fall of 2009 I found it interesting how treatments for different medical problems can have negative effect on the patients‘ outcome. While keeping in mind that doing nothing can be far worse. In medicine and not least in neurosurgery this is not an option. Neurosurgery is a high-risk speciality and as such certainly not without risks of adverse events or complications. In this thesis the aim is to explore risk factors for adverse events during treatment for aneurysmal subarachnoid hemorrhage and evaluate how these examined events possibly impact the patients‘ outcome.

Context of this thesis

From the year 2014 and until the year 2018, the neurosurgical departments in Sweden treating patients with spontaneous subarachnoid hemorrhage gathered information on patients admitted and treated for the disease at the respective clinics. These departments are located at the University Hospitals in Gothenburg, Lund, Linköping, Stockholm, Uppsala and Umeå. Years before this was initiated, prominent vascular neurosurgeons at these clinics had formed a steering group and planned the work with frequent meetings. The aim of this was to gather information on the treatment on a nationwide basis. The database was thoroughly planned, and the aim was to work on and publish several research projects based on the information in the database, with different focus areas. This PhD thesis is based on this work, and I have had the pleasure of being able to analyse factors related to my area of interest. Which variables were included, which projects would be done, and the primary research questions were decided before the first patient was registered in the database. The patients were clinically followed up one year after the bleeding, this was either done by a visit at an outpatient clinic or by a telephone interview. The assessments were performed by following a questionnaire, making the follow-ups as standardized as possible. This thesis was carried out at the Neurosurgical department in Lund, Skåne University Hospital in Lund, Sweden under the years 2020 - 2025.

Introduction

Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) is a bleeding that is located between the pia membrane and the arachnoid membrane, which both cover the brain. There can also be a concomitant bleeding in the ventricle system (intraventricular hemorrhage; IVH), in the brain parenchyma (intracerebral hemorrhage; ICH) and/or in the subdural space (subdural hematoma; SDH). The most common cause of SAH is trauma. Spontaneous SAH is in majority of cases (85%) due to a ruptured intracerebral aneurysm, i.e. aneurysmal subarachnoid hemorrhage (aSAH).[5] The initial symptom of aSAH is most often a sudden, intense headache. Other common symptoms are neck stiffness, nausea, vomiting, photophobia, dysphasia, paresis, epileptic seizure, loss of consciousness.[5,6] A sudden-onset, extreme headache should always make aSAH a differential diagnosis. Diagnosis is generally confirmed with a non-contrast head computed tomography (CT), in certain cases the diagnosis is confirmed with a lumbar puncture.[7] A head CT with contrast and angiographical sequences (CTA) often discloses an underlying aneurysm as a culprit for a spontaneous subarachnoid hemorrhage. In certain cases, digital subtraction angiography (DSA) needs to be performed to reveal the causative aneurysm.[8] Primary treatment depends on patients' symptoms and alertness. If the patient is comatose it is vital to intubate the patient. The patients often have elevated blood pressure. This can be due to underlying hypertension and/or due to physical stress reaction following the bleeding. It is of importance to actively reduce the blood pressure to minimize the risk of a re-bleeding, which is a re-rupture of the aneurysm.[8] Multiple scales have been defined in regards to aSAH.[9] Commonly used scales are the Fisher scale for grading the magnitude/location of blood on CT and the World Federation of Neurosurgical Societies (WFNS) scale which describes patients' clinical status.[9-11]

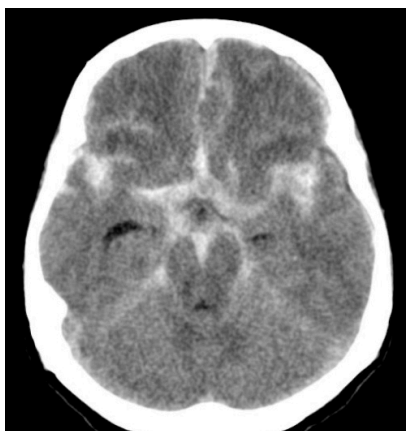

Figure 1. Computed tomography (CT) scan showing a typical finding of aneurysmal subarachnoid hemorrhage. *Source: Radiopaedia (www.radiopaedia.org)*

Table 1. Grading of subarachnoidal bleeding according to Fisher et al.[6]

Fisher grade	Description
I	No blood
II	Diffuse or thin layer, all vertical layers of blood < 1 mm thick
III	Localised clots and/or vertical layers of blood ≥ 1 mm thick
IV	Intraventricular or intraparenchymal blood

Table 2. WFNS scale[11] describing clinical status of patients.

WFNS	GCS	Motor deficit
I	15	Absent
II	13 - 14	Absent
III	13 - 14	Present
IV	7 - 12	Absent or present
V	3 - 6	Absent or present

Epidemiology

The incidence of aSAH varies between 2 – 25 / 100.000 person-years. The incidence has quite a large geographical difference but is usually about 9.1 / 100.000 person-years.[12,13] The median age of patients is 55 years.[14] Well defined risk factors are hypertension, cigarette smoking, and female gender.[15,16]

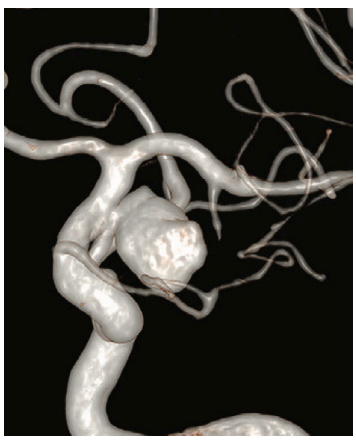

Figure 2. 3D angiogram of 7 Tesla magnetic resonance angiography (MRA). Showing aneurysm on the internal carotid artery (ICA). *Source: Journal of Neurointerventional Surgery*[4]

The reason for increased risk in females, especially middle aged, is not completely understood but a hormonal factor has been suggested. Pro-inflammation cytokine, Tumor necrosis factor-alpha (TNF-α) is associated with aneurysm formation (and aneurysm rupture).[17] Estrogen suppresses TNF-α.[18] As such, decreasing estrogen levels in women around menopause has been associated with increased risk of aneurysms (and aSAH) in post-menopausal women.[16,19] Anatomical factors have also been theorized. Arterial diameter and shear stress on the arterial walls, which lead to increased hemodynamic in the intracranial vessels of females, can contribute to the risk of aneurysm formation.[20] Additionally, the impact of hypertension on the risk of aSAH seems to be stronger in females than in males.[15] The risk of aSAH decreases with smoking cessation but is however increased in former

smokers, compared to those that have never smoked.[15,21]

The prevalence of intracerebral aneurysms is 2 - 7%, overall about 3%. The fluctuating numbers reported are due to geographical variations, gender differences, diverse definitions of what constitutes as aneurysm and because of varying radiological techniques.[22-25]

Historical perspectives

Around the year 2725 before Christ, the founder of Egyptian medicine, Imhotep, likely described aneurysm on an artery with the words: "*This is a vessel swelling, a disorder I will treat. It is the vessels that cause it. It originates from an injury upon the vessel."* Imhotep described that he would treat this vessel swelling with a heated knife.[26] Exactly how the treatment would be performed and if there were any risk assessments made regarding possible adverse events related to this treatment is to my knowledge unknown.

Galen of Pergamon (years alive: 129 - 210) presented the word "aneurysm".[26] Although it appears that intracranial aneurysms were not described until many centuries later or in the year 1761 by Morgagni of Padua.[26] In 1810, John Blackall presented the connection between a ruptured intracranial aneurysm and subarachnoid hemorrhage.[26] In 1885, Victor Horsley described a ligation of an intracranial aneurysm and this seems to be the first description of treating such an aneurysm. John Hunter (1728 – 1793) had previously described ligation of aneurysm on the popliteal artery (artery in the leg) and this type of ligation was termed "Hunterian ligation".[26,27] Harvey Cushing (1869 – 1939) described several intracranial aneurysms in his operative notes and how they would bleed if perforated with a needle and how it was possible to treat a bleeding aneurysm by wrapping it with muscle. Cushing was a mentor to Norman Dott (1897 – 1973) who in 1931 likely was the first to successfully treat a ruptured aneurysm on the internal carotid artery with wrapping.[26-28] During tumor surgeries, Cushing used a clip he had designed in 1911.[26] Walter Dandy (1886 – 1946) used a modified version of this "Cushing-clip" when he in 1937 reportedly was the first to successfully clip an intracranial aneurysm.[26,29] It is important to remember that these pioneers did not have a microscope when performing their operations. It wasn't until 1957 that Theodore Kurze clipped an aneurysm while operating under a microscope.[26] Since then, more neurosurgical pioneers have come forward and the microsurgical technique has evolved with different types of clips, variations in the clip applicators, more advanced microscopes, not to mention the exoscope.

The invention of digital subtraction angiography (DSA) by Egas Moniz in 1927 has to be seen as a major breakthrough in the diagnosis of intracerebral aneurysms.[26] This technique is also the cornerstone of the endovascular treatment. A technique that decades later started to evolve as an efficient treatment of intracranial

aneurysms. From the year 1933, the previously mentioned Norman Dott used DSA to aid in planning the surgical treatment of intracranial aneurysms. Following the invention of DSA, and even prior, several ideas and methods came forward regarding how different foreign materials could be inserted into the aneurysm to exclude it from the cerebral circulation. The use of materials like wires, needles, muscle and horse hair have been described.[26] Serbinenko described in 1974 how microcatheter-balloons could be used to close off the bloodflow into an aneurysm.[26,30] In 1990 a major breakthrough came when Guglielmi treated an intracerebral aneurysm by filling it with a wire coated with platinum that he inserted through a guide-wire, the so-called detachable coil.[26] Since then the endovascular technique has continued to evolve with new endovascular devices almost constantly being presented. The latest to-date being Woven-EndoBridge (WEB), Artisse, Medina, Contour and Cerus.[31]

The intensive care of patients having aneurysmal subarachnoid hemorrhage has evolved in the last decades. Transcranial doppler (TCD) has been used since 1986 and by giving information on the intracerebral hemodynamics it aids in diagnosing vasospasm following aSAH.[32] Since 1992, cerebral microdialysis has been used to monitor aSAH patients with the aim to diagnose vasospasm. This, by analysing the intracerebral metabolism.[33] These techniques are very valuable, especially in the comatose or sedated patient where routine clinical neurological evaluations are not available.

Figure 3. Aneurysmal subarachnoid hemorrhage due to a ruptured MCA aneurysm, as depicted by my friend Hedvig Redebrandt (age 6).

Intracerebral aneurysms

An intracerebral aneurysm is a bulging on an artery that perfuses the brain. Arterial wall is composed of endothelium or internal layer (tunica intima), middle layer (tunica media) which includes muscle cells and elastic fibers, and an outmost connective tissue layer (tunica adventitia).[34] Aneurysms can include one or more of these layers.[22,35-37] Why aneurysms form (and/or rupture) on arteries perfusing the brain is not completely understood. Several factors most likely come into play. Such as the structure of the arterial walls. Intracerebral arteries have fewer elastic fibers

and thinner connective tissue layer than arteries elsewhere in the body. This is probably an important factor in intracerebral aneurysm formation. Transformation of collagen is also thought to be a key factor in aneurysm formation/rupture.[38-40]

There can be genetical factors regarding formation of intracerebral aneurysms, with increased risk in certain families.[41] Genesis of intracerebral aneurysms is related to several systemic diseases, e.g. polycystic kidney disease, Ehlers-Danlos, Marfan's and neurofibromatosis.[22,41,42]

Circle of Willis is an arterial structure that is located at the base of the brain and is in the subarachnoid space.[43] Aneurysms are most often located on the arteries that constitute Circle of Willis; anterior cerebral artery/anterior communicating artery (ACA/ACoA), internal carotid artery (ICA), middle cerebral artery (MCA), basilar artery (BA), vertebral artery (VA).[22] Aneurysms on ACA/ACoA, ICA or MCA are regarded to be in the anterior circulation and aneurysms on BA or VA ("vertebrobasilar")[44] in the posterior circulation. The posterior communicating arteries (PComms) are branches from the ICAs. They connect the anterior and posterior circulations, as a passage between ICA and the posterior cerebral artery (PCA).[45,46]

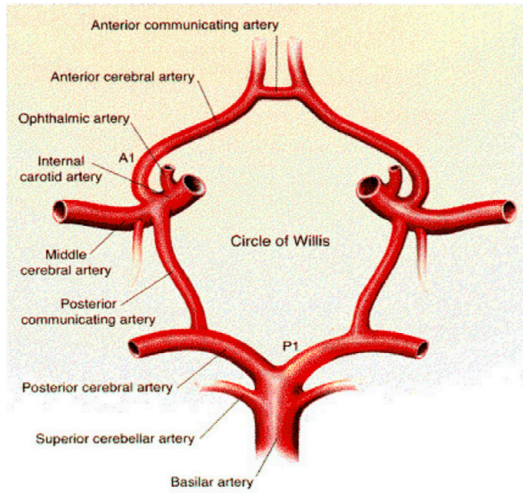

Figure 4. Circle of Willis. *Source: The New England Journal of Medicine.*[1]

Aneurysm location in the posterior circulation or on the anterior communicating artery are related to increased risk of rupture. The risk of rupture is also increased with hypertension, smoking, female gender, irregular aneurysm shape, history of previous aSAH, Japanese or Finnish descent.[23,47] Every unruptured intracerebral aneurysm has to be individually assessed with regards to possible treatment or radiological follow-up.[47]

The most common types of intracerebral aneurysms are saccular, fusiform, dissecting, blister, and mycotic. The single most common being saccular aneurysm (about 85-90%).[22,48] Saccular aneurysms have a defined neck and most often form where an artery diverges into two or more arteries.[22,48] Fusiform aneurysms are 3 - 13% of intracerebral aneurysms and are due to weakening in the vessel wall which causes the artery to dilate on all sides.[35] With dissection aneurysms there is a formation of a false lumen within the vessel wall. This is usually due to a defect in tunica intima which causes blood to flow/dissect between tunica intima and tunica media. Dissection aneurysms most often occur on the ICA and in the Vertebrobasilar circulation.[49,50] Blister aneurysms are rare, about 0.7 - 2% of intracerebral aneurysms. They are thin and fragile (often lacking tunica intima and tunica media) and have an especially high risk of rupture. Their angiographical finding has been described to be ”thornlike”[3], see Figure 6. Due to the fragility they are often difficult to treat. They form on non-branching part of arteries and are most often located on ICA.[51-54] Mycotic aneurysms are very rare (about 0.6% of all aneurysms). They are usually caused by a bacterial infection (most often *Staphylococcus aureus*), often due to endocarditis and are most often located on small distal intracerebral arteries, generally small MCA branches.[37,55]

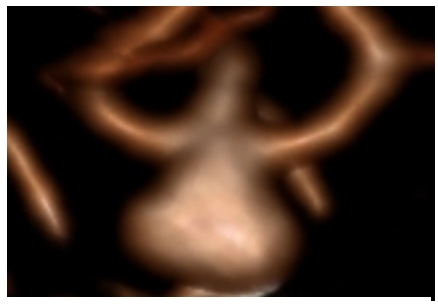

Figure 5. Angiography showing a saccular aneurysm, located on MCA. bifurcation.

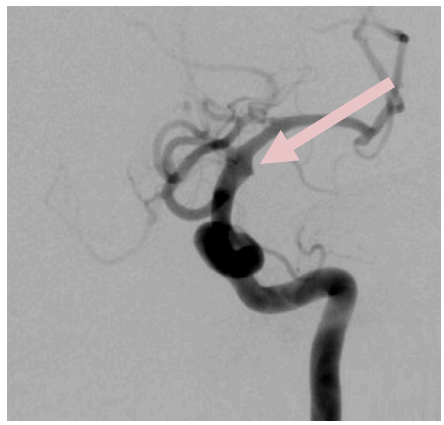

Figure 6. The arrow is pointing at a “thornlike“ (blister) aneurysm. Source: Vascular malformations of the central nervous system.[3]

One of the most important factors regarding intracerebral aneurysms, aside from their location and size, is the neck of the aneurysm. Wide neck aneurysms are generally more difficult to treat than small neck aneurysms, both with microsurgery and with endovascular treatment. Generally, the definition of a wide neck aneurysm varies in the literature. Some use only the definition of a neck diameter ≥ 4 mm. Others also use the dome/neck ratio, where varying ratios (1, 1.2, 1.5, 1.6, 1.8, <2) are described.[56]

Neck diameter ≥ 4 mm and/or

$$maximal\ dome\ diameter / neck\ diameter < 2$$

is the single most commonly used definition (39.8% of studies)[56]. It is often used in clinical practice and reflects the geometry of the aneurysms.

The diagnosis of intracerebral aneurysms is made with angiographical radiology. Most commonly by computed tomography angiography (CTA). CTA has about 98% sensitivity for intracerebral aneurysms, but it is possible to miss small aneurysms with CTA.[57,58] The gold standard to diagnose aneurysms remains to be digital subtraction angiography (DSA). Another imaging technique to diagnose and/or follow up aneurysms is magnetic resonance angiography (MRA).[57]

Treatment of intracerebral aneurysms

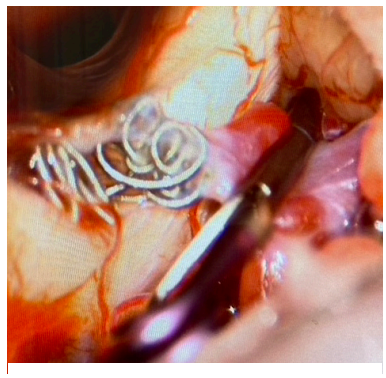

Figure 7. Aneurysm that was previously treated by coiling. The coils had eroded the aneurysmal wall. Therefore, titanium clip was applied.

Re-bleedings before treatment of the ruptured aneurysm most often occur in the first hours following the bleeding and occur in up to 16% of patients.[59,60] At some centers, patients receive tranexamic acid prior to aneurysm occlusion. This to possibly minimize the risk of re-bleeding, although its use can be put into question.[61,62] To hinder re-bleedings it is important to occlude the ruptured aneurysm as soon as feasible.[8,63,64] The occlusion can either be done by microsurgical or endovascular approach. The aim of both modalities is to occlude the aneurysm from the circulating arterial blood flow so there will be no flow into the aneurysm. Many factors can impact how soon the aneurysm is occluded after rupture. Among others, the selection of method can be a factor. Several studies have been published where the aim has been to compare the two different approaches and analyse which method is more suitable. After publication of the International Subarachnoid Aneurysm Trial (ISAT)[65] endovascular method emerged as the optimal method for majority of aneurysms. Ten-year follow-up analysis of patients treated in Barrow Ruptured Aneurysm Trial (BRAT)[66] showed certain benefits of microsurgery over endovascular treatment in regard to aneurysms in the anterior circulation and the grade of aneurysm occlusion and frequency of re-treatments. Re-treatments are more commonly indicated after endovascular treatment than after microsurgery.[67]

Microsurgery is a commonly used term for the surgical approach where the aneurysm is occluded. This to distinctly distinguish it from endovascular approach. The most common way of microsurgically occluding a ruptured aneurysm is to put a titanium clip on the neck (or base) of the aneurysm. Another variation is "trapping" or "wrapping" the aneurysm. Trapping is when the aneurysm is isolated from the cerebral circulation by putting a clip on the parent and distal arteries. Sometimes it is necessary to perform bypass at the same time. With wrapping, the aneurysm wall is strengthened by coating the aneurysm with i.e., cotton gauze, muslin gauze, oxidized cellulose, or muscle. This wrapping leads to fibrosis around the aneurysm wall which strengthens it.[68,69] The most dreaded complication or adverse event with microsurgery is a re-rupture of the aneurysm during operation. Others are occlusion of adjacent vessels, and the need to have a temporary occlusion of the parent artery for more than five minutes. The exact time of safe temporary occlusion varies depending on several factors; i.e., collateral circulation, sedation, oxygenation.[70] It has been shown that unplanned occlusion for more than five minutes can lead to ischemia but occlusion for a shorter time period is considered safe.[71]

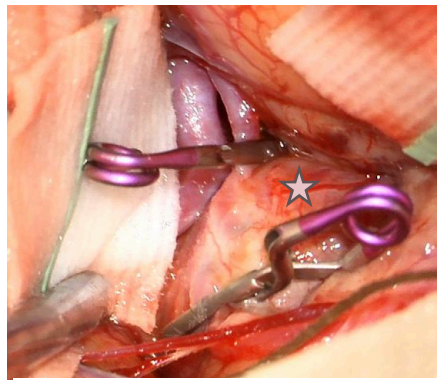

Figure 8. Trapping of a large MCA aneurysm (temporal M2 branch). With clips applied on a proximal and a distal artery, respectively to the aneurysm (star).

Endovascular treatment is a method where the aneurysm is occluded from inside of the blood vessel. Most often a catheter is inserted in the femoral artery in the groin and then gradually moved up to the cerebral circulation. The most common endovascular method is coiling where the aneurysm is packed with coil material. In some cases, especially when the neck of the aneurysm is wide, a balloon (balloon-assisted coiling) or stent (stent-assisted coiling) is used to aid with the coiling. A stent can also be used as the only treatment option. Another version of a stent is a flow diverter which has tighter meshwork than a classical stent. As a result, the aneurysm becomes thrombosed (occluded by a coagulated blood). The disadvantage with stents and flow diverters, regarding aSAH, is the concomitant need for dual antiplatelet therapy.[72] New endovascular methods are continually evolving. To date, the newest devices are expanding devices that are inserted into the aneurysm. These are Woven-EndoBridge (WEB), Artisse, Medina, Contour and Cerus Intrasaccular

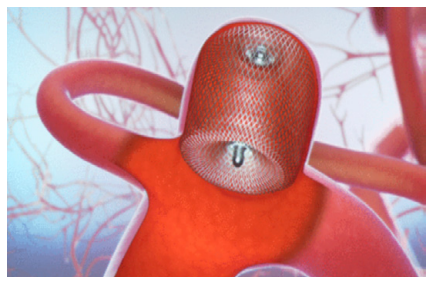

Figure 9. Aneurysm treated with WEB. *Source: Journal of Neurointerventional Surgery*[2]

Stent.[31] Specific complications during endovascular occlusion of a ruptured intracerebral aneurysm are thromboembolism, re-rupture of the aneurysm, and a vessel dissection.[73,74]

Other treatment factors

Epileptic seizure is seen in 4 - 26% of patients at the time of bleeding (onset seizure) and can cause a loss of consciousness. A seizure can also be a clinical sign of re-bleeding. A seizure due to the bleeding can also occur later in the clinical phase.[75] Another potential cause of impaired consciousness is hydrocephalus. The frequency of acute hydrocephalus with aSAH varies in studies with numbers from 6% to 67% being reported. The large variation is likely due to different definitions of hydrocephalus.[76,77] The primary treatment for hydrocephalus is insertion of an external ventricular drain (EVD). Another efficient treatment is insertion of a lumbar drain.[78,79] Some patients do not fare well without this assisted drainage and are therefore operated with insertion of a ventriculo-peritoneal (VP) shunt later during the hospital stay. In the literature the frequency of VP shunt-operations following aSAH has been described to be about 18%.[76,80,81]

Following aSAH, intracerebral arteries can start to constrict, this is called vasospasm. Exactly why this happens is not clear, but several theories exist. Examples of theories: 1) Blood products, i.e., oxyhemoglobin, are spasmogenic. 2) Influx of Ca^{2+} causes muscle contraction in the arterial walls. 3) Production of endothelin-1 protein, a vasoconstrictor, following aSAH. 4) Formation of free radicals, i.e., lipid peroxides, that can cause vasospasm.[82] Clinical worsening following aSAH can be due to vasospasm and vasospasms most often occur 4 to 14 days after the bleeding.[83,84] The risk of vasospasm is related to the amount of blood, clinical status, and patient age. With increased risk being related to amount of bleeding, worse clinical status, and younger age.[10,85-87] Patients are generally evaluated regularly with transcranial doppler (TCD) where increased rate of blood flow is usually an indicator of vasospasm.[84] Microdialysis can also be used for this, where increased lactate/pyruvate quotient is an indicator of increased anaerobic metabolism and thereby a sign of vasospasm.[88]

Radiographical, angiographic vasospasm can be noted in up to 70% of cases.[84,89] Delayed ischemic neurological deficit (DIND) is a term used for symptomatic vasospasm and occurs in about 17 - 40% of aSAH patients.[79,85] DIND most often occurs 4 – 10 days after the bleeding.[90] DIND is usually defined as a neurological deficit in the days following aSAH that is not attributed to other possible causes, i.e. re-bleeding, hydrocephalus, epileptic seizure, meningitis/ventriculitis, and where angiography shows vasospasm.

Nimodipine, a calcium antagonist, has been proven to reduce the risk of cerebral infarcts and improve patients‘ outcome.[91] Every patient suffering aSAH should

therefore be administered nimodipine.[8] Treatment of symptomatic vasospasm involves optimizing cerebral perfusion pressure (CPP) to avoid cerebral infarction. The primary treatment approach is to elevate the blood pressure with intravenous fluids and vasopressors. Often with elevation of the systolic blood pressure at least 20% above baseline values.[83,92] In some cases, endovascular angioplasty must be performed to dilate the constricting vessel/s. This can be performed with local calcium-antagonist and/or balloon dilation.[79,83,84,93]

In certain cases it is necessary to perform decompressive craniectomy (DC) following aSAH.[94,95] Patients needing DC following aSAH have in general unfavorable outcome.[96-98] Varying frequencies of DC following aSAH have been reported in the literature with a mean frequency of 10.9%, but a range of 3.3 – 25.6%.[99]

Outcome

Aneurysmal subarachnoid hemorrhage is a very severe type of intracranial bleeding. It is estimated that 11 - 25% of patients die a sudden death and are not admitted to a hospital.[68,100] The risk of unfavorable outcome increases with higher age.[100,101] Outcome is also strongly related to clinical status (alertness) before treatment, magnitude of bleeding, clinical vasospasm, underlying comorbidities such as hypertension, ischemic heart disease, and diabetes. As well as certain lifestyle factors (smoking, alcohol use).[14,83,102] Outcome usually gets better over time, i.e., with improved functional outcome reported after one year compared to the first months following the bleeding.[102,103] At one year follow-up, about one-third of all treated patients have unfavorable outcome, meaning they are either deceased or are not able to take care of themself. Conversely, up to 67% of treated patients have favorable outcome (are alive and able to take care of themself) one year after the bleeding.[102,103]

What constitutes as favorable outcome can certainly be debated. The common definition is being able to take care of one-self without the assistance of others. For this assessment, a commonly used scale is the modified Rankin scale (mRS), which is a scale from 0 to 6 and describes the functional level during daily life. With 0 being the best function with no symptoms and 6 being worst, deceased.[104] Other commonly used scales are the Glasgow outcome scale (GOS) and Glasgow outcome scale extended (GOSE). As the name implies, GOSE is an extension of GOS and its benefit over GOS is that the questions are more standardized. GOSE is a scale from 1 to 8, where 1 equals dead and 8 describes a patient that has fully recovered or may have minor symptoms that do not affect daily life. GOSE 1 - 4 is generally used to describe a patient that has had unfavorable outcome (dead or dependent on others) and GOSE 5 – 8 is used to describe patients with favorable outcome (alive and not dependent on others). GOSE is useful as its thorough questionnaire can be used to

help assess the functional outcome of the patients.[105] The major difference between GOSE and mRS is that GOSE includes questions on return to work. GOSE is more often used in studies on traumatic brain injury and mRS is more often used in studies on stroke. This is mostly a tradition and not a general rule. The two outcome scales are comparable, and interconversion is relatively easy.[106]

Although the functional status of an individual after aSAH might be the same it was before the bleeding, cognitive problems are common following aSAH. It has been described that approximately 25 - 50% of patients suffer depression and that up to 40% have anxiety at one year follow-up.[103,107] Headaches, tiredness, memory problems and problems with focusing on tasks are quite common and patients often have difficulties with returning to work.[103,108,109]

Table 3. Description of Glasgow outcome scale extended (GOSE).[105]

Glasgow outcome scale extended	Description
8 = Upper good recovery	Fully recovered or may have minor symptoms not affecting daily life
7 = Lower good recovery	Able to return to previous life roles, but with symptoms that affect daily life
6 = Upper moderate disability	Some disability exists, but able to partly return to previous life roles
5 = Lower moderate disability	Independent, but cannot return to one or more life roles
4 = Upper severe disability	Dependent, needs infrequent assistance in basic activities in daily life, or help with activities outside the home
3 = Lower severe disability	Dependent, needs frequent assistance in basic activities in daily life
2 = Vegetative state	No awareness of self or environment
1 = Dead	Dead

Rationale

Aneurysmal subarachnoid hemorrhage (aSAH) is a complicated disease. It is complicated because several adverse events might occur during the clinical course, and the disease can be unpredictable. Multiple factors have impact on how the hospital stay evolves. There are many variables that affect how the patients‘ fare at discharge, the upcoming years and the rest of their lives.

An important aspect is the treatment itself. The wrong choice of treatment, adverse events or complications during the treatment or even completely unexpected events during treatment or through the hospital stay can have major negative effects on patients‘ lives. The occlusion of a ruptured aneurysm is one of the cornerstones of the treatment for aSAH; a procedure that may be both complicated and risky. However, not particularly much has been published about what can happen during the aneurysm treatment and how the patients’ outcome can be affected by different adverse events or complications related to the treatment.

Aims

This PhD thesis focuses on adverse events related to treatment of ruptured intracerebral aneurysms and how they can affect the patients‘ functional outcome. The specific aims of the included papers are:

I. Examine adverse events with microsurgical occlusion of a ruptured aneurysm and to identify risk factors for these events and assess the effect on functional outcome.

II. Study adverse events with endovascular treatment of a ruptured aneurysm and to identify possible risk factors for adverse events during the treatment and examine how the adverse events can impact the patients‘ functional outcome.

III. Analyse the use of decompressive craniectomy in patients treated for aneurysmal subarachnoid hemorrhage. Assess which factors primarily make it necessary to perform decompressive craniectomy, how these patients might differ from those not having the operation and explore how adverse events related to aneurysm treatment might affect these patients.

IV. Evaluate patients that are in a good clinical grade just prior to treatment of the ruptured aneurysm but have unfavorable outcome at one-year follow-up. With focus on how adverse events with aneurysm treatment affect the outcome in this group of patients.

Ethical considerations

The patients in these studies were included while being treated for a life-threatening disease, the informed consents were gathered from either the patient or their next of kin. As such, it is important to consider if they feeled obliged to the caregiver to give their consent. To my knowledge, no patient or their next of kin declined the request to have the relevant information registered in the database.

While storing immense information in a large nationwide database, the patient-specific informations are anonymous with the patient‘s IDs and the ID numbers stored at another location than the database. No study-specific interventions were made on the patients due to these studies and the patients‘ treatments were no different to the treatment given to patients treated at the respective clinics just before or after the sampling of data. No other study on patients with aneurysmal subarachnoid hemorrhage was performed at the including departments during the study period.

The protocol for the database and the study was approved by the Regional Ethical Review Board in Stockholm (2014/990-3). Furthermore, informed consent to be included in this database was obtained either from the patients or their next of kin.

Methods

Papers I – IV: Study designs

Patients admitted and treated for aneurysmal subarachnoid hemorrhage at the neurosurgical departments in the University Hospitals in Gothenburg, Lund, Linköping, Stockholm, Uppsala and Umeå from September 2014 until March 2018 were registered in a database. There were no age limits. The only inclusion criteria was that the ruptured aneurysm was occluded. There were no exclusion criterias. Patients with a citizenship and/or a residency out of Sweden (e.g. travellers) were included.

Representatives from each center formed a steering group that designed the database and convened regularly to assure that the study protocol was followed. Study variables were established and defined before sampling of patients was initiated. For registration in the database, Microsoft Access® (Microsoft, Redmond, WA) was used.

Papers I – IV: Outcome measurements

The patients‘ outcome was assessed with a clinical follow-up. Which included either an outpatient visit or a telephone interview. This was in general performed one year after the bleeding. The questionnaire for Glasgow outcome scale extended (GOSE) was used to have the follow-ups as standardized as possible. GOSE is an assessment tool where a scale is used to evaluate the patients' daily functionality. The scale stretches from 1 to 8, where 1 describes a deceased patient and 8 describes a patient that has no functional problems. The scale is often dichotomized to favorable outcome (numbers 5 to 8) and unfavorable outcome (numbers 1 to 4). The assessments were primarily made directly from how the patients‘ themselves answered the questions. Answers were gathered from the next of kin when the patient was unable to answer.

Paper I

Study variables

Variables registered in this study were age, sex, body mass index (BMI), comorbidities (previous stroke, coronary heart disease, hypertension, diabetes, regular alcohol use, cigarette smoking). Clinical status prior to aneurysm treatment, graded by the World Federation of Neurosurgical Societies (WFNS).[110] It was also registered if the patients had, at the same time, focal neurological deficits (paresis, dysphasia) and if they had a pathological pupillary response as assessed by the treating physician. Preoperative radiological findings, such as: severity of bleeding based on the Fisher scale,[10] hydrocephalus, cerebral edema, cerebral infarction. Angiographical features of the ruptured aneurysm. Anatomical location, type (saccular, blister or other, i.e. dissecting, fusiform, mycotic). Aneurysm size (maximal diameter). Neck width (small or wide), defined as a wide neck when the neck was $\geq$ 4 mm and/or the dome-to-neck ratio was < 2. Method of microsurgical aneurysm treatment (clipping, trapping or wrapping). Computed tomography (CT) scan was performed in the first days following surgery to see if new ischemic lesions had occurred. The occurrence of delayed ischemic neurological deficit (DIND)[79] was registered. DIND was reported if the patient had a neurological worsening in the days following the bleeding that was not found to be of other potential causes, such as a re-bleeding, hydrocephalus, epileptic seizure, or meningitis/ventriculitis. And where vasospasm was noted on angiography. It was also registered if decompressive craniectomy was performed or not. Adverse events during microsurgery were defined as re-rupture of the aneurysm during the operation, temporary occlusion of a parent artery for more than five minutes (total occlusion time), and injury to adjacent vessels causing cerebral infarction. Adverse events related to the microsurgery were furthermore bone flap infection necessitating a re-operation, postoperative hematoma demanding re-operation, and leakage of cerebrospinal fluid due to the surgery and requiring another operation or other specific treatment, e.g. leakage due to opening into frontal sinus. Outcome was assessed with GOSE questionnaire.[111,112]

Statistical methods

Every statistical analysis was performed with SPSS (IBM), version 26. Descriptive statistics were used for basic analysis of data, such as for clinical and radiological characteristics, and for the adverse events related to microsurgery. Binary logistic regression analyses were used for binary results. P-values < 0.05 were considered statistically significant.

Paper II

Study variables

Variables of interest in this study were patients' age, sex, body mass index (BMI), co-existing health problems (previous stroke, coronary heart disease, hypertension, diabetes, alcohol use, cigarette smoking). The WFNS grade[110], describing clinical status before aneurysm treatment. As well as focal neurological deficits and pathological pupillary response. Primary radiological results, such as bleeding severity (Fisher scale[10]), hydrocephalus, cerebral edema, and/or cerebral infarction. Aneurysm location, aneurysm type (saccular, blister, dissecting, fusiform or mycotic), aneurysm size, aneurysm neck configuration (wide or not). The method of endovascular treatment was registered: coiling, insertion of a stent, a flow diverter or a woven-endo-bridge (WEB) device, parent artery occlusion. It was also registered if the patient had received tranexamic acid prior to the endovascular treatment. Adverse events during endovascular treatment were identified as aneurysmal re-rupture during treatment, thromboembolism, and a vessel dissection. Another adverse event related to the endovascular approach was a puncture site hematoma requiring specific treatment (i.e., administration of blood products or another intervention). CT scan was performed in the first days after endovascular treatment, time of CT was not specifically defined. The presence of DIND[79] was registered. As well as if decompressive craniectomy was performed. GOSE[111,112] was used for outcome assessment.

Statistical methods

Clinical characteristics, radiological characteristics and adverse events with the treatment were summarized with descriptive statistics. Logistic regressions were used to analyse factors related to binary results of interest in this study; thromboembolic events, intraprocedural aneurysm re-rupture, and unfavorable outcome. Statistical significance was limited to p-values < 0.05. SPSS (IBM) version 28 was used for statistical analysis.

Paper III

Study variables

Baseline patients' parameters gathered in this study were age, sex, body mass index (BMI), previous stroke, coronary heart disease, hypertension, diabetes, alcohol use, and cigarette smoking. Clinical factors such as clinical status according to WFNS,[110] focal neurological deficits and pupillary response were sampled. Radiological findings, such as bleeding severity (Fisher[10]), hydrocephalus, cerebral edema,

cerebral infarction, aneurysm location, type, size and neck formation were registered. The method of occluding the ruptured aneurysm (microsurgery or endovascular treatment) and if adverse events (AEs) occurred related to that treatment were noted. These AEs were for patients treated by microsurgery: re-rupture during surgery, temporary parent artery occlusion over 5 minutes, and adjacent vessel injury causing cerebral infarction. For patients treated with endovascular approach the AEs were: re-rupture during treatment, perioperative thromboembolism, and vessel dissection. When it came to analysing the results, all the different AEs were grouped together as: Adverse events during aneurysm occlusion. If used during the intensive care, the use of thiopental was registered. The occurrence of DIND[79] was recorded. The operation of decompressive craniectomy (DC) was registered when performed. The timing of DC was registered with operations executed within 24 hours from the time of bleeding defined as early and operations done after more than 24 hours following the bleeding being defined as late. Outcome was measured with Glasgow outcome scale extended.[111,112]

Statistical methods

Basic analysis of data was performed with descriptive methods. To directly compare clinical factors between patients operated with decompressive craniectomy (DC) and those not operated with DC, Chi-square test was performed. Logistic regression analysis was used to analyse factors related to risk for decompressive craniectomy being performed and for variables impacting risk of unfavorable outcome. Statistics were analysed with SPSS (IBM), version 28, and the threshold for significance was set at 0.05.

Paper IV

Study variables

Parameters registered in this study were age, sex, body-mass index (BMI), comorbidities such as previous stroke, coronary heart disease, hypertension, diabetes, alcohol use, and current/previous cigarette smoking. Clinical, neurological status before aneurysm treatment was ranked according to WFNS.[110] With good clinical grade defined as WFNS I – III and poor clinical grade as WFNS IV – V. Outcome was assessed by the Glasgow outcome scale extended[111,112] where scores 1 – 4 were unfavorable outcome and scores 5 – 8 were favorable outcome. The pupillary response (normal or pathological) and focal neurological deficits (present or not) were registered. Registered radiological factors were magnitude of bleeding on CT, as defined by Fisher,[10] hydrocephalus, cerebral edema, cerebral infarction, as well as angiographical findings such as aneurysm location, type, size and neck width (wide or not). Wide aneurysm neck was defined as neck size ≥ 4 mm and/or

dome-to-neck ratio < 2. Adverse events (AEs) related to aneurysm treatment (microsurgery or endovascular) were registered. For microsurgically treated patients these were intraoperative aneurysm re-rupture, temporary parent artery occlusion for more than five minutes in total, or adjacent vessel injury causing cerebral infarction. For endovascular treated patients the defined AEs were perioperative thromboembolism, re-rupture, or vessel dissection. Other adverse events related to the following clinical course were registered, these were sedation with thiopental, epileptic seizure, meningitis, development of a delayed ischemic neurological deficit (DIND).[79]

Statistical methods

Descriptive analysis was used for primary data analysis. Chi-square test was used for comparing patients' characteristics between good grade patients either having unfavorable or favorable outcome. The relation of unfavorable outcome to clinical and radiological variables was analysed with univariate- and multivariate logistic regression. In all statistical analysis a p-value of <0.05 was considered statistically significant. The odds ratios and 95% confidence intervals (CI) were calculated through logistic regression analysis. IBM SPSS® Statistics version 29 (IBM Corp., Armonk, NY) was used for the statistical analysis.

Results

Paper I

Adverse events associated with microsurgial treatment for ruptured intracerebral aneurysms: a prospective nationwide study on subarachnoid haemorrhage in Sweden

Study population

Of totally 1037 patients treated for a ruptured intracerebral aneurysm, 322 patients (31%) were treated with microsurgical occlusion of a ruptured aneurysm. These 322 patients made up the cohort in this study. The median age of patients was 57.5 years. Two-thirds (66%) of patients were women. Majority, 59.5%, were in a good clinical grade (WFNS I - III) just prior to operation for the aneurysm. Focal neurological deficits were seen in 22.5% and pathological pupillary light reflexes noted in 8%. The three most common comorbidities were cigarette smoking (52%), hypertension (37%) and alcohol use (22%).

Aneurysms

The aneurysms were almost always (97%) located in the anterior circulation. Fifty percent were located on the middle cerebral artery (MCA). Thirty-one percent of aneurysms were on the anterior cerebri artery or anterior communicating artery (ACA/ACoA). Most aneurysms (94%) were saccular. Three percent were blister aneurysms and another three percent were other types (dissecting, fusiform, mycotic). Majority of the aneurysms (83%) had a wide neck.

Table 4. Baseline radiological characteristics of patients and aneurysms treated by microsurgery.

Fisher grade (n=318)	
1	15 (5%)
2	47 (15%)
3	67 (21%)
4	189 (59%)
Other radiological factors	
Hydrocephalus	110 (34%)
Infarction	20 (6%)
Oedema	59 (18%)
Aneurysm location (n=322)	
ACA/ACoA	99 (31%)
ACA-Proximal to ACoA	10
ACoA	79
ACA-Distal to ACoA	10
ICA	52 (16%)
ICA-Posterior communicating	38
ICA-Anterior choroidal	4
ICA-Ophthalmic	2
ICA-Bifurcation	4
ICA-Unspecified	4
MCA	161 (50%)
VA/BA	10 (3%)
Largest aneurysm dome diameter (n=310)	
0 – 4.9 mm	82 (27%)
5 – 9.9 mm	149 (48%)
10 – 14.9 mm	50 (16%)
15 – 24.9 mm	21 (7%)
25 mm or more	8 (3%)
Aneurysm neck size (n=285)	
Neck size $\geq$ 4 mm and/or dome-to-neck ratio $<$ 2	236 (83%)

ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery

Adverse events

Adverse events (AEs) were in total 105, in 97 patients. Which is 30% of all patients treated by microsurgal occlusion of the ruptured aneurysm. Intraoperative re-rupture was seen in 13% of cases, temporary parent artery occlusion for more than five minutes in 8%, and adjacent vessel injury leading to cerebral infarction also in 8%. Postoperative adverse events were seen in eleven patients. Bone flap infection was noted in 9 patients and 2 patients had postoperative hematoma that needed operation. Risk factors for the intraoperative adverse events were with multivariate logistic regression analysis assessed to be higher Fisher grade (OR 1.53, p=0.03) and edema on the initial CT (OR 2.07, p=0.048). Furthermore, aneurysm location on the anterior cerebral artery/anterior communicating artery (ACA/ACoA) was coupled to increased risk (OR 1.97, p=0.04) of intraoperative re-rupture using univariate analysis.

Table 5. Microsurgical adverse events.

Surgical adverse event	n (%)
Intraoperative re-rupture	43 (13%)
Temporary parent artery occlusion > 5 minutes	26 (8%)
Adjacent vessel injury with cerebral infarction	25 (8%)
Bone flap infection	9 (2.8%)
Postoperative hematoma, evacuated	2 (0.6%)
Cerebrospinal fluid leakage	0

Table 6. Logistic regression analysis. Intraoperative adverse events (aneurysmal re-rupture, temporary parent artery occlusion > 5 minutus, adjacent vessel injury with cerebral infarction), n=79.

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	1.01 (0.99– 1.03)	0.32	1.01 (0.99 – 1.03)	0.51
Female sex	0.86 (0.51 – 1.46)	0.58		
Initial WFNS grade (worse)	1.11 (0.94 – 1.30)	0.22	0.99 (0.81 – 1.20)	0.88
Pathological pupil reaction	0.26 (0.06 – 1.11)	0.07		
Aneurysm location: ACA/ACoA	1.54 (0.91 – 2.63)	0.11		
Aneurysm location: ICA	1.03 (0.52 – 2.05)	0.93		
Aneurysm location: MCA	0.74 (0.44 – 1.23)	0.25		
Aneurysm location: VA/BA	0.33 (0.04 – 2.67)	0.30		
Aneurysm size (larger)	0.99 (0.95 – 1.03)	0.68	1.00 (0.95 – 1.04)	0.89
Wide neck aneurysm	1.69 (0.78 – 3.68)	0.19	1.81 (0.79 – 4.15)	0.16
Fisher grade (higher)	1.51 (1.08 – 2.09)	0.02	1.53 (1.03 – 2.28)	0.03
Infarction on initial CT	1.37 (0.51 – 3.70)	0.53	1.15 (0.40 – 3.30)	0.80
Edema on initial CT	2.16 (1.16 – 4.00)	0.02	2.07 (1.01 – 4.24)	0.048
ICH evacuated	1.09 (0.57 – 2.09)	0.80	0.61 (0.28 – 1.34)	0.22

WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; CT, computed tomography; ICH, intracerebral hematoma

Outcome

Clinical follow-up about one year after the bleeding was found for 271 patients (84%). Of these, 167 (62%) had favorable functional outcome (GOSE 5 - 8) and 104 (38%) had unfavorable functional outcome (GOSE 1 - 4). Patients that had an intraoperative AE had 2.3 times ($p<0.01$) more often unfavorable outcome than those not having any intraoperative AE. When further analysed, it was seen that temporary clip on a parent artery for more than five minutes was related to 5.6 times ($p<0.01$) increased risk of unfavorable outcome. Other factors independently related to increased risk of unfavorable outcome were higher age (OR 1.05, $p<0.01$), worse clinical (WFNS) grade just prior to treatment (OR 1.70, $p<0.01$), and higher Fisher grade (OR 1.98, $p=0.02$).

Table 7. Logistic regression analysis. Unfavorable outcome (n=104).

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	1.05 (1.02 – 1.07)	<0.01	1.05 (1.02 – 1.09)	<0.01
Female sex	0.67 (0.40 – 1.13)	0.13		
History of smoking	1.74 (1.03 – 2.94)	0.04		
Alcohol	0.56 (0.30 – 1.03)	0.06		
Diabetes	3.42 (0.84 – 14.0)	0.09		
Coronary heart disease	1.68 (0.67 – 4.18)	0.27		
Hypertension	0.80 (0.48 – 1.34)	0.40		
Previous stroke	3.45 (0.84 – 14.1)	0.09		
BMI (higher)	0.10 (0.95 – 1.04)	0.67		
Initial WFNS grade (worse)	2.14 (1.76 – 2.60)	<0.01	1.70 (1.33 – 2.17)	<0.01
Pathological pupil reaction	3.28 (1.17 – 9.18)	0.02	1.51 (0.40 – 5.75)	0.55
Aneurysm location: ACA/ACoA	0.68 (0.39 – 1.16)	0.16		
Aneurysm location: ICA	0.87 (0.44 – 1.69)	0.67		
Aneurysm location: MCA	1.50 (0.91 – 2.45)	0.11		
Aneurysm location: VA/BA	1.07 (0.18 – 6.53)	0.94		
Aneurysm size (larger)	1.00 (0.97 – 1.04)	0.93		
Wide neck aneurysm	0.58 (0.29 – 1.15)	0.12		
Fisher grade (higher)	3.77 (2.40 – 5.94)	<0.01	1.98 (1.14 – 3.43)	0.02
Infarction on initial CT	3.87 (1.42 – 10.5)	<0.01	3.55 (0.90 – 14.1)	0.07
Edema on initial CT	5.84 (2.98 – 11.4)	<0.01	2.27 (0.96 – 5.38)	0.06
ICH evacuated	6.82 (3.41 – 13.6)	<0.01	2.15 (0.88 – 5.28)	0.09
DIND	1.50 (0.83 – 2.70)	0.18		
Adjacent vessel injury	2.98 (1.13 – 7.84)	0.03	2.56 (0.78 – 8.46)	0.12
Intraoperative re-rupture	1.49 (0.77 – 2.88)	0.23	1.12 (0.44 – 2.88)	0.82
Temporary clip > 5 minutes	4.16 (1.74 – 9.96)	<0.01	5.59 (1.63 – 19.2)	<0.01

BMI, body mass index; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; CT, computed tomography; ICH, intracerebral hematoma; DIND, delayed ischemic neurological deficit

Paper II

Adverse events during endovascular treatment of ruptured aneurysms: A prospective nationwide study on subarachnoid hemorrhage in Sweden

Study population

In this study, the population consisted of patients treated with endovascular approach, a total of 715 patients (69% of all treated). The patients were in a median age of 59 years and 68% were women. Just prior to aneurysm treatment, good clinical grade (WFNS I - III) was seen in 60% and poor clinical grade (WFNS IV - V) in 40%. Focal neurological deficits were noted in 13% of patients and pathological pupillary light reflexes in 4.5%. The comorbidities that were most frequently seen were cigarette smoking (55%), hypertension (40%) and alcohol use (14%).

Aneurysms

Of the treated aneurysms, majority were in the anterior circulation. Of which 6.6% were on the middle cerebral artery (MCA). 41% were on the anterior cerebral artery/anterior communicating artery (ACA/ACoA) and 29% were on the internal carotid artery (ICA). 23% of the aneurysms were in the posterior circulation, most often on the vertebral artery or the basilar artery. The aneurysms were most often saccular (72%). Blister aneurysms were noted in 3.5% of cases. Other types (dissecting, fusiform, mycotic) were seen in 24.5%. About half, 52%, of the aneurysms had a wide neck.

Table 8. Baseline radiological characteristics of patients and aneurysms treated by endovascular approach.

Fisher grade (n=700)	
1	23 (3.3%)
2	145 (21%)
3	211 (30%)
4	321 (46%)
Other radiological factors (n=715)	
Hydrocephalus	355 (50%)
Infarction	36 (5%)
Edema	82 (11%)
Aneurysm location (n=715)	
ACA/ACoA	296 (41%)
ACA-Proximal to ACoA	9
ACoA	260
ACA-Distal to ACoA	27
ICA	207 (29%)
ICA-Posterior communicating	127
ICA-Anterior choroidal	20
ICA-Ophthalmic	33
ICA-Bifurcation	13
ICA-Unspecified	14
MCA	47 (6.6%)
Posterior circulation	165 (23%)
VA/BA	84
PICA	37
SCA	21
PCA	21
AICA	2
Largest aneurysm dome diameter (n=684)	
< 5 mm	244 (36%)
5 – 10 mm	345 (50%)
>10 mm	95 (14%)
Aneurysm neck size (n=616)	
Neck size ≥ 4 mm and/or dome-to-neck ratio < 2	320 (52%)

ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; PICA, posterior inferior communicating artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery; AICA, anterior inferior communicating artery

Adverse events

Here, adverse events during endovascular occlusion for the ruptured aneurysm are defined as thromboembolism, re-rupture during treatment, a vessel dissection, and a puncture site hematoma.

Adverse events (AEs) during endovascular treatment for the ruptured aneurysm was seen in 113 patients (16%), number of AEs was 115 in total. Thromboembolism was the one most commonly noted, or in 78 patients (11%). Re-rupture during

endovascular treatment was marked in 28 patients (3.9%), and vessel dissection during the procedure was evident in 4 patients (0.6%). Puncture site hematoma needing special intervention was found in 5 patients (0.7%).

Table 9. Endovascular adverse events.

Endovascular adverse events	
Thromboembolism	78 (11%)
Re-rupture	28 (3.9%)
Vessel dissection	4 (0.6%)
Puncture site hematoma	5 (0.7%)

Patient-specific factors found to be related to increased risk of tromboembolism were alcohol use (OR 1.99, p=0.03), if the patient had received tranexamic acid (with unspecified timing of the last dose prior to treatment; OR 3.00, p<0.01), if the aneurysm was located on MCA (OR 3.11, p=0.01), if there was edema on the initial CT (OR 3.07, p<0.01), if the endovascular method was other than coiling (OR 1.99, p=0.03). The risk for re-rupture during aneurysm treatment was increased if the aneurysm was smaller than 5 mm (OR 2.88, p=0.01) and also with endovascular treatment of blister aneurysm (OR 6.34, p<0.01).

These aforementioned risk factors were significant and independent of others, as analysed by multivariate logistic regression analysis.

Table 10. Logistic regression analysis for thromboembolic events (n=78).

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	0.98 (0.97 – 0.99)	0.03	0.98 (0.96 – 0.99)	0.03
Gender (female)	0.81 (0.50 – 1.33)	0.41		
BMI (higher)	1.03 (0.98 – 1.08)	0.22		
Alcohol use	2.03 (1.14 – 3.61)	0.02	1.99 (1.06 – 3.73)	0.03
Cigarette smoking	1.14 (0.71 – 1.83)	0.59		
Hypertension	0.83 (0.51 – 1.36)	0.47		
Diabetes	1.13 (0.39 – 3.31)	0.82		
Coronary heart disease	1.35 (0.64 – 2.86)	0.43		
Initial clinical status, WFNS (worse)	0.79 (0.66 – 0.94)	0.01	0.68 (0.55 – 0.83)	<0.01
Received tranexamic acid prior to endovascular treatment	3.09 (1.86 – 5.14)	<0.01	3.00 (1.74 – 5.18)	<0.01
Aneurysm location: ACA/ACoA	0.82 (0.51 – 1.33)	0.42		
Aneurysm location: ICA	0.71 (0.41 – 1.24)	0.23		
Aneurysm location: MCA	2.06 (0.95 – 4.43)	0.07	3.11 (1.32 – 7.34)	0.01
Aneurysm location: Posterior circulation	1.36 (0.80 – 2.30)	0.26		
Aneurysm diameter < 5 mm	0.55 (0.32 – 0.94)	0.03	0.48 (0.27 – 0.85)	0.01
Aneurysm diameter 5 – 10 mm	1.31 (0.82 – 2.11)	0.26		
Aneurysm diameter > 10 mm	1.57 (0.85 – 2.88)	0.15		
Wide neck aneurysm	0.83 (0.51 – 1.36)	0.47		
Higher Fisher grade on initial CT	1.05 (0.94 – 1.19)	0.39		
Infarction on initial CT	1.02 (0.35 – 2.97)	0.97		
Edema on initial CT	2.03 (1.09 – 3.76)	0.03	3.07 (1.51 – 6.24)	<0.01
Hydrocephalus on initial CT	0.76 (0.47 – 1.22)	0.26		
Aneurysm type: Saccular	1.57 (0.89 – 2.80)	0.12		
Aneurysm type: Blister	1.12 (0.33 – 3.83)	0.86		
Treatment: Coiling	0.53 (0.31 – 0.93)	0.03		
Treatment: Other than coiling	1.87 (1.08 – 3.25)	0.03	1.99 (1.08 – 3.68)	0.03

BMI, body mass index; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; CT, computed tomography

Table 11. Logistic regression analysis for intraprocedural aneurysm re-rupture (n=28).

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	0.99 (0.97 – 1.02)	0.64		
Gender (female)	1.74 (0.70 – 4.35)	0.28		
BMI (higher)	1.04 (0.98 – 1.11)	0.22		
Alcohol use	3.69 (1.65 – 8.24)	<0.01		
Cigarette smoking	1.29 (0.59 – 2.79)	0.52		
Hypertension	0.60 (0.26 – 1.37)	0.22		
Diabetes	1.63 (0.37 – 7.17)	0.52		
Coronary heart disease	1.21 (0.36 – 4.12)	0.76		
Initial clinical status, WFNS (worse)	1.05 (0.82 – 1.34)	0.72		
Received tranexamic acid prior to endovascular treatment	0.62 (0.28 – 1.40)	0.25		
Aneurysm location: ACA/ACoA	1.44 (0.67 – 3.06)	0.35		
Aneurysm location: ICA	0.81 (0.34 – 1.94)	0.64		
Aneurysm location: MCA	0.52 (0.07 – 3.88)	0.52		
Aneurysm location: Posterior circulation	0.91 (0.36 – 2.27)	0.83		
Aneurysm diameter < 5 mm	3.43 (1.56 – 7.54)	<0.01	2.88 (1.28 – 6.50)	0.01
Aneurysm diameter 5 – 10 mm	0.45 (0.20 – 1.01)	0.053		
Aneurysm diameter > 10 mm	0.22 (0.03 – 1.65)	0.14		
Wide neck aneurysm	0.85 (0.39 – 1.85)	0.69		
Higher Fisher grade on initial CT	1.05 (0.89 – 1.25)	0.55		
Infarction on initial CT	0.69 (0.09 – 5.23)	0.72		
Edema on initial CT	1.30 (0.44 – 3.85)	0.63		
Hydrocephalus on initial CT	1.37 (0.64 – 2.94)	0.42		
Aneurysm type: Saccular	0.97 (0.42 – 2.24)	0.94		
Aneurysm type: Blister	9.59 (3.49 – 26.4)	<0.01	6.34 (1.82 – 22.1)	<0.01
Treatment: Coiling	0.34 (0.15 – 0.76)	<0.01		
Treatment: Other than coiling	2.95 (1.32 – 6.55)	<0.01	1.47 (0.54 – 4.00)	0.45

BMI, body mass index; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; CT, computed tomography

Outcome

Outcome measurements as a clinical follow-up after one-year was in place for 623 patients (87%). Of the followed up patients, 393 (63%) had favorable functional outcome and 230 (37%) had unfavorable functional outcome. The risk of unfavorable outcome was related to higher patient age (OR 1.04, p<0.01), worse clinical grade prior to treatment (OR 1.72, p<0.01), cerebral infarction on the first CT (OR 3.08, p=0.02), as well as edema (OR 2.31, p=0.01) and/or hydrocephalus (OR 2.36, p<0.01) on the first CT. Adverse event with a re-rupture of the aneurysm during endovascular occlusion was related to almost seven-fold increased risk of unfavorable outcome (OR 6.92, p<0.01).

Table 12. Logistic regression analysis, unfavorable outcome (n=230).

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	1.05 (1.03 – 1.06)	<0.01	1.04 (1.02 – 1.06)	<0.01
Female sex	1.00 (0.70 – 1.43)	0.995		
BMI (higher)	1.02 (0.99 – 1.05)	0.24		
Alcohol use	1.32 (0.83 – 2.08)	0.24		
Cigarette smoking	1.26 (0.90 – 1.75)	0.18		
Hypertension	2.04 (1.46 – 2.84)	<0.01	1.30 (0.85 – 1.99)	0.23
Diabetes	3.25 (1.47 – 7.17)	<0.01	1.74 (0.56 – 5.45)	0.34
Coronary heart disease	3.62 (2.07 – 6.32)	<0.01	1.48 (0.70 – 3.11)	0.30
Initial WFNS grade (worse)	1.90 (1.68 – 2.16)	<0.01	1.72 (1.48 – 2.00)	<0.01
Received tranexamic acid prior to endovascular treatment	1.38 (0.99 – 1.93)	0.056	1.08 (0.67 – 1.74)	0.76
Aneurysm location: ACA/ACoA	0.89 (0.64 – 1.24)	0.50		
Aneurysm location: ICA	0.75 (0.52 – 1.08)	0.12		
Aneurysm location: MCA	1.53 (0.82 – 2.86)	0.18		
Aneurysm location: Posterior circulation	1.38 (0.94 – 2.01)	0.10		
Aneurysm diameter < 5 mm	0.85 (0.60 – 1.20)	0.35		
Aneurysm diameter 5 – 10 mm	1.20 (0.86 – 1.67)	0.29		
Aneurysm diameter > 10 mm	0.95 (0.58 – 1.54)	0.82		
Wide neck aneurysm	0.98 (0.69 – 1.39)	0.92		
Fisher grade (higher)	1.18 (1.01 – 1.38)	0.04	1.20 (0.89 – 1.62)	0.23
Infarction on initial CT	4.88 (2.31 – 10.3)	<0.01	3.08 (1.24 – 7.65)	0.02
Edema on initial CT	4.13 (2.43 – 7.01)	<0.01	2.31 (1.19 – 4.49)	0.01
Hydrocephalus on initial CT	3.94 (2.78 – 5.59)	<0.01	2.36 (1.52 – 3.64)	<0.01
DIND	0.47 (0.14 – 1.55)	0.22		
Aneurysm type: Saccular	1.64 (1.12 – 2.40)	0.01	1.31 (0.80 – 2.17)	0.29
Aneurysm type: Blister	1.38 (0.54 – 3.55)	0.50		
Aneurysm type: Dissection	1.37 (0.72 – 2.59)	0.34		
Endovascular treatment: Coiling	0.84 (0.54 – 1.30)	0.43		
Endovascular treatment: Other than coiling	1.19 (0.77 – 1.85)	0.43		
Thromboembolic event	0.78 (0.44 – 1.35)	0.37		
Periprocedural aneurysm re-rupture	3.19 (1.39 – 7.34)	<0.01	6.92 (2.28 – 20.9)	<0.01

BMI, body mass index; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; CT, computed tomography; DIND, delayed ischemic neurological deficit

Paper III

Decompressive craniectomy following subarachnoid hemorrhage: A prospective Swedish multicenter study

Study population

This study focuses on patients that were operated with decompressive craniectomy following aneurysmal subarachnoid hemorrhage. Of totally 1037 patients treated, 35 were operated with decompressive craniectomy (DC). Which is 3.4% of all treated. DC was more common in patients having the aneurysm treated by microsurgery than by endovascular approach. Of the patients undergoing microsurgery, DC was performed in 7.5%, compared to 1.5% of patients treated by endovascular method.

Decompressive craniectomy, timing and risk factors

The operations were performed in a median of two days following the bleeding. Significant, independent, risk factors for having DC were poor clinical grade (WFNS IV – V) just prior to the aneurysm treatment (OR 7.25, $p<0.01$), aneurysm location on MCA (OR 2.86, $p=0.01$), edema on the initial CT (OR 3.62, $p<0.01$), and adverse event during occlusion of the ruptured aneurysm (OR 3.61, $p<0.01$). Early DC, within 24 hours following the bleeding, was performed in 15 of the patients (43%). Late DC, after 24 h, was performed in the other 20 patients. Patients having early DC had more often Fisher grade 4 bleeding ($p=0.02$), intracerebral hematoma that was evacuated ($p=0.04$), and had higher mortality ($p=0.04$).

Table 13. Patients operated with decompressive craniectomy (n=35). Logistic regression analysis.

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	0.99 (0.96 – 1.01)	0.25		
Female sex	0.92 (0.45 – 1.87)	0.82		
History of smoking	1.40 (0.66 – 2.98)	0.38		
Alcohol	1.36 (0.58 – 3.19)	0.49		
Diabetes	1.37 (0.32 – 5.90)	0.67		
Coronary heart disease	2.03 (0.76 – 5.39)	0.16		
Hypertension	1.40 (0.71 – 2.78)	0.33		
Previous stroke	0.69 (0.09 – 5.20)	0.72		
BMI (higher)	0.99 (0.93 – 1.07)	0.92		
Poor clinical grade (WFNS IV - V)	8.84 (3.39 – 23.1)	<0.01	7.25 (2.41 – 21.8)	<0.01
Aneurysm location: ACA/ACoA	0.47 (0.21 – 1.05)	0.07		
Aneurysm location: ICA	0.61 (0.25 – 1.49)	0.28		
Aneurysm location: MCA	5.11 (2.58 – 10.1)	<0.01	2.86 (1.26 – 6.49)	0.01
Aneurysm location: VA/BA	0.29 (0.07 – 1.22)	0.09		
Aneurysm size (larger)	1.01 (0.97 – 1.04)	0.71		
Aneurysm occluded with microsurgery	5.15 (2.49 – 10.7)	<0.01		
Wide neck aneurysm	1.68 (0.77 – 3.67)	0.19		
Fisher grade 4	5.12 (2.11 – 12.4)	<0.01		
Infarction on initial CT	4.37 (1.72 – 11.1)	<0.01		
Edema on initial CT	7.35 (3.46 – 15.6)	<0.01	3.62 (1.59 – 8.26)	<0.01
Hydrocephalus on initial CT	0.97 (0.49 – 1.92)	0.92		
ICH evacuated	9.34 (4.41 – 19.8)	<0.01		
DIND	0.99 (0.44 – 2.22)	0.98		
Adverse event during aneurysm occlusion	3.95 (1.99 – 7.84)	<0.01	3.61 (1.58 – 8.26)	<0.01

BMI, body-mass index; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; ICH, intracerebral hematoma; DIND, delayed ischemic neurological deficit

Table 14. Logistic regression analysis. Patients treated with aneurysm occlusion having unfavorable outcome, n=334.

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (older)	1.05 (1.04 – 1.06)	<0.01	1.05 (1.03 – 1.06)	<0.01
Female sex	0.88 (0.66 – 1.81)	0.40		
History of smoking	1.38 (1.04 – 1.82)	0.03	0.37 (0.07 – 1.94)	0.24
Alcohol	0.95 (0.66 – 1.36)	0.77		
Diabetes	3.28 (1.65 – 6.53)	<0.01	1.46 (0.61 – 3.51)	0.40
Coronary heart disease	2.94 (1.83 – 4.71)	<0.01	0.95 (0.49 – 1.83)	0.88
Hypertension	1.54 (1.17 – 2.03)	<0.01	0.96 (0.66 – 1.39)	0.83
Previous stroke	4.72 (2.39 – 9.32)	<0.01	3.22 (1.38 – 7.55)	<0.01
BMI (higher)	1.01 (0.98 – 1.04)	0.43		
Poor clinical grade (WFNS IV - V)	6.81 (5.02 – 9.23)	<0.01	4.41 (3.05 – 6.36)	<0.01
Aneurysm location: ACA/ACoA	0.82 (0.62 – 1.09)	0.17		
Aneurysm location: ICA	0.77 (0.56 – 1.06)	0.11		
Aneurysm location: MCA	1.41 (1.01 – 1.96)	0.04	1.04 (0.63 – 1.70)	0.88
Aneurysm location: VA/BA	1.31 (0.92 – 1.87)	0.14		
Aneurysm size (larger)	0.99 (0.97 – 1.01)	0.20		
Wide neck aneurysm	0.91 (0.67 – 1.22)	0.52		
Fisher grade 4	3.10 (2.33 – 4.11)	<0.01	1.29 (0.89 – 1.87)	0.18
Infarction on initial CT	4.51 (2.48 – 8.21)	<0.01	3.96 (1.85 – 8.47)	<0.01
Edema on initial CT	4.66 (3.08 – 7.04)	<0.01	1.90 (1.12 – 3.23)	0.02
Hydrocephalus on initial CT	3.17 (2.39 – 4.21)	<0.01	2.32 (1.60 – 3.37)	<0.01
ICH evacuated	6.55 (3.48 – 12.3)	<0.01	3.87 (1.53 – 9.75)	<0.01
DIND	2.55 (1.86 – 3.49)	<0.01	1.13 (0.32 – 3.97)	0.85
Adverse event during aneurysm occlusion	1.57 (1.11 – 2.20)	0.01	1.84 (1.17 – 2.90)	<0.01
Decompressive craniectomy	5.58 (2.49 – 12.5)	<0.01	2.88 (0.90 – 9.23)	0.08

BMI, body-mass index; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; ICH, intracerebral hematoma; DIND, delayed ischemic neurological deficit

Outcome

Of all treated patients (n=1037), 32% had unfavorable functional outcome. In the group of patients operated with decompressive craniectomy (n=35), 71% had unfavorable outcome. Independent risk factors for having unfavorable outcome in the total cohort (n=334) were higher age (OR 1.05, p<0.01), previous stroke (OR 3.22, p<0.01), poor clinical grade (WFNS IV – V) prior to aneurysm treatment (OR 4.41, p<0.01), cerebral infarction (OR 3.96, p<0.01), cerebral edema (OR 1.90, p=0.02) and/or hydrocephalus (OR 2.32, p<0.01) on the initial CT scan, intracerebral hematoma being evacuated (OR 3.87, p<0.01), and adverse event during aneurysm occlusion (OR 1.84, p<0.01).

Patients operated with DC and having favorable outcome were significantly younger (median age: 49 years) than patients operated with DC and having unfavorable outcome (median age: 57 years), p=0.02.

Paper IV

Causes of unfavorable outcome in patients with good grade subarachnoid hemorrhage prior to aneurysm treatment: impact of adverse events

Study population

The study cohort in this study is comprised of patients that were in a good clinical condition (WFNS I – III; GCS 13 – 15) just prior to aneurysm treatment. Of a totally 1037 treated patients, 607 were in a good clinical condition when the aneurysm was treated. Of these patients, 86% had a clinical follow-up. Making 520 patients relevant for further analysis in this study. Of these, 102 patients (20%) had unfavorable outcome at one year follow-up.

Radiological factors

Radiological factors at admission such as Fisher grade 4, cerebral edema and/or infarction, and hydrocephalus were all more commonly seen in patients having unfavorable outcome. There was no difference in factors regarding the aneurysms (i.e., location, size, neck width) between patients having unfavorable or favorable outcome.

Adverse events during aneurysm treatment

Microsurgery was performed in 154 (29.6%) of the good grade patients and endovascular treatment in the other 366 patients (70.4%). Adverse events (AEs) related to these treatments differed between the two outcome groups. AEs were seen in 31.4% of patients having unfavorable outcome and in 16% of patients having favorable outcome. Multivariate analysis showed that AEs during aneurysm treatment was significantly related to risk of unfavorable outcome (OR 2.38, $p<0.01$).

Table 15. Patients in a good clinical grade (WFNS I - III) prior to aneurysm treatment with either unfavorable or favorable functional outcome.

	Unfavorable outcome (GOSE 1-4); n=102	Favorable outcome (GOSE 5-8); n=418
Clinical characteristics		
Female sex	68 (67%)	296 (71%)
Age in years (median, range)	65 (28 – 88)	55 (18 – 85)
Smoking	54 (53%)	226 (54%)
Hypertension	53 (52%)	143 (34%)
Diabetes	7 (7%)	9 (2%)
Alcohol use	16 (16%)	80 (19%)
Coronary heart disease	16 (16%)	20 (5%)
Previous stroke	11 (11%)	9 (2%)
BMI (median)	26 (16 – 46)	26 (16 – 49)
Focal neurological deficit	2 (2%)	13 (3.1%)
Pathological pupillary reflex	9 (8.8%)	5 (1.2%)
Radiology (initial CT/angio)		
Fisher grade 4	51 (50%)	125 (29.9%)
Cerebral edema	14 (13.7%)	24 (5.7%)
Cerebral infarction	13 (12.7%)	9 (2.2%)
Hydrocephalus	56 (54.9%)	127 (30.4%)
Aneurysm location: ACA/ACoA	43 (42.2%)	168 (40.2%)
Aneurysm location: ICA	25 (24.5%)	118 (28.2%)
Aneurysm location: MCA	14 (13.7%)	71 (17%)
Aneurysm location: Posterior circulation	20 (19.6%)	61 (14.6%)
Aneurysm, max diameter (mm), median	6.0 (1 - 46)	5.0 (1 - 95)
Aneurysm, wide neck	53 (52%)	221 (52.9%)
Treatments		
Surgical approach	28 (27.5%)	126 (30.1%)
Endovascular approach	74 (72.5%)	292 (69.9%)
ICH evacuated	4 (3.9%)	2 (0.5%)
EVD	59 (57.8%)	109 (26.1%)
Length of EVD (days), median	4 (<1 – 25)	5.5 (<1 – 22)
Thiopental sedation	7 (6.9%)	5 (1.2%)
Adverse events		
Adverse event during aneurysm occlusion	32 (31.4%)	67 (16%)
DIND	40 (39.2%)	65 (15.6%)
Epileptic seizure	8 (7.8%)	6 (1.4%)
Meningitis/Ventriculitis	25 (24.5%)	34 (8.1%)

BMI, body-mass index; CT, computed tomography; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; ICH, intracerebral hematoma; EVD, external ventricular drain; DIND, delayed ischemic neurological deficit

Table 16. Good grade patients and unfavorable outcome, n=102.

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Clinical characteristics				
Female sex	0.82 (.052 – 1.31)	0.41		
Age (older, per year)	1.06 (1.04 – 1.08)	<0.01	1.05 (1.03 – 1.07)	<0.01
Smoking	1.00 (0.65 – 1.56)	0.99		
Hypertension	2.08 (1.34 – 3.22)	<0.01	1.51 (0.89 – 2.58)	0.13
Diabetes	3.38 (1.23 – 9.32)	0.02		
Alcohol use	0.82 (0.46 – 1.48)	0.52		
Coronary heart disease	3.74 (1.86 – 7.51)	<0.01	1.95 (0.82 – 4.64)	0.13
Previous stroke	5.68 (2.29 – 14.1)	<0.01		
BMI	1.03 (0.98 – 1.07)	0.23		
Focal neurological deficit	3.02 (1.25 – 7.26)	0.01		
Pathological pupillary reflex	1.65 (0.32 – 8.64)	0.55		
Radiology (initial CT/angio)				
Fisher grade 4	2.27 (1.46 – 3.53)	<0.01	1.14 (0.66 – 1.97)	0.63
Cerebral edema	2.61 (1.30 – 5.25)	<0.01	1.82 (0.78 – 4.26)	0.17
Cerebral infarction	6.61 (2.74 – 15.9)	<0.01		
Hydrocephalus	2.78 (1.79 – 4.33)	<0.01	1.80 (1.04 – 3.14)	0.04
Aneurysm location: ACA/ACoA	1.09 (0.70 – 1.68)	0.72		
Aneurysm location: ICA	0.83 (0.50 – 1.36)	0.45		
Aneurysm location: MCA	0.78 (0.42 – 1.44)	0.43		
Aneurysm location: Posterior circulation	1.43 (0.82 – 2.50)	0.21		
Aneurysm size (larger)	0.98 (0.96 – 1.01)	0.18		
Aneurysm, wide neck	0.84 (0.53 – 1.33)	0.46		
Treatments				
Aneurysm occluded with microsurgery	0.88 (0.54 – 1.42)	0.59		
ICH evacuated	8.49 (1.53 – 47.0)	0.01		
EVD	0.25 (0.16 – 0.40)	<0.01		
Length of EVD (longer)	1.11 (1.07 – 1.14)	<0.01	1.04 (0.99 – 1.09)	0.15
Thiopental sedation	6.15 (1.91 – 19.8)	<0.01		
Adverse events				
Adverse event during aneurysm occlusion	2.40 (1.46 – 3.92)	<0.01	2.38 (1.30 – 4.38)	<0.01
DIND	3.66 (2.26 – 5.92)	<0.01	3.43 (1.96 – 6.00)	<0.01
Meningitis/Ventriculitis	3.76 (2.12 – 6.66)	<0.01	1.81 (0.82 – 4.03)	0.14
Epileptic seizure	5.88 (1.99 – 17.3)	<0.01		

BMI, body-mass index; CT, computed tomography; ACA, anterior cerebral artery; ACoA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; ICH, intracerebral hematoma; EVD, external ventricular drain; DIND, delayed ischemic neurological deficit

Other events

During the clinical course following aneurysm treatment, factors such as DIND, thiopental sedation, epileptic seizure, and meningitis/ventriculitis were more often noted in patients having unfavorable outcome.

Outcome

Twenty percent of all good grade patients had unfavorable outcome (GOSE 1 – 4), i.e., either deceased or dependent on others in their daily activities. Factors significantly, and independently, associated with risk of unfavorable outcome in this group of patients were higher age (OR 1.05, $p<0.01$), hydrocephalus (OR 1.80, $p=0.04$), AE during aneurysm treatment (OR 2.38, $p<0.01$), and DIND (OR 3.43, $p<0.01$).

Discussion

In this thesis, the focus is on adverse events related to treatment for aneurysmal subarachnoid hemorrhage.

The study cohort comprises in total of 1037 patients that were treated for aneurysmal subarachnoid hemorrhage at six neurosurgical university clinics in Sweden over a 3.5-year period. Clinical condition before aneurysm treatment was the WFNS grade closest in time prior to treatment. This was chosen as it is a better predictor of outcome than grade at admission.[113] Of the treated patients, roughly two-thirds had a favorable outcome at one year follow-up. Adverse events related to the treatment had significant impact on clinical outcome.

This PhD thesis is foremost of interest for clinicians treating patients with aneurysmal subarachnoid hemorrhage.

Microsurgery

Of the 322 patients treated by microsurgery, 97 had adverse events (AEs) related to the surgery. 79 of these events being intraoperative AEs, giving a rate of 25%. With the expanding use of endovascular treatment, the number of aneurysms being treated by surgery is decreasing. As endovascular treatment is often the first choice of method it is easy to theorize that more troublesome aneurysms/bleedings are nowadays, especially in historical comparison, treated by microsurgery. This is reflected in the results as 83% of microsurgically treated aneurysms had a wide neck, 59% had a Fisher grade 4 bleeding and 18% had intracerebral hematoma that was evacuated at the same time the aneurysm was occluded with surgery. More complex surgery is related to increased risk of adverse events.

What constitutes as an adverse event can be debated. Here, the conscious choice was made to include all events that were undesired and could possibly jeopardize the patients' outcome. Intraoperative AEs were re-rupture during the operation, temporary occlusion of the parent artery > 5 minutes, and adjacent vessel injury causing cerebral infarction. Postoperative AEs were bone flap infection, postoperative hematoma needing evacuation, and cerebrospinal fluid leakage related to the microsurgery.

Intraoperative aneurysmal re-rupture

The rate of re-rupture during surgery is 8.9 - 17.5%.[114-118] Even if a re-rupture is seen as an adverse event related to the operation it is well known that ruptured intracerebral aneurysms are prone to re-rupture. A re-rupture can happen at any time point in the operating theater but most commonly occurs during dissection and clip application. A re-rupture during dissection, before the aneurysm has been clearly isolated can be a particularly stressful situation and technically difficult to manage. In comparison, a small bleeding from the aneurysm during clip application that stops when the aneurysm has been occluded is a whole different situation. In Paper I we see an intraoperative aneurysmal re-rupture rate of 13%, which is within the rate published in the literature. Aneurysmal location on ACA/ACoA was related to increased risk of re-rupture, according to univariate logistic regression analysis. This relation of ACA/ACoA aneurysms and intraoperative re-rupture has been noted in previously published studies[117,118] and a possible explanation for this increased frequency is that ACA/ACoA aneurysms are located at a complicate junction where the access, aneurysmal dissection and clip application can be tricky. In Paper I, re-ruptures were not associated with risk of unfavorable outcome. Possibly indicating a very competent approach of treating this adverse event. A well-established method of treating intraoperative aneurysmal re-rupture is to apply a temporary clip on the parent artery. This halts the blood flow to the aneurysm. Aiding the surgeon in applying the permanent clip. Other ways to treat an intraoperative re-rupture but are very seldomly used are i.e., cross-clamping the carotid artery in the neck, endovascular balloon occlusion, and injection of Adenosine, inducing a short (<1 minute) episode of asystole and concomitant hypotension.[119]

Temporary occlusion of parent artery > 5 minutes

Paper I reveals that temporary clipping was commonly used, in 54% of cases. The use of a temporary clip when a rupture has not occurred is a strategical decision made by the surgeon. The use of so-called temporary clipping makes the dissection less stressful and the aneurysm softer, leading to easier clipping of the aneurysm.[120,121] It differs between surgeons (and centers) which routines apply regarding temporary occlusion of a parent artery. Some use it routinely and prepare the patient for it, others use it during the last part of the dissection and during application of the clip, others only use it when the aneurysm ruptures intraoperatively. The first mentioned approach is not a common practice in Sweden. However, a prolonged temporary occlusion of a parent artery is a routine practice in some neurosurgical centers worldwide. In such cases the patient is prepared for this by increasing the sedation where burst suppression is noted on an electroencephalogram (EEG).[122] Burst suppression is a finding on EEG that reflects

a reduced cerebral metabolism and is thereby protective against cerebral ischemia.[123]

The time frame of a definite safe temporary parent artery occlusion is principally unknown. This, as there are many factors that affect the risk of cerebral ischemia. Factors such as sedation, ventilation, blood pressure, and anatomy are all important aspects in this context.[70] A definite cut-off time relevant for all patients is probably out of reach. In clinical practice, the five-minute time frame is often used. Studies have shown that an occlusion for less than five minutes is generally safe but occlusion for a longer time (> 5 minutes) can be related to harmful ischemia.[70,71] To analyse the clinical effect of temporary parent artery occlusion, in Paper I the five-minute cut-off is selected. Of all treated patients, 8% had a temporary parent artery occlusion for more than five minutes. Half of these patients had quite a clear explanation for this, having an intraoperative aneurysmal re-rupture. The cause of the prolonged occlusion in the other half is unclear. Logistic regression analysis showed that temporary parent artery occlusion > 5 minutes was significantly and independently related to more than five-fold increased risk of unfavorable outcome. The same type of analysis showed that intraoperative aneurysmal re-ruptures did not affect the patient outcome. This is a reflection on the risks related to prolonged temporary artery occlusion and why we should strive to minimize occlusion to less than 5 minutes, especially in an unplanned occlusion.

Adjacent vessel injury causing cerebral infarction

During surgical occlusion of an intracerebral aneurysm, vessels adjacent to the aneurysm are carefully dissected and all effort is made to avoid damage to them. Unavoidably, these vessels get injured at times. Consequently, cerebral infarction can be noted after the operation. The clinical effects of these are directly related to which vessels are involved.

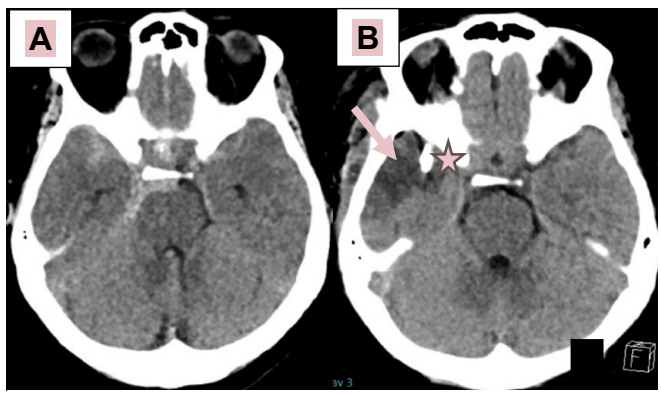

Figure 10. CT scan before (A) and after (B) clipping of a ruptured MCA aneurysm. In (B) the arrow is pointing at an infarction caused by adjacent vessel injury and the star indicates the titanium clip.

Adjacent vessel injury causing cerebral infarction is seen in 8% of operated cases in Paper I, with an increased risk (OR 2.3) being related to higher Fisher grade with univariate logistic regression. This is however not noted in the adjusted analysis.

This relation to more bleeding severity is clinically relatable as the difficulty of the microsurgical dissection and the operation in general is directly related to the severity of the bleeding. Injury to vessels adjacent to the aneurysm can i.e., be caused by directly including these vessels within the clip, with injuries occurring during the dissection, or with injuries during retraction. When adjusted for other variables, this type of AE was not independently related to increased risk of unfavorable outcome. Which indicates that the injured vessels were minor, and concomitant infarctions did not have major negative impact on the patients.

Endovascular treatment

Of analysed patients, 715 were treated by endovascular approach, 113 of those (16%) had AEs related to the treatment. The most common AEs being thromboembolism and aneurysmal re-rupture during the treatment.

Thromboembolism

As reported in Paper II, thromboembolism during endovascular treatment was seen in 78 patients (11%). A rate which is comparable to published studies (5 - 16%).[73,124-126] Thromboembolism is most often treated with trombolysis.[125,126] In Paper II, patients having thromboembolism had more often received tranexamic acid (TXA) prior to treatment (OR 3.0). The interval between administration of TXA before treatment is though unclear. However, this raises questions if TXA should be administered to patients where we know the aneurysm is suitable for endovascular treatment.

Aneurysmal location on MCA was related to increased risk of thromboembolism. This likely as MCA aneurysms are at times, due to anatomical factors, complex to treat with endovascular methods. The risk for thromboembolism was also increased when the endovascular occlusion was more complicated than ”simple” coiling. This can easily be explained by the fact that an advanced treatment takes longer time. With catheters inserted in the vessels for a longer time, which increases the risk of thrombosis.

Furthermore, patients with thromboembolism had more often edema on the initial CT scan (OR 3.1). Theoretical explanation for this association is that increased intracranial pressure, due to edema, could affect the hemodynamics of intracerebral vessels through increased sympathetic activity.[127] Increasing the risk of thromboembolism. Also, prothrombotic state is possibly increased in patients having intracerebral edema.[128,129] Thereby increasing the risk for thromboembolism. A risk-relation with thromboembolism was also seen with alcohol use (OR 2.0), this association is difficult to explain.

Intraprocedural aneurysm re-rupture

Just like with microsurgery for a ruptured intracerebral aneurysm, re-rupture during endovascular treatment is an overhanging threat. Re-rupture during such treatment is often managed by inflating a balloon catheter in the parent artery or at the neck of the aneurysm. Inserting coils quickly into the aneurysm is also an effective way. Re-rupture can also necessitate an operation with external ventricular drainage (EVD) and/or decompressive craniectomy.

As seen in Paper II, 28 patients (3.9%) had a re-rupture during the endovascular occlusion. In the literature, a frequency between 1.4 – 5% has been described.[116,130] Patients having re-rupture during treatment had more often small aneurysms, < 5 mm, (OR 2.9). This has also been described in other studies[73,131] and can be explained as small aneurysms have less space for catheter maneuvers and at times more difficult angles, compared to larger aneurysms. Blister-type aneurysms were related to much increased risk of re-rupture (OR 6.3) in this cohort. This is not surprising as blister-type aneurysms are known to be difficult to treat, are fragile and have a high risk of rupture.[3,132]

Re-rupture during treatment was associated with highly increased (OR 6.9) risk of unfavorable outcome at one year follow-up. Reflecting how immense negative impact this type of adverse event has on patient outcome.

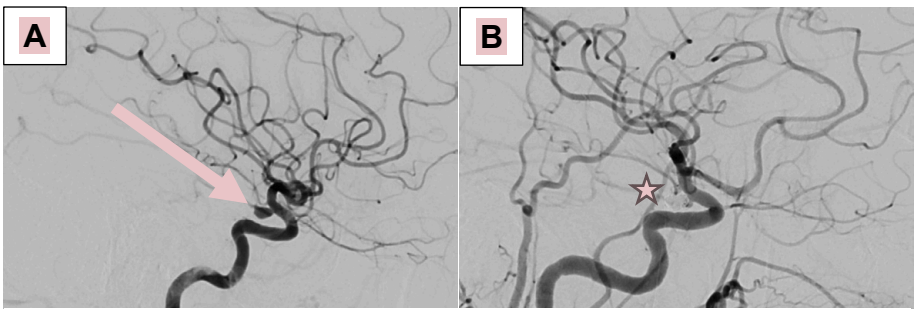

Figure 11. In (A) the arrow is pointing at an aneurysm on the posterior communicating artery before coil-occlusion. In (B) the same aneurysm has been coiled (star).

Decompressive craniectomy

Following aSAH, the intracranial pressure (ICP) can be highly elevated. Usual initial measures to lower the ICP are at times insufficient. These being i.e., elevation of the patients' head, treatment of fever, infections, epileptic seizures, and electrolyte disturbances, drainage of cerebrospinal fluid (CSF), optimizing

respiration and increasing sedation.[94-96] In such situations, decompressive craniectomy (DC) is often, at least in the neurosurgical clinics in Sweden, the next step. However, sometimes the ICP elevation is so critical that no time can be given to first try out the other treatment measures mentioned. In Paper III a DC frequency of 3.4% following aSAH is described. A rate which is in the lower range (3.3 – 25.6%; mean: 10.9%) of what has been published in the literature.[99]

Why the rate is lower on a nationwide basis in Sweden compared to a mean ratio of 10.9% should perhaps be evaluated further. It is possible that the threshold to perform DC in these patients is higher in Sweden compared to many other countries. Also, it can be theorized that patients that would be operated with DC following aSAH in other countries are excluded from these operations in Sweden. It can also be speculated that with advanced neurointensive care, the real need for DC is perhaps limited. On the other hand, the conservative stepwise measures to treat elevated ICP in Sweden are perhaps counterintuitive. With the patients having more and longer sedation than what would be optimal. Increasing the risks of other treatment-related complications such as infections, thrombosis and pressure wounds. Furthermore, DC in the early stages could also help minimize the patients' ICP fluctuations. However, as complications following DC are relatively common[133] it is gainful when these operations can be avoided.

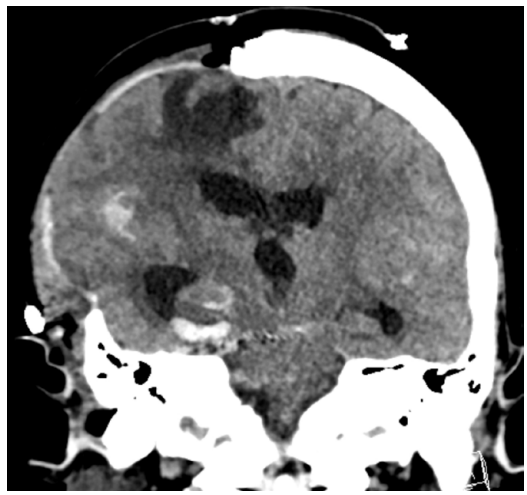

Figure 12. Postoperative CT scan after decompressive craniectomy following aSAH.

In Paper III, as well as previously published in the literature,[134-136] the factors associated with risk of DC being performed were aneurysm on MCA and aneurysm occlusion with microsurgery. Two factors that are often cojoined. As well as poor clinical grade at treatment, cerebral edema, and an AE with aneurysm treatment. The independent association of AEs during aneurysm treatment and DC having to be performed has not been described in the literature before.

As described in Paper III, 29% of patients operated with DC were able to live independently at one year follow-up. Reminded of how clinically ill most of these patients are during the neurointensive care the finding that one in three can live without the assistance of others is quite interesting. There was a significant difference regarding the age of patients having favorable vs. unfavorable outcome in the group of patients operated with DC. Where patients having favorable outcome

were younger. It could be of clinical interest to seek a definite cut-off regarding age and outcome in these patients, but this was not within the scope of this study.

Unfavorable outcome in good grade patients

Good grade patients were defined as patients that were GCS 13 – 15 (WFNS I – III) prior to aneurysm treatment. Excluding patients that did not have a clinical follow-up, analysis was performed on 520 patients. The focus was on patients that at one-year follow-up had unfavorable outcome (dead or dependent on others). This constituted 102 patients or 20% of all patients that were initially in a good clinical grade and were followed up. These outcome rates of good grade patients are similar to what has previously been described in the literature.[137-139] Although, the relation to treatment-related AEs in this patient group has hitherto not been taken into account. In Paper IV we see that AEs during aneurysm treatment (microsurgery or endovascular treatment) was significantly and independently associated with risk of unfavorable outcome at one-year follow-up in patients that were clinically quite well (GCS 13 – 15) prior to treatment. Revealing how much impact these events have on patients, even those that in general have the best odds of favorable outcome.

Strengths and weaknesses

The strength of the included studies lies in the nature of the gathered data. With all variables clearly defined before data gathering was initiated and this being performed on a nationwide level. With senior vascular neurosurgeons at six different clinics in the country forming a steering group, the experience, oversight and dedication of seeing this through was immense. As such, the data gathering was vast and organized with clinical follow-up of patients being structured. The database can be defined as prospective as all variables were defined prior to start of patients' inclusion and as their progress was followed. Whereas a retrospective database collects historical data which were not initially gathered in a study purpose. This prospective set-up can be seen as a strength.

Despite this prospective framework and the best intentions of sampling data while the patients were admitted at the neurosurgical centers, some data was registered after the patients were discharged. This should not affect the prospective composition of the database or the prospective structure with all variables being clearly defined before data was gathered.

With the complexity of data registration, formation of different queries for the included factors, and the possible broad use of the included information, the gathered data form a database and not a disease-register. This can be seen as a certain strength.

Upon reflecting on possible study weaknesses, it felt like there were certain weaknesses when analysing the data. That, we perhaps were missing certain factors that could have enhanced the manuscripts. For example, data on intracranial pressure just prior to decompressive craniectomy (DC) and further information on the DC operations would have given Paper III more depth. At the same time, this can be seen as an opportunity to look further into these factors in another study in this type of cohort. The clinical follow-up was standardized using GOSE-questionnaires. In most published research on clinical follow-up following aSAH, modified Rankin scale is used. One could see this as a weakness, making comparisons to other published studies perhaps suboptimal. However, the two scales are comparable. It can also be argued that GOSE is a better scale as its questions are more thorough.

As a multicenter database, the data sampling was performed by several individuals. To err is human and while keeping that in mind, the data collection was hopefully as correct as it could be.

Clear limitations are that the results are primarily relevant for centers with a similar healthcare system and the study findings should be carefully extrapolated to clinics that have different possibilities and approach to treatment.

Conclusions

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening disease. Patients surviving the initial bleeding and can receive optimal care at a neurosurgical clinic have a long road ahead to recovery. Adverse events related to the treatment are at times principally unavoidable, however it is of outmost importance to try everything to hinder them. Even in the most expertised hands this might not be possible.

This PhD thesis brings to light the frequency of such adverse events in a northern-European welfare country. Where opportunities to give each patient the best possible care are available every day. The published studies bring forth adverse events related to aneurysm treatment and how they impact the clinical outcome. Risk factors and clinical outcome of patients having operation with decompressive craniectomy following aSAH are, among other factors, analysed. Patients that are in a good clinical condition just prior to aneurysm treatment but unfortunately have unfavorable outcome one year later are the focus of the fourth article, which is currently an unpublished manuscript.

The overall clinical implications of the included papers are that adverse events during aneurysm treatment can have major effect on outcome. They should by all means sought to be avoided. This thesis presents information on cerebral edema increasing risk of adverse events during aneurysm treatment. With risk of thromboembolism related to endovascular occlusion, using current methods, MCA

aneurysms are maybe more suitably treated by microsurgery. With the risk of re-rupture during endovascular treatment in mind, certain patients with small aneurysms (< 5 mm) are possibly at times more optimally treated by microsurgery than by endovascular treatment. As ACA/ACoA aneurysms have an increased risk of re-rupture with microsurgery, endovascular treatment is perhaps at times a better option for these aneurysms. We should not be too hesitant to perform decompressive craniectomy in aSAH patients, especially in young patients. One in every five patients that are in good clinical condition just prior to aneurysm treatment are unable to live independently after one year. Adverse events have impact on the outcome even in these patients.

Future perspectives

The treatment of aSAH patients is well established, with the primary focus on occluding the ruptured aneurysm. Followed by optimal medical treatment, preferably at a neurosurgical clinic.

As most things in medicine, the treatment for aSAH is constantly evolving. The microsurgical occlusion of a ruptured aneurysm is well established but with fewer aneurysms being treated with microsurgery nowadays, in historical comparison, it leaves us with the risk of losing certain surgical competence. At the same time, the aneurysms that are now microsurgically treated are often complicate and that is perhaps an important factor in withholding the surgical competence. The endovascular treatment is ever evolving, with new devices regularly being presented. Some of them making endovascular approach more suitable to treat aneurysms that hitherto have been seen as optimally treated by microsurgery. Despite this, there presumably will continue to be aneurysms around that are best treated by microsurgery.

Regarding more research-focused perspectives, in the future I would like to study the long-time follow up of patients treated for intracerebral aneurysms. Particularly with focus on adverse events, outcome and re-treatment.

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